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Effect of whole-body and local heating on cutaneous vasoconstrictor responses in humans

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Abstract

Animal studies suggest that α-adrenergic-mediated vasoconstriction is compromised during whole-body heating. The purpose of this study was to identify whether whole-body heating and/or local surface heating reduce cutaneous α-adrenergic vasoconstrictor responsiveness in human skin. Protocol I: Six subjects were exposed to neutral skin temperature (i.e., 34 °C), whole-body heating, and local heating of forearm skin to increase skin blood flow to the same relative magnitude as that observed during whole-body heating. Protocol II: In eight subjects forearm skin was locally heated to 34, 37, 40, and 42 °C. During both protocols, α-adrenergic vasoconstrictor responsiveness was assessed by local delivery of norepinephrine (NE) via intradermal microdialysis. Skin blood flow was continuously monitored over each microdialysis membrane via laser-Doppler flowmetry. In protocol I, whole-body and local heating caused similar increases in cutaneous vascular conductance (CVC). The EC_{50} (log NE dose) of the dose–response curves for both whole body (-4.2 ± 0.1 M) and local heating (-4.7 ± 0.4 M) were significantly greater (i.e., high dose required to cause 50% reduction in CVC) relative to neutral skin temperature (-5.6 ± 0.0 M; $P < 0.05$ for both). In both local and whole-body heated conditions CVC did not return to pre-heating values even at the highest dose of NE. In protocol II, calculated EC_{50} for 34, 37, 40, and 42 °C local heating was -5.5 ± 0.4, -4.6 ± 0.3, -4.5 ± 0.3, -4.2 ± 0.4 M, respectively. Statistical analyses revealed that the EC_{50} for 37, 40 and 42 °C were significantly greater than the EC_{50} for 34 °C. These results indicate that even during administration of high concentrations of NE, α-adrenergic vasoconstriction does not fully compensate for local heating and whole-body heating induced vasodilatation in young, healthy subjects. Moreover, these data suggest that elevated local temperatures, above 37 °C, and whole-body heating similarly attenuate cutaneous α-adrenergic vasoconstriction responsiveness. © 2002 Published by Elsevier Science B.V.

Keywords: Heat stress; Alpha-adrenergic receptors; Norepinephrine; Cutaneous microdialysis

1. Introduction

Cutaneous vasoconstriction is mediated through sympathetic vasoconstrictor nerves which, upon propagation of an action potential, release a quanta of norepinephrine (NE) from presynaptic varicosities. NE diffuses across the synaptic cleft and binds both to α_1- and α_2-adrenergic receptors on the postsynaptic membrane causing vasoconstriction leading to a reduction in tissue blood flow (van Zwieten, 1999). Although, both α_1- and α_2-adrenergic receptors are located on the postsynaptic membrane, α_2-adrenergic receptors predominate in distal arteries and have been reported to be more important for thermoregulatory control (Flavahan et al., 1987). Temperature, as well as other factors, likely play a role in α-adrenergic receptor affinity, contractile properties of vascular smooth muscle, and sensitivity to sympathetic activation of the peripheral vasculature (Vanhoutte et al., 1981).

The majority of work investigating the effects of temperature on vasculature responsiveness to adrenergic agents has concentrated on veins and isolated vessel preparations in animal models. Local cooling increases the affinity of α_2-adrenergic receptors (Flavahan et al., 1985), while local heating decreases the sensitivity of these receptors in canine leg veins (Cooke et al., 1984). Although there is no direct evidence, it is assumed that responses at the cutaneous arterioles will be similar to those observed in veins. Mesenteric arteries in the rat have reduced vascular reactivity during exposure to high local temperatures

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(Kregel and Gisolfi, 1990; Massett et al., 1998). Taken together, these studies suggest that local, and possibly whole-body heating, may change vasoconstriction characteristics.

During orthostatic stress of a heated individual, blood flow to the skin is reduced primarily through withdrawal of cutaneous active vasodilator activity, as opposed to increases in cutaneous vasoconstrictor activity (Crandall et al., 1996; Kellogg et al., 1990). However, it is possible that the lack of contribution of cutaneous vasoconstriction in mediating decreases in skin blood flow during these conditions is due to inhibition of α-adrenergic vasoconstrictor responsiveness by the thermal exposure, as has been shown in other vascular beds in animals (Kregel and Gisolfi, 1990; Massett et al., 1998). A decrease in cutaneous vasoconstrictor responsiveness could contribute to increased orthostatic intolerance observed in the heated human (Lind et al., 1968; Shvartz et al., 1975). Without testing this question in humans, the effects of heating on cutaneous vasoconstrictor responsiveness in humans will remain unknown.

To the authors' knowledge, there has yet to be a study comparing the effects of local and whole-body heating on α-adrenergic vasoconstriction of nonglabrous skin. Such a study may be beneficial in understanding the effects of heat stress on blood pressure control and cutaneous autonomic nervous responses. Therefore, the purpose of this project was to identify whether heating reduces cutaneous α-adrenergic vasoconstrictor responsiveness in humans. To address this question two hypotheses were tested: (a) whole-body heating reduces cutaneous α-adrenergic vasoconstrictor responsiveness in humans, and (b) local heating reduces α-adrenergic vasoconstrictor responsiveness in a temperature-dependent manner.

2. Material and methods

2.1. Subjects

Six subjects (two males and four females) participated in protocol I and eight subjects (five males and three females) participated in protocol II. The participants' mean age was 27 ± 1 and 30 ± 2 years and all were of typical height (170 ± 3 and 173 ± 3 cm), weight (64.6 ± 3.5 and 74.7 ± 5.1 kg), and body surface area (1.75 ± 0.06 and 1.89 ± 0.07 m^2; (Du Bois and Du Bois, 1916) for protocols I and II, respectively. The protocols and informed consent received institutional approval. Written informed consent was obtained from all participants prior to enrolling in this study.

2.2. Measurements

Internal temperature was indexed from a thermistor placed in the sublingual sulcus (T_{sl}). Mean skin temperature (T_{sk}) was measured via the weighted average of six thermocouples attached to the skin (Taylor et al., 1989). Arterial blood pressure was obtained via auscultation of the brachial artery (Dinamap). Local skin blood flow was measured via laser-Doppler flowmetry (Perimed) attached to the dorsal aspect of the forearm located directly above microdialysis membranes (see below). Integrating flow probes were used, as opposed to single point flow probes, due to the larger sampling area of the integrating probes. Cutaneous vascular conductance (CVC) was indexed by dividing laser-Doppler flux values by mean arterial blood pressure and multiplying that number by 100.

2.3. Protocol I

Two intradermal microdialysis membranes were placed in dorsal forearm skin. This technique involves placing a small (outer diameter: 200 μm, length: 10 mm) sterile semi-permeable membrane intradermally using a 25-gauge needle. Construction of microdialysis probe and assembly system as well as insertion details are reported elsewhere (Crandall et al., 1997). The microdialysis membranes were perfused with Ringer's solution at a rate of 2 μl min via an infusion pump (Harvard). The protocol commenced once skin blood flow returned to normal levels after needle insertion trauma (after 60–120 min).

In each of the conditions described below, four doses of NE were perfused through the intradermal microdialysis membranes in the following order (1×10^{-8}, 1×10^{-6}, 1×10^{-4}, and 1×10^{-2} M) at a rate of 2 μl min, with each dose being delivered for 5 min. These doses were selected following pilot studies in which these doses were found to encompass both pre-threshold and saturation of dose–response curves under normothermic conditions. The number of doses and the duration of administration of each dose were selected to minimize the duration of heating during the whole-body heating protocol. For each condition skin blood flow was averaged between sites during the final minute of each dose of NE.

The protocol consisted of performing the aforementioned procedures under whole-body heated, local heated, and control conditions. Whole-body heating was performed by perfusing 46 °C water through a tube-lined suit (Carleton Technologies) worn by each subject. This suit covered the entire body with the exception of the head, hands, feet, and the forearm from which the measurements were recorded. Thus, during the whole-body heating protocol skin blood flow was measured from an area not exposed to the water-perfused suit. This method of heating typically increases skin temperature to ~ 38 °C and T_{sl} by 0.6–1.0 °C after 30–60 min of heating. In the present protocol, water temperature perfusing the suit was slightly reduced to 44–45 °C 10 to 15 min prior to drug infusion in an attempt to cause T_{sl} and skin blood flow to plateau during NE administration.

On a separate day, the outlined procedures were again performed after sufficient local heating to cause the same

Table 1
Temperature and hemodynamic responses to whole-body and local heating

Variable	Whole-body heating		Local heating	
	Pre	Post	Pre	Post
T_{sl} (°C)	36.4 ± 0.2	37.2 ± 0.1[a]	36.4 ± 0.1	36.7 ± 0.1
Mean T_{sk} (°C)	33.8 ± 0.7	38.2 ± 0.2[a]	34.6 ± 0.3	34.7 ± 0.3
HR (bpm)	52 ± 2	74 ± 3[a]	57 ± 3	55 ± 2
CVC (flux units)	39 ± 4	139 ± 13[a]	24 ± 2	87 ± 11[a]
CVC (%)	100	380 ± 47[a]	100	361 ± 47[a]

Local heating was applied to cause a similar percentage increase in CVC observed during whole-body heating.

T_{sl} (sublingual temperature), mean T_{sk} (mean skin temperature), HR (heart rate), CVC (cutaneous vascular conductance). CVC is expressed both in absolute units (flux units) and as a percent of the pre-heating value, which was designated as 100%. Values are expressed as means ± S.E.

[a] Denotes a significant difference relative to the pre-heating value.

relative increase in skin blood flow as that observed during the preceding whole-body heating protocol. The goal of the local heating protocol was to serve as a control for the whole-body heating protocol by causing the same relative increase in skin blood flow as that observed during whole-body heating but via a different mechanism. Local heating was performed by placing a 3-cm-diameter heating element (Perimed), which housed the laser-Doppler probe, directly over the microdialysis membrane and surrounding area. Local heating was preformed until stable blood flows were achieved (~ 30 min). The typical local temperature for this protocol was between 39 and 40 °C.

Participants then returned to the laboratory a third time to identify NE dose–response relationships when local skin temperature was neutral (i.e., 34 °C). Maintenance of this local temperature was also achieved via local heating elements placed directly over the microdialysis membranes. This procedure was performed as a control for both whole-body heating and local heating trials.

2.4. Protocol II

On the subject's initial visit, two microdialysis membranes were inserted into forearm skin as described in protocol I. After the initial hyperemic response subsided, two of four local temperatures (34, 37, 40, and 42 °C) were randomly selected and applied via local heating elements surrounding the microdialysis membranes. On a subsequent visit to the laboratory, the same procedure was performed using the remaining two local temperatures. To insure the accuracy of the local heating temperature, a thermocouple was placed between the heating element and the skin for each trial. Once stable blood flows were achieved (~ 30 min), at each local temperature, six doses of NE were delivered (1×10^{-7} through 1×10^{-2} M, via 1×10^{-1} M increments) at a flow rate of 2 μl min for 5 min per dose. Laser-Doppler flowmetery was preformed as previously described to index cutaneous blood flow during NE administration.

2.5. Data analysis

Data were continuously acquired throughout both protocols at a sampling rate of 50 Hz using a data collection system (Biopac). The final minute for each dose of NE was averaged and analyzed. For interpretation purposes, data are presented in the following three formats: (a) as absolute data, (b) as normalized data relative to pre-heated values, and (c) as normalized data relative to post-heated values. Both absolute and normalized CVC were mathematically modeled via nonlinear regression curve fitting (GraphPad) to obtain dose–response curves. The model identified the effective drug concentration causing 50% of the vasoconstrictor response (i.e., EC_{50}), as well as minimum and maximum skin blood flows. Thermal and cardiovascular

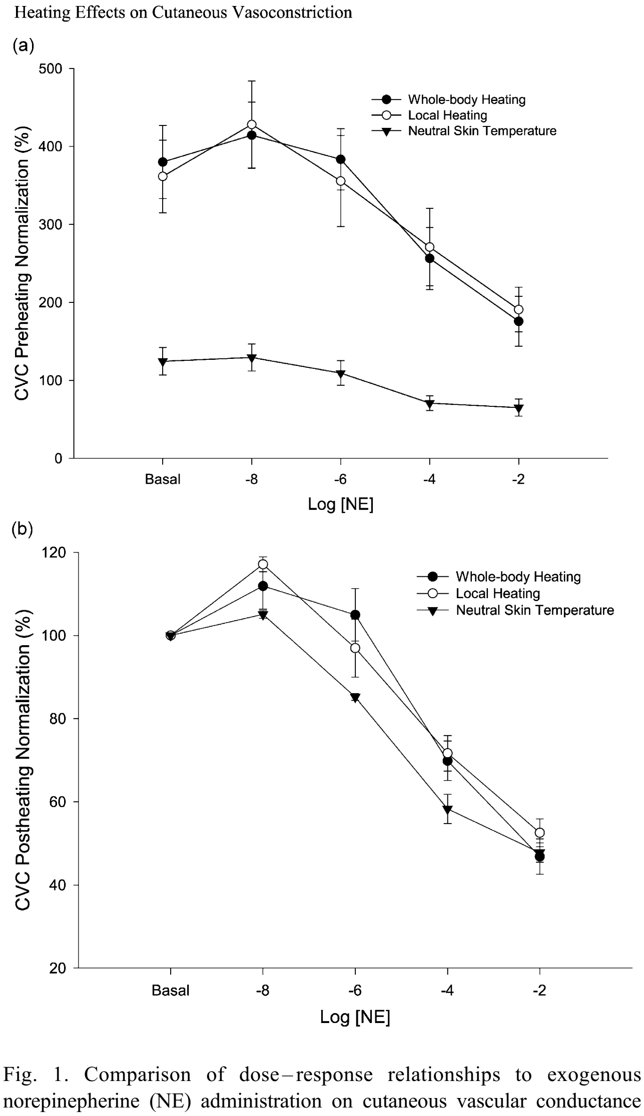

Fig. 1. Comparison of dose–response relationships to exogenous norepinepherine (NE) administration on cutaneous vascular conductance (CVC) during whole-body heating, local heating to a similar percentage increase in CVC observed during whole-body heating, and neutral skin temperature (i.e., 34 °C). Panel (a) depicts data normalized relative to pre-heating values. Panel (b) depicts data normalized relative to post-heating values. NE dose depicted as log-molar concentration.

variables from protocol I were compared between whole-body heating and local heating trials via paired *T*-tests. Variables from the mathematical model were analyzed across each thermal condition (i.e., whole-body heating, local heating, and neutral skin temperature trials) for protocol I and local temperatures (i.e., 34, 37, 40, 42 °C) for protocol II using a one-way repeated measures ANOVA. Multiple comparison post-hoc tests were conducted to identify paired differences when a significant main factor was identified. Differences were considered statistically significant at $P \leq 0.05$.

3. Results

3.1. Protocol I

Whole-body heating increased T_{sl}, mean T_{sk}, heart rate, and CVC (see Table 1). Local heating to the same relative increase in skin blood flow as that observed during whole-body heating did not alter these variables except for CVC (see Table 1). Neither thermal condition altered mean arterial blood pressure. Both methods of heating caused a ~ 3.7-fold increase in CVC. This relative increase in CVC was not significantly different between these heating treatments.

Normalized (relative to pre-heating and post-heating baselines) CVC for protocol I are depicted in Fig. 1. The reduction in normalized CVC with NE administration was virtually identical between whole-body heating and local heating protocols (Fig. 1a). The control treatment (i.e., clamping skin temperature to 34 °C) showed lower cutaneous blood flow responses throughout each dose of NE when compared to the other two treatments. CVC during administration of the highest dose of NE (1×10^{-2} M) were 54 ± 5% and 47 ± 4% above pre-heated baseline for whole-body heating and local heating trials, respectively ($P < 0.05$ for both).

Table 2
Effect of whole-body heating, local heating, and control skin temperatures (34 °C) on responses from the nonlinear regression model during exogenous norepinephrine (NE) administration

Thermal condition		EC_{50}	Minimum	Maximum
Whole-body heating	Pre-heating normalization		184 ± 39^a	407 ± 51^a
	Post-heating normalization	-4.2 ± 0.1^a	47 ± 5	107 ± 5
Local heating	Pre-heating normalization		184 ± 44^a	388 ± 74^a
	Post-heating normalization	-4.7 ± 0.4^a	53 ± 5	109 ± 1
Control	Pre-heating normalization		68 ± 11	128 ± 20
	Post-heating normalization	-5.6 ± 0.1	53 ± 3	102 ± 1

Local heating was applied to cause a similar percentage increase in CVC observed during whole-body heating.

EC_{50}: the effective concentration of NE resulting in half of the cutaneous vasoconstrictor response. Units are expresses as log dose of NE. Minimum and maximum values are from the model. Values are expressed as means ± S.E.

[a] Denotes a significant difference from control conditions.

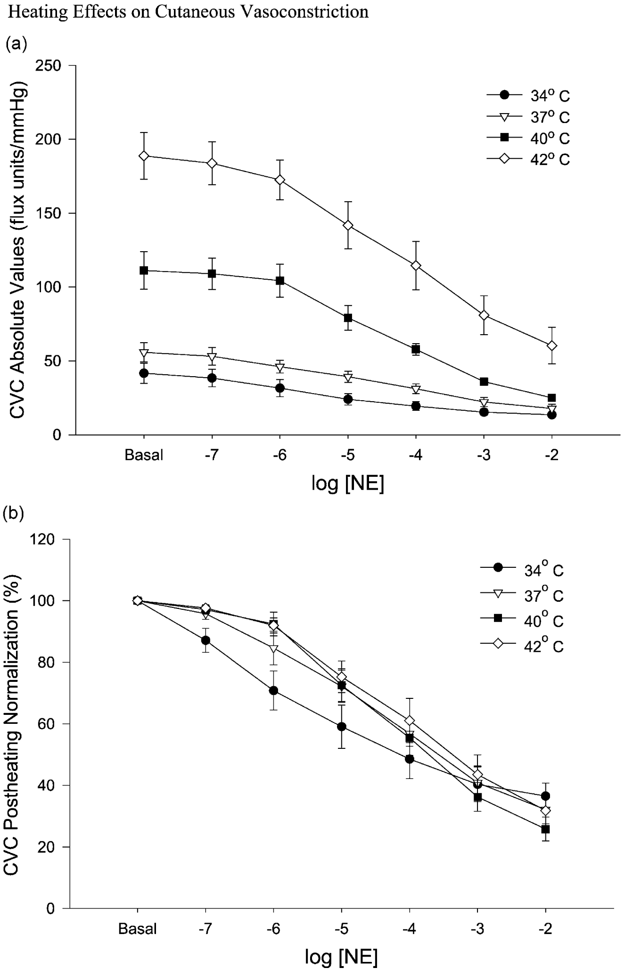

Fig. 2. Comparison of dose–response relationships to exogenous norepinephrine (NE) administration on cutaneous vascular conductance (CVC) during local heating to 34, 37, 40, and 42 °C. Panel (a) depicts the data expressed as absolute CVC. Panel (b) depicts data normalized relative to post-heating values. NE dose depicted as log-molar concentration.

The average goodness-of-fit (R^2) for the post-heating normalized values from the nonlinear regression model had an R^2 of 0.94, 0.89, and 0.97 for the whole-body heating, local heating, and control procedures, respectively. Values for EC_{50}, minimum, and maximum variables for protocol I are reported in Table 2. The EC_{50} for whole-body heating and local heating trials were significantly less relative to the EC_{50} for the control trial. This finding suggests that for both whole-body heating and local heating trials a greater dose of NE is needed to achieve a similar degree of vasoconstriction relative to the control trial. The minimum and maximum responses where significantly higher for whole-body heating and local heating conditions relative to the control trial when values were normalized relative to pre-heated baseline (Fig. 1a) but not when normalized relative to heated baseline (Fig. 1b).

3.2. Protocol II

CVC prior to NE administration was significantly affected by the level of local heating, and this difference remained throughout NE administration (see Fig. 2a). Prior to NE administration the difference in CVC ranged from a low of 41.6 ± 6.9 perfusion units for 34 °C to a high of 184.4 ± 17.5 perfusion units for 42 °C local heating. However, when data were normalized relative to a percent change from heated baseline, the only dose–response curve that deviated from the others was the 34 °C local heating trial (see Fig. 2b).

The average goodness of fit for the post-heating normalized values from the nonlinear regression model had an R^2 of 0.94, 0.95, 0.97, and 0.97 for 34, 37, 40, and 42 °C of local heating, respectively. EC_{50}, minimum, and maximum variables for protocol II are shown in Table 3. The EC_{50} during the application of 34 °C local heating was significantly less relative to the EC_{50} when the skin was locally heated to 37, 40, and 42 °C. This findings suggests that when local temperature is greater than 37 °C a larger dose of NE is needed to achieve a similar degree of vasoconstriction relative to a neutral skin temperature. No differences, however, were observed in the EC_{50} between the three highest local heating temperatures. Both the maximum and the minimum values of the absolute CVC data were significantly affected by local heating (see Table 3). As expected, maximum CVC was highest with the highest level of local heating and lowest with the lowest level of local heating. The minimum responses were significantly elevated with 40 and 42 °C local heating relative to 34 °C of local heating. This finding suggests that during local heating of 40 and 42 °C, CVC was significantly elevated at the highest dose of NE relative to CVC when this dose of NE was administered when local skin temperature was 34 °C. The maximum and minimum responses across the differing local temperatures were not significantly different when data were normalized relative to the heated baseline (Fig. 2b).

Table 3
Effect of local heating on responses from the nonlinear regression model during exogenous norepinephrine (NE) administration

Local temperature		EC_{50}	Minimum	Maximum
34 °C	Absolute values		16 ± 2	39 ± 6
	Post-heating normalization	− 5.5 ± 0.4	45 ± 3	96 ± 1
37 °C	Absolute Values		21 ± 3	53 ± 6[a]
	Post-heating normalization	− 4.6 ± 0.3[a]	39 ± 5	96 ± 2
40 °C	Absolute Values		37 ± 7[a]	106 ± 11[a]
	Post-heating Normalization	− 4.5 ± 0.3[a]	37 ± 4	97 ± 1
42 °C	Absolute values		59 ± 13[a]	176 ± 21[a,b,c]
	Post-heating normalization	− 4.2 ± 0.4[a]	32 ± 3	97 ± 1

Local temperature depicts the skin temperature under the local heater. EC_{50}: the effective concentration of NE resulting in half of the cutaneous vasoconstrictor response. Values are expressed as means ± SE.

[a] Denotes a significant difference from 34 °C.

[b] Denotes a significant difference from 37 °C.

[c] Denotes a significant difference from 40 °C.

4. Discussion

Two major findings were identified as a result of this study: (1) whole-body heating and local heating (above 37 °C) reduce cutaneous vasoconstrictor responses during exogenous NE administration (i.e., change in EC_{50}); and (2) the ability of the skin to vasoconstrict via exogenous NE administration is reduced when cutaneous vasodilation is present regardless of whether vasodilation occurred via whole-body or local heating methods. Taken together, these results indicate that during a heat stress, when skin temperature and/or internal temperature are elevated, the cutaneous vasculature has reduced vasoconstrictor responses via α-adrenergic mechanisms per given dose of exogenous NE.

Previous research indicated that rat mesenteric arteries have reduced vasoconstrictor capacity when the vessels are heated (Kregel and Gisolfi, 1990; Massett et al., 1998). Findings from the present study in humans are in agreement with these studies as evidenced by the observation that cutaneous vasodilation induced by increases in T_{sl}, as well as application of local temperatures above 37 °C, attenuated cutaneous vasoconstriction to exogenous NE administration. However, an interesting contrast between the present findings and the cited findings in rats is that in rats depressed vasoconstrictor responsiveness was only observed when vessel temperature reached 41 °C (Massett et al., 1998). Differences in method of heating, species, vessel structure, or preparations (i.e., intact versus isolated vessels) may play a role in the differences seen between these studies.

Previous data indicate reduced α_2-adrenergic vasoconstrictor responsiveness with local high temperatures in the finger vasculature of humans (Freedman et al., 1992). In that study, α-adrenergic receptor agonists and antagonists were infused via the brachial artery into the entire hand circulation. The finger and hand contain both glabrous and nonglabrous skin. These two classifications of skin contain differing anatomical structures (e.g., arteriovenous anastomosis) and have functional differences of modulating skin blood flow. For example, glabrous skin does not have an active vasodilator mechanism to increase skin blood flow, as has been observed in nonglabrous skin (Johnson et al., 1995; Roddie, 1983). Another important difference between our study and that of Freedman et al. (1992) involves the methodology of monitoring blood flow (i.e., laser-Doppler flowmetry versus finger occlusion plethysmography). In the current study, laser-Doppler flowmetry was used to continuously monitor blood flow of the skin, as opposed to intermittent plethysmography measures. Moreover, finger plethysmography cannot distinguish between changes in skin blood flow relative to changes in blood flow in the underling tissue of the finger. Nevertheless, the present findings suggests that local heating and whole-body heating reduce vasoconstrictor responses specifically in nonglabrous skin, as demonstrated by elevated EC_{50} values during serial administration of NE and reduced cutaneous vasoconstriction at the highest dose of NE during these heat stresses. These findings could be due to altered α-adrenergic responsiveness of the cutaneous vasculature, as previously identified in the canine leg veins with local heating (Cooke et al., 1984).

Attenuated vasoconstrictor responses (e.g., EC_{50} and altered minimal CVC) were observed regardless of the method of heating (i.e., local temperature above 37° or whole-body heating). Indirect whole-body heating increases skin blood flow through the co-release of an unknown neurotransmitter from cholinergic nerves (Kellogg et al., 1995). In contrast, local heating does not need intact sympathetic nerves to elicit the response (Pergola et al., 1993; Wenger et al., 1986), and is primarily mediated through a nitric oxide mechanism (Kellogg et al., 1999; Minson et al., 2001). Since both methods of cutaneous vasodilation similarly impaired NE-induced vasoconstriction, a potential mechanism responsible for the observed results could simply be a competition between vasodilation and α-adrenergically mediated vasoconstriction. However, the present data do not exclude the possibility that a substance is released as a result or consequence of heat-induced vasodilation (regardless of the method of heating) that modifies vasoconstrictor responsiveness.

It is interesting to note that at the highest dose of NE, when local or internal temperatures were elevated, CVC remained elevated above pre-heated conditions (Figs. 1a and 2a). This observation indicates that regardless of the method of dilating skin blood vessels, a dose of NE that causes a clear plateau in vasoconstrictor responses under normothermic conditions (see Fig. 1) does not completely overcome the influence of cutaneous vasodilation via either whole-body or local heating. These results are consistent with prior findings reporting that although forearm skin blood flow decreased during lower-body negative pressure in heated individuals, forearm skin blood flow remained above pre-heated levels even in subjects experiencing pre-syncopal symptoms (Johnson et al., 1973).

Impaired cutaneous vasoconstriction could have important implications with respect to the control of blood pressure via modulation of CVC during conditions of orthostatic stress in heated individuals. Although prior findings suggest reductions in CVC with baroreceptor unloading in heated individuals occurs primarily though withdrawal of the cutaneous active vasodilator system (Crandall et al., 1996; Kellogg et al., 1990), those findings do not eliminate the possibility that reduced cutaneous α-adrenergic vasoconstriction contributes to reduced venous return and reductions in orthostatic tolerance known to occur in heated individuals (Lind et al., 1968; Shvartz et al., 1975). Nevertheless, it is recognized that the hypothesized contribution of reduced α-adrenergic vasoconstrictor responsiveness in decreasing tolerance to orthostatic and gravitational stress observed in heated individuals remains speculative.

The present findings suggest that increases in local T_{sk} of ≥ 37 °C alter cutaneous vasoconstrictor responses to exogenous administration of NE. Local T_{sk} at this level are not "unphysiological" since in high ambient temperature environments such as 45–50 °C, skin can achieve temperatures above 38 °C. Moreover, at more moderate ambient temperatures, especially in the presence of high relative humidity, T_{sk} has been reported to reach 36.5–38 °C (Robinson, 1972). Finally, exercise (i.e., walking 4.0 mile/h, 10% grade) has been shown to increase superficial blood temperatures from ~ 33 °C to above 36–37 °C in as little as 5 min of locomotion (Gisolfi and Robinson, 1970). Thus, it is not uncommon for T_{sk} to reach temperatures that the present data suggest impairs α-adrenergic vasoconstrictor responsiveness.

4.1. Limitations

Doses of NE were chosen based on carefully collected pilot data of normothermic subjects. However, at the highest temperatures (during both local and whole-body heating) vasoconstrictor responses were not saturated in some subjects, despite the present and prior observation of a plateau in the vasoconstrictor response at this dose of NE under normothermic conditions. It should be emphasized that the last dose of NE was very concentrated (1×10^{-2} M), and perhaps was even unphysiological. Thus, we recognize the possibility of errors in the mathematical modeling at these high temperatures because of the apparent lack of plateau of CVC. However, it must stressed that even if this limitation is present, absolute and pre-heating normalized CVC values (i.e., non-modeled data) still show that at the highest dose of NE administered, less vasoconstrictor response was observed during whole-body and local heating (see Figs. 1a and 2a).

We also recognize the possibility that as skin blood flow decreases the effective delivery of NE may be modified. Since blood flow is elevated during local and whole-body heating, it may be postulated that less NE is delivered due to "washout" of this substance given higher skin blood flows relative to normothermic conditions. However, we are unaware of data to support the hypothesis that changes in blood flow alter deliver of drug to vascular smooth muscle when the drug is continuously delivered via the interstitial space. On the contrary, it may be that changes in blood flow will not alter the interstitial concentration of a substance during microdialysis administration, particularly when the concentration of that substance is quite elevated.

Insertion of the microdialysis membrane causes trauma to the skin. The contribution of this trauma to the observed responses in the present study is not clear. However, prior work demonstrated that vasodilator substances such as histamine substantially decrease within 40 min following membrane insertion in the skin (Anderson et al., 1992). In the present experiment, no procedures were performed until skin blood flow returned to normal levels (typically 60–120 min after membrane insertion). Thus, it is unlikely that vasodilator substance associated with membrane insertion affected the present findings.

4.2. Conclusions

In conclusion, data from the present study suggest both indirect whole-body heating and direct local heating impair α-adrenergic vasoconstrictor responsiveness as evidenced by: (1) a significant increase in the NE concentration required to cause 50% of the vasoconstrictor response (i.e., EC_{50}) during local and indirect whole-body heating, and (2) absolute CVC being significantly elevated above pre-drug and pre-heated baseline at the highest concentration of NE during either method of heating. These results indicate that during a heat stress, when skin and/or internal temperatures are elevated, the cutaneous vasculature has reduced α-adrenergic vasoconstrictor responsiveness during exogenous administration of NE in young, healthy subjects.

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