

Nitric oxide and cutaneous active vasodilation during heat stress in humans

D. L. KELLOGG, JR.,^{1,2,3,4} C. G. CRANDALL,^{5,6} Y. LIU,⁴
N. CHARKOUDIAN,² AND J. M. JOHNSON²

¹Geriatric Research, Education, and Clinical Center, Department of Veterans Affairs, South Texas Veterans Health Care System, Audie L. Murphy Division, San Antonio 78284; Departments of ²Physiology, ³Medicine, and ⁴Pharmacology, University of Texas Health Science Center at San Antonio, San Antonio, 78284; ⁵Institute for Exercise and Environmental Medicine, Presbyterian Hospital of Dallas, Dallas, 75231; and ⁶University of Texas Southwestern Medical Center, Dallas, Texas 75235

Kellogg, D. L., Jr., C. G. Crandall, Y. Liu, N. Charkoudian, and J. M. Johnson. Nitric oxide and cutaneous active vasodilation during heat stress in humans. *J. Appl. Physiol.* 85(3): 824–829, 1998.—Whether nitric oxide (NO) is involved in cutaneous active vasodilation during hyperthermia in humans is unclear. We tested for a role of NO in this process during heat stress (water-perfused suits) in seven healthy subjects. Two forearm sites were instrumented with intradermal microdialysis probes. One site was perfused with the NO synthase inhibitor *N*^G-nitro-L-arginine methyl ester (L-NAME) dissolved in Ringer solution to abolish NO production. The other site was perfused with Ringer solution only. At those sites, skin blood flow (laser-Doppler flowmetry) and sweat rate were simultaneously and continuously monitored. Cutaneous vascular conductance, calculated from laser-Doppler flowmetry and mean arterial pressure, was normalized to maximal levels as achieved by perfusion with the NO donor nitroprusside through the microdialysis probes. Under normothermic conditions, L-NAME did not significantly reduce cutaneous vascular conductance. During hyperthermia, with skin temperature held at 38–38.5°C, internal temperature rose from 36.66 ± 0.10 to 37.34 ± 0.06°C ($P < 0.01$). Cutaneous vascular conductance at untreated sites increased from 12 ± 2 to 44 ± 5% of maximum, but only rose from 13 ± 2 to 30 ± 5% of maximum at L-NAME-treated sites ($P < 0.05$ between sites) during heat stress. L-NAME had no effect on sweat rate ($P > 0.05$). Thus cutaneous active vasodilation requires functional NO synthase to achieve full expression.

skin blood flow; microdialysis; laser-Doppler flowmetry

IN NONGLABROUS AREAS OF SKIN in humans, thermoregulatory reflex alterations of skin blood flow (SkBF) are mediated by sympathetic efferent nerves of two types: active vasoconstrictor and active vasodilator nerves (6, 10, 13, 20). Cutaneous vasoconstrictor nerves are noradrenergic and act through postjunctional α_1 - and α_2 -receptors (13, 17). This system is activated during periods of cold stress to reduce SkBF and conserve body heat. Studies of thermoregulatory reflexes in resting subjects have shown that during heat stress there is an initial abolition of any extant vasoconstrictor tone. As internal temperature increases further, the active vasodilator system is activated along with sweat production. The active vasodilator system is responsible for 80–95% of the elevation in SkBF accompanying heat stress (13). Cutaneous active vasodilation is effected by a cholinergic cotransmitter system, as the process is completely abolished by intradermal botulinum toxin

(16) but not by atropine. Muscarinic blockade with atropine slightly reduces or delays vasodilator responses to hyperthermia, although it completely abolishes the response to exogenous acetylcholine (ACh) (16, 20). The failure to block vasodilation has generally been taken as evidence against a role for ACh as the neurotransmitter substance involved; however, the partial inhibitory effect of atropine on the process suggests a role for ACh.

The suggestion that ACh plays a role in active vasodilation also suggests a mechanistic role for nitric oxide (NO) in the process. Studies in rabbits suggest that NO produced by endothelial cells acts in conjunction with a neurotransmitter released during hyperthermia to increase ear blood flow (7). In humans, NO donors can increase SkBF (26), and NO contributes to a basal dilator tone in forearm and finger skin (4). Evidence contrary to a mechanistic role for NO in active vasodilation has also been found. In humans, NO synthase (NOS) blockade was found to reduce blood flow in the ventral finger, which appears to lack active vasodilation, but not in the dorsal finger where active vasodilation is present (12, 17). Most germane to our study, Dietz et al. (5) found that intra-arterial infusion of the NOS inhibitor *N*^G-monomethyl-L-arginine (L-NMMA) blunted NO-mediated vasodilator responses to ACh but did not significantly affect the rise in SkBF during hyperthermia in humans.

Given this disparate evidence, we sought to test the hypothesis that NO does play a mechanistic role in the cutaneous active vasodilator response to heat stress in humans.

METHODS

To test our hypothesis, we examined alterations of the SkBF response to heat stress in humans during local intradermal administration of the NOS inhibitor *N*^G-nitro-L-arginine methyl ester (L-NAME; Ref. 9). The approach we chose was to combine local SkBF measurements by laser-Doppler flowmetry (LDF) from a small volume of skin (~1 mm³) with local administration of L-NAME by intradermal microdialysis. Intradermal microdialysis permits local administration of pharmacological agents directly into the interstitial space of a small area of dermis. Monitoring LDF over a skin site instrumented with an intradermal microdialysis probe permits monitoring of local drug effects with high local concentrations without risking confounding systemic effects. Because there is no question about the locus of measurement or the locus of drug delivery, the combination of LDF with local

administration of L-NAME provided an innovative and unambiguous approach to study the role of NO in the control of SkBF.

Our studies were conducted at the same time that an independent group (23) was following a different, but complementary, approach to the same problem. In their study, intra-arterial administration of NOS inhibitors was combined with LDF measurements of forearm SkBF and plethysmographic measurements of total forearm blood flow (FBF) during body heating. Our results and conclusions are consistent with those presented in that complementary study (23).

Seven subjects (4 men and 3 women) participated in this study. Their average age was 30 ± 4 (SE) yr, average weight 79 ± 4 kg, and average height 176 ± 3 cm. All subjects were in good health and were taking no medications. All subjects gave informed consent to participate in these institutionally approved studies. There was no caffeine intake on the day of the study. All subjects were nonsmokers. The menstrual phase was not assessed in the female subjects.

Thermoregulatory reflexes were induced as follows. Subjects wore a tube-lined suit used to control skin temperature (T_{sk}) by perfusion with water of different temperatures (11, 21, 24). Over the suit, subjects wore a water-impermeable plastic garment to insulate them from the room environment and to prevent evaporation of sweat. The suit and garment covered the entire body except for the head, arms, and feet. The suit was perfused with warm water to raise T_{sk} to 38–39°C during heating periods and with cold water to lower T_{sk} from 34–34.5 to 31.5–32°C for cold stress.

Internal (oral; T_{or}) temperature was monitored with a thermocouple placed in the sublingual sulcus. T_{sk} was recorded as the weighted electrical average from six thermocouples taped on the skin surface. Heart rate was recorded continuously from the electrocardiogram. Mean arterial pressure was recorded continuously from a finger (Finapres BP Monitor, Ohmeda).

After being instrumented as outlined above, subjects had an intradermal microdialysis probe placed at each of two sites on the ventral aspect of one forearm. The probes were of our own manufacture and were made from borosilicate glass tubing and a 1-cm length of capillary microdialysis membrane (200- μ m diameter, molecular cutoff 20 kDa; Spectrum Medical Industries, Houston, TX) reinforced by a 51- μ m-diameter coated stainless steel wire placed in the lumen of the membrane and tubing. Placement of the microdialysis probe was accomplished at each site as follows. First, a 25-gauge needle was inserted through the dermis by using sterile technique. Entry and exit points were ~ 2.5 cm apart. The microdialysis probe was threaded through the internal lumen of the needle. The needle was then withdrawn, leaving the probe in place. The microdialysis membrane was entirely within the dermis, with entry and exit through the skin via the borosilicate tubing. Ultrasound measurements showed that probes placed with this technique are 0.3–0.9 mm under the epidermal surface and thus well within the dermis. Subjects then waited 140 min or more to allow for insertion trauma to resolve before additional instrumentation was placed. Anderson et al. (1) reported that the injury caused by insertion of an intradermal microdialysis probe resolves during a period of 90–135 min, thereafter allowing *in vivo* studies without the confounding effects of trauma. Subjects were then placed in the supine position and instrumented to measure LDF from skin at the two microdialysis sites (MBF3D dual-channel flowmeter, Moor Instruments, Devon, UK). LDF measurements are specific to skin, being uninfluenced by blood flow in the underlying tissues (22). Sweat rate (SR) was assessed at the two LDF-microdialysis sites by relative-

humidity monitors (HX92V, Omega Engineering; IH 3602-L humidity sensors, HY-CAL Engineering). LDF probes were held in special probe holders that permit simultaneous LDF and SR measurements (16). After the LDF probes were placed, both microdialysis probes were perfused with Ringer solution at a rate of 2 μ l/min by using a microinfusion pump.

As illustrated in Fig. 1, data collection began with a 5- to 20-min control period followed by a 3-min application of whole body cooling. Body cooling was used to verify that active vasoconstrictor function was intact at the microdialysis sites and that the trauma of probe placement had not caused either a loss of neural or vessel reactivity. Subjects were returned to normothermia, and one of the microdialysis probes was then perfused with a 5-mM solution of L-NAME (Sigma Chemical, St. Louis, MO) dissolved in Ringer solution. This dose was chosen based on studies of the role of NOS in the vasodilation induced by local warming (15). In those studies, we examined the effect of 1.25-, 2.5-, 5-, 10-, and 20-mM concentrations of L-NAME delivered by intradermal microdialysis and found no significant difference in the vasoconstriction induced by the higher three doses. Thus the 5-mM concentration was chosen for the present study.

After 40 min of perfusion with L-NAME, the 3-min period of cold stress was repeated to test for any effects of the drug on vasoconstrictor function. After a few minutes of recovery, T_{sk} was raised to 38–39°C and was maintained at that level for 35–50 min to induce heat stress and thus activate the vasodilator system. After hyperthermia, subjects were cooled to normothermia, and both microdialysis probes were perfused with 28 mM of nitroprusside (Sigma Chemical) in Ringer solution for 20–40 min to effect maximal vasodilation (15). Nitroprusside infusion was chosen for maximal vasodilation, in lieu of local skin warming (14, 24), since NOS activity is required for cutaneous vasodilation as induced by local warming (15). Thus the administration of L-NAME in the present study precluded the use of local warming of the skin to achieve maximal levels of blood flow. The dose of nitroprusside chosen dilates cutaneous vessels to maximal levels no different from those achievable by raising the local temperature of the skin to 42°C (15).

Data are means \pm SE. For data analysis, cutaneous vascular conductance (CVC) was indexed as LDF (in mV) divided by MAP (in mmHg) and normalized to the maximal levels, as achieved with nitroprusside to allow site-to-site and subject-to-subject comparisons of responses in CVC (14, 15). The vasomotor responses during each of the separate periods of cold stress were analyzed by comparing the pre-cold stress levels of CVC with the levels achieved during the last minute of cold stress. The vasomotor responses to heat stress were analyzed by comparing pre-heat stress levels of CVC with the levels achieved during the last minute of heat stress. The degree of vasodilation was compared between untreated and L-NAME-treated sites on the basis of the percentage of maximal CVC for those sites. Sudomotor responses were analyzed by comparing pre-heat stress levels of SR with the levels achieved during the last minute of heat stress. Internal temperature thresholds (the level of T_{or} at which CVC began to rise during whole body heating) were chosen from plots of CVC vs. T_{or} by an investigator blinded to the conditions, subjects, and drug treatments involved. T_{or} responses were analyzed by paired *t*-test that compared internal temperature thresholds at L-NAME-treated and untreated sites. CVC and SR responses were analyzed by repeated-measures ANOVA followed by planned contrasts.

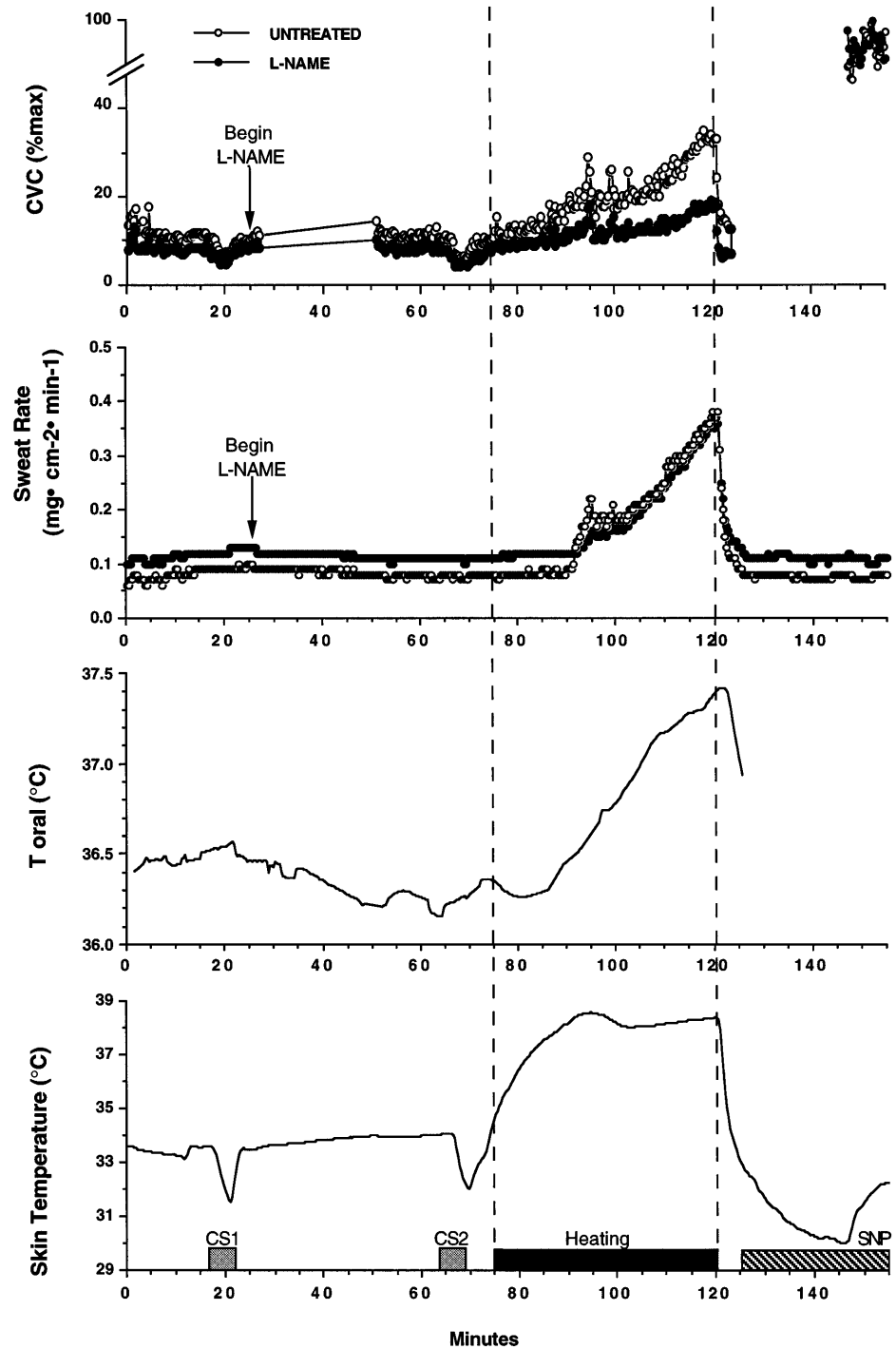


Fig. 1. Illustration of protocol and results of the study in 1 subject. Periods of cold stress (CS; CS1 and CS2), whole body heating, and sodium nitroprusside infusion (SNP) are noted at *bottom*. Beginning of perfusion of 1 microdialysis probe with 5 mM *N*^c-nitro-L-arginine methyl ester (L-NAME) in Ringer solution is also shown. Note that increase in cutaneous vascular conductance (CVC) during whole body heating was attenuated at the site receiving L-NAME, but sweat rate response was unaltered. T oral, oral temperature.

RESULTS

Figure 1 illustrates the results from one subject. Before the perfusion of one microdialysis site with L-NAME, CVC for the entire subject group did not differ significantly between sites, nor did the responses differ during whole body cooling ($P > 0.05$). During the initial control period, CVC levels at the two microdialysis sites averaged 15 ± 4 and $20 \pm 6\%$ of the maximal level (%max; $P > 0.05$). During the initial cold stress, CVC fell by 4 ± 0.5 ($P < 0.05$ vs. control) and $7 \pm 2.0\%$ ($P < 0.05$ vs. control) of the maximal CVCs at the different

microdialysis sites. These responses were not statistically different ($P > 0.05$). Up to this point in the protocol, both sites were perfused with Ringer solution only. (Data for the probe to be perfused with the L-NAME solution are given second.)

Under normothermic conditions, perfusion with L-NAME for 40 min did not significantly reduce CVC at the treated site ($20 \pm 6\%$ max pre-L-NAME to $13 \pm 2\%$ max post-L-NAME, $P > 0.05$). During the repetition of cold stress, at the site treated with L-NAME, CVC fell by $4 \pm 0.6\%$ max ($P < 0.05$ vs. pre-cold stress). CVC fell

by $4 \pm 1.0\%$ max ($P < 0.05$ vs. pre-cold stress) of the maximal level at the untreated sites. These responses did not significantly differ ($P > 0.50$) and are summarized in Fig. 2.

Before initiation of whole body heating, T_{or} averaged $36.66 \pm 0.10^\circ\text{C}$. During whole body heating, vasodilation began at the untreated microdialysis sites when T_{or} reached a threshold value of $37.00 \pm 0.10^\circ\text{C}$. At the L-NAME-treated sites, vasodilation began when T_{or} reached $37.08 \pm 0.06^\circ\text{C}$ ($P > 0.15$ between sites). T_{or}

reached $37.34 \pm 0.05^\circ\text{C}$ at the peak of heat stress ($P < 0.01$ preheating vs. peak heat stress). During heat stress, CVC rose at both untreated and L-NAME treated sites; however, the rise was attenuated by L-NAME treatment. At the peak of heat stress, CVC at the untreated site reached $44 \pm 2\%$ max levels ($P < 0.05$ vs. preheating), whereas at the L-NAME-treated sites CVC reached only $30 \pm 5\%$ max levels ($P < 0.05$ vs. preheating). Thus L-NAME treatment significantly attenuated the thermoregulatory increase in CVC during whole body heating ($P < 0.05$ between sites). These results are summarized in Fig. 2. SR responses did not differ between untreated and L-NAME-treated sites during heat stress ($P > 0.25$).

DISCUSSION

The results of this study show that full expression of cutaneous active vasodilation in humans requires NOS activity. This conclusion derives from the observation that blockade of NOS by L-NAME significantly attenuated the reflex increase in CVC in response to whole body heat stress. The attenuation was not likely due to any antimuscarinic effects of L-NAME (3), as the SR response to heat stress was not altered by the agent.

The results of the initial cold stress, during the perfusion with Ringer solution only, demonstrated that the ability of the cutaneous vessels to respond to increased noradrenergic vasoconstrictor tone persisted after microdialysis probe placement. Thus trauma associated with placement of the probes did not render the vessels incapable of responding to neural inputs. The ability of the vessels to vasoconstrict during cold stress was also preserved after treatment with L-NAME. This demonstrates that NOS inhibition did not alter responses to activation of noradrenergic vasoconstrictor nerves. This finding is consistent with those of Coffman (4), who found that NOS inhibition with L-NMMA had no effect on the reduction in finger blood flow or FBF accompanying whole body cooling. This evidence suggests little or no role for NO in the control of SkBF during cooling.

Over the course of L-NAME infusion during normothermia, there was a trend for a reduction in CVC, although this did not reach statistical significance. Such a reduction was reported by Coffman (4), who recorded reductions in LDF during intra-arterial infusion of L-NMMA during normothermia; however, no reduction was found under cool conditions. In support of Coffman's work, Dietz et al. (5) reported that FBF was reduced during infusion of L-NMMA into the brachial artery, although the distribution of this reduction between skin and muscle is not known. In contrast, Noon et al. (18) reported that, despite reduction in FBF during intra-arterial infusion of L-NMMA at doses of 1, 2, and 4 $\mu\text{M}/\text{min}$, there was no reduction in LDF from skin on the dorsum of the finger. The different findings might be attributable to differing thermal conditions, reductions in SkBF by NOS inhibition being evident at the higher levels of blood flow due to inhibition of flow-induced NO release in normothermia.

Our results contrast with those of Dietz et al. (5), in which unilateral infusion of L-NMMA into the brachial

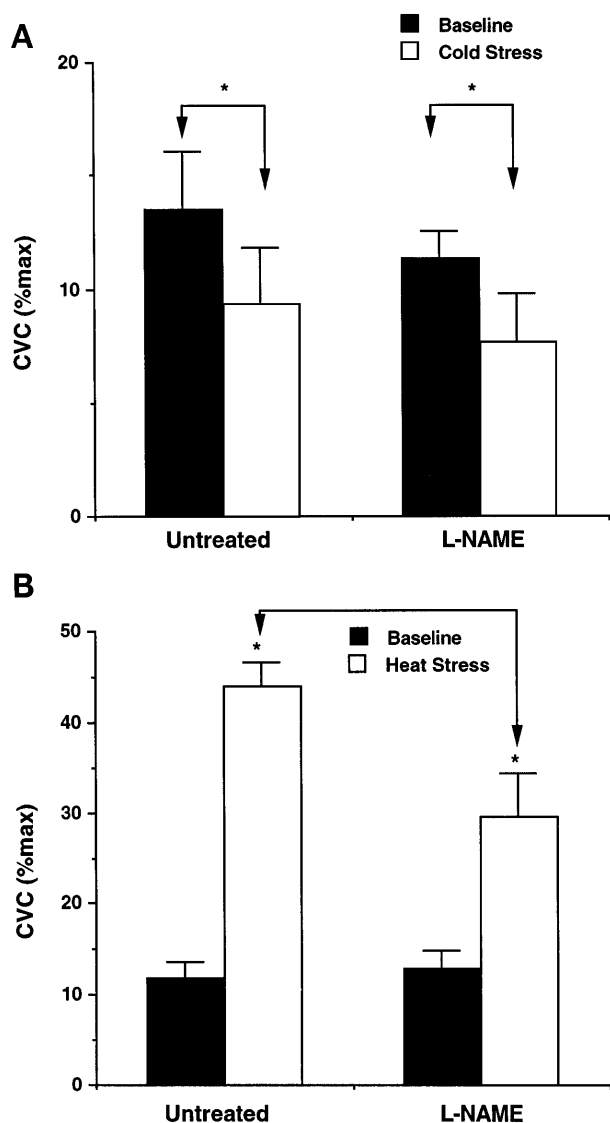


Fig. 2. A: summary of CVC responses to cold stress during L-NAME infusion. Whole body cooling reduced CVC significantly at microdialysis site perfused with Ringer solution alone and at site perfused with 5 mM L-NAME in Ringer ($*P < 0.05$ for both sites). These responses were not different from each other ($P > 0.15$). These results show that blockade of nitric oxide synthase by L-NAME did not alter cutaneous active vasoconstrictor responses. B: summary of CVC responses to heat stress during L-NAME infusion. Whole body heating increased CVC significantly at microdialysis site perfused with Ringer solution alone and at the site perfused with 5 mM L-NAME in Ringer ($*P < 0.05$ for both sites). Response was significantly attenuated at site treated with L-NAME ($P < 0.05$ between sites). These results show that blockade of nitric oxide synthase by L-NAME attenuated, but did not abolish, cutaneous active vasodilation during heat stress.

artery did not attenuate the increase in forearm SkBF during hyperthermia. As acknowledged by the authors, they were only able to consistently verify L-NMMA blockade of the vasodilator response to exogenous ACh during normothermia, allowing the possibility that blockade of NOS was incomplete during heat stress. This possibility is strengthened by the more recent results from that laboratory, presented in a companion study (23). It is also possible that our doses of L-NAME did not block NOS activity completely. Thus we are not able to say whether the mechanism is entirely NO-dependent or whether NO-independent pathways are involved in cutaneous active vasodilation.

Inhibition of the elevation of SkBF with L-NMMA during hyperthermia by Shastry et al. (23) confirms that the choice of NOS inhibitor does not explain the differences in results between our study and that of Dietz et al. (5). However, our use of intradermal microdialysis to continuously deliver relatively large doses of drug ensured significant NOS inhibition throughout the study. However, given the similar results from the different approaches of microdialysis with LDF, and intra-arterial infusion with venous-occlusion plethysmography (25), we are confident that full expression of active vasodilation requires the presence of functional NOS.

The cutaneous active vasodilator system is known to be a cholinergic cotransmitter system, as active vasodilation is abolished by cholinergic nerve blockade with botulinum toxin but is only attenuated by atropine (16). These observations suggest a number of possible roles for NO in active vasodilation, although the present data do not distinguish among those possibilities. For example, a relationship between active vasodilation and sudomotor activity has been postulated (2, 8). It is interesting to speculate that released ACh causes hyperemia around activated sweat glands. Because ACh elicits vasodilation through an NO-dependent mechanism, it is possible that NOS blockade attenuated full expression of active vasodilation by reducing ACh-mediated glandular hyperemia. The cotransmitter could cause vasodilation in areas of skin remote from sweat glands and need not be NO dependent.

An alternative to the foregoing hypothesis derives from work by Farrell and Bishop (7). This hypothesis and its supporting evidence are derived from studies in the rabbit ear and suggest that NO produced by endothelial cells acts in conjunction with a neurotransmitter released during hyperthermia to effect increases in ear blood flow. According to this scheme, NO generated by endothelial cells mediates increases in cGMP, which is necessary for thermoregulatory reflex active vasodilation. However, this tonically produced NO acts in a permissive fashion with a neurogenic reflex activation of cAMP synthesis. Given the above results from Dietz et al. (5), Farrell and Bishop (7) speculated that humans may possess mechanisms other than NO that contribute to the level of cGMP. In that case, even with complete NOS blockade, the level of cGMP would be sufficient to permit vasodilation in the hyperthermic human. Our observation and that of Shastry et al. (23)

of attenuation, but not abolition, of active vasodilation during heat stress is consistent with this proposal. Furthermore, it is possible that the NO involved in the vasodilation might be induced by shear stress and not by heat stress (4).

A third possibility is that nitroxidergic nerves partially effect active vasodilation in humans. Such neurally mediated vasodilation has been reported in other regions (19, 25). Such nerves are generally considered to be nonadrenergic, noncholinergic in nature (19, 25). Although the results of the present study do not exclude the possibility that nitroxidergic nerves are involved in cutaneous active vasodilation, the observation that botulinum toxin abolishes vasodilation argues against such a role (16).

In summary, we found that blockade of NOS with L-NAME attenuates, but does not abolish, thermoregulatory reflex-mediated cutaneous active vasodilation in humans. Thus NO generation is involved in the mechanism of cutaneous active vasodilation in humans.

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Address for reprint requests: D. L. Kellogg, Jr., Divisions of Geriatrics and Gerontology and of Clinical Pharmacology, Dept. of Medicine, Univ. of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr., San Antonio, TX 78284 (E-mail: kellogg@uthscsa.edu).

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