Active cutaneous vasodilation in resting humans during mild heat stress

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Kamijo, Yoshi-Ichiro, Kichang Lee, and Gary W. Mack. Active cutaneous vasodilation in resting humans during mild heat stress. J Appl Physiol 98: 829–837, 2005. First published October 15, 2004; doi:10.1152/japplphysiol.00235.2004.—The role of skin temperature in reflex control of the active cutaneous vasodilator system was examined in six subjects during mild graded heat stress imposed by perfusing water at 34, 36, 38, and 40°C through a tube-lined garment. Skin sympathetic nerve activity (SSNA) was recorded from the peroneal nerve with microneurography. While monitoring esophageal, mean skin, and local skin temperatures, we recorded skin blood flow at bretylium-treated and untreated skin sites by using laser-Doppler velocimetry and local sweat rate by using capacitance hygrometry on the dorsal foot. Cutaneous vascular conductance (CVC) was calculated by dividing skin blood flow by mean arterial pressure. Mild heat stress increased mean skin temperature by 0.2 or 0.3°C every stage, but esophageal and local skin temperature did not change during the first three stages. CVC at the bretylium tosylate-treated site (CVCBT) and sweat expulsion number increased at 38 and 40°C compared with 34°C (P < 0.05); however, CVC at the untreated site did not change. SSNA increased at 40°C (P < 0.05, different from 34°C). However, SSNA burst amplitude increased (P < 0.05), whereas SSNA burst duration decreased (P < 0.05), at the same time as we observed the increase in CVCBT and sweat expulsion number. These data support the hypothesis that the active vasodilator system is activated by changes in mean skin temperature, even at normal core temperature, and illustrate the intricate competition between active vasodilator and the vasoconstrictor system for control of skin blood flow during mild heat stress.

Skin sympathetic nerve activity; amplitude-to-duration ratio; skin temperature; thermoneutral; bretylium

Cutaneous Vasodilation During heat stress promotes heat transfer from body core to skin and compliments evaporative heat loss mechanisms in homeostatic regulation of core temperature. Thermoregulatory control of cutaneous vasodilation during heat stress is governed by changes in body core and skin temperature (8, 31, 32), with the change in core temperature being 10–20 times more effective than the change in skin temperature (19, 31, 32). Cutaneous vasodilation during heat stress is induced through two mechanisms: withdrawal of sympathetic vasoconstrictor activity and enhancement of an active sympathetic vasodilator system (5, 10, 18). Core temperature is considered the major factor driving active sympathetic vasodilator activity during exercise and severe heat stress. Changes in skin temperature clearly drive changes in cutaneous sympathetic vasoconstrictor tone; however, it also modulates active cutaneous vasodilation (23). Specifically, Pergola et al. (23) demonstrated that during dynamic exercise, when core temperature was elevated, an increase in skin temperature from 32 to 37°C increased skin blood flow. This increase in skin blood flow was mediated primarily by active cutaneous vasodilation. In contrast, at rest with normal core temperature, a similar increase in skin temperature seemed to only produce a withdrawal of vasoconstrictor activity (23). One interpretation of these findings is that the reflex control of skin blood flow in response to changes in skin temperature reflects a net balance between the vasodilator and vasoconstrictor activities. At elevated core temperatures, modulation of the active vasodilator system appears to dominate. Within the normal range of core temperature, one may presume that the active vasoconstrictor system dominates; however, the role of the active vasodilator system is unclear.

One problem with evaluating the impact of changes in skin temperature on thermoregulatory function at rest is that, during mild heat stress, the impact of changes in mean skin temperature (Tsk) has a paradoxical effect on body core temperature. Savage and BRENGELMANN (25) reported that changes in Tsk between 33 and 35°C (the thermoneutral zone) cause rapid reflex adjustments in skin blood flow. They observed that an increase in Tsk resulted in cutaneous vasodilation and a small decrease in body core temperature (~0.1°C) (25). As such, mild heat stress within this thermoneutral zone leads to paradoxical changes in the sensory input from central and peripheral thermosensors into the hypothalamic thermoregulatory center. On the basis of the work by Savage and BRENGELMANN (25), we suspect that changes in Tsk within or just above the thermoneutral zone would not produce sufficient change in the integrated thermal input to the hypothalamus to initiate active cutaneous vasodilation.

Skin sympathetic nerve activity (SSNA), which includes at least three components [sudomotor, vasoconstrictor, and vasodilator activities (21, 27, 30)], responds rapidly to changes in skin temperature. Bini et al. (1, 2) reported that multunit SSNA, recorded from nerves innervating hairy and nonhairy skin, increased and then decreased with an increase in ambient temperature from 27 to 35°C, respectively. The authors showed an elevation in sudomotor activity and/or a reduction in vasoconstrictor activity within this temperature range (2). More recently, SugenoYa et al. (27, 28) identified vasoconstrictor and/or sudomotor components of SSNA after inducing generalized sweating with heating or mild exercise. These studies indicate that mild heat stress, especially when Tsk increases above the thermoneutral zone, enhances an active sympathetic vasodilator activity and modulates both vasodilator and vasoconstrictor nerve activity.

The purpose of this study was to determine the net balance between active cutaneous vasodilator and vasoconstrictor systems during mild heat stress in resting humans and whether the

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activation of vasodilator system is associated with an enhancement of SSNA. We assessed the thermoregulatory characteristics of SSNA, active cutaneous vasodilation, and sweating responses during mild graded heat stress. We applied bretylium tosylate locally to selectively inhibit the vasoconstrictor system (11) and measured skin blood flow at both bretylium-treated and untreated sites. Our hypotheses were that, during mild heat stress in resting humans, 1) an enhancement of cutaneous vasodilation would be greater at the bretylium-treated skin site than that at the untreated skin site, and 2) an increase in active cutaneous vasodilation would be associated with an increase in SSNA.

METHODS

Subjects
Six healthy subjects (4 men, 2 women) participated in the present study. Each subject was informed of all aspects of the experiment before written, informed consent was obtained. The Yale University School of Medicine Human Investigation Committee approved the experimental protocol. The subjects’ characteristics were the following: age, 30 ± 5 yr; body weight, 69.5 ± 13.1 kg; and height, 169 ± 8 cm (means ± SD). All subjects were nonsmokers and were asked to refrain from caffeine, alcohol, and heavy exercise for the 24 h before the experiment.

Experimental Design and Protocol

Subjects arrived at our laboratory at 8:00 AM and ingested ~200 ml of water to ensure proper hydration status. Subjects wore a water-perfused suit covering the entire skin surface except for the knee where SSNA was measured, the feet, hands, face, and head. Subjects sat in the semirecumbent position at a controlled room temperature of ~28°C and a relative humidity between 30 and 40%. An area (7.0 cm²) of skin on the dorsal foot devoid of any superficial veins or scars was chosen for measuring skin blood flow. Bretylium tosylate (100 mM) was applied to a 3.5-cm² area of skin by iontophoresis (Iontophor II model 6111PM/DX, Life-Tech, Stafford, TX) to block cutaneous sympathetic vasoconstriction by presynaptic inhibition of norepinephrine release from sympathetic nerve terminals (11, 17). The iontophoresis protocol consisted of 30 min at a current density of 140 μA/cm². Effectiveness of the cutaneous sympathetic vasoconstrictor blockade was tested 120 min after the procedure by perfusing 2°C water through the water-perfused suit while monitoring skin blood flow and arterial blood pressure. After the cold test, the water perfusing the suit was returned to 34°C, and microelectrodes were then inserted for the measurement of SSNA. After adjustment of the microelectrodes to obtain an adequate skin sympathetic nerve recording, the subject was instrumented for measurement of heart rate (HR), arterial blood pressure, and local sweat rate. During this period, 34°C water was continuously perfused through the water-perfused suit, and local foot temperature (Tfoot) was maintained between 32 and 34°C.

After the first 10-min data collection at 34°C (stage I), water temperature perfusing through the water-perfused suit was increased to 36°C (stage II), 38°C (stage III), and then 40°C (stage IV) every 30 min. Skin temperature stabilized during the first 20 min, and data were collected during the last 10 min of each stage. Subjects maintained a fixed respiratory rate of 0.2 Hz (2.5 s for inspiration, 2.5 s for expiration) during each data collection period. At the end of each collection period, we evoked a SSNA burst by delivering a sudden noise. Similarities in the evoked SSNA bursts were used to verify that electrode tip placement had not changed. At the end of the experiment, a second cold challenge was presented to confirm persistent blockade of cutaneous sympathetic vasoconstriction at the bretylium-treated skin site.

Measurements

Microneurography. Multunit postganglionic SSNA was recorded from cutaneous nerve fascicles in the peroneal nerve. The general procedures for recording and identifying SSNA are described in detail by Bini et al. (1), Hagbarth et al. (6), and Yamauchi et al. (33). After tracking of the nerve course on the skin surface, a tungsten microelectrode with an impedance of 3–5 MΩ at 1 kHz, 1–5 μm of tip, and 200 μm of shaft diameter was inserted percutaneously into the peroneal nerve at the posterior aspect of the head of the fibula. A reference electrode was inserted 2–3 cm apart from the active electrode. Minor adjustments of the active electrode were based on the response to local stimulation through the electrodes with ±1 V, 2-ms duration, and at a frequency of 1–2 Hz (model S88, Grass-Telefactor, West Warwick, RI). The nerve signal was preamplified 10,000-fold (model DAM80, WPI, Sarasota, FL) and passed through a band-pass filter (500–1,500 Hz; model 440, Brownlee Precision, San Jose, CA). The filtered signal was sent to a loudspeaker and an oscilloscope (model 2212, Tektronix, Beaverton, OR), and then it rectified and integrated with a time constant of 0.1 s. Total gain was by a factor of 26,000–60,000. SSNA burst was defined by the criteria described by Bini et al. (1) and Hagbarth et al. (6): 1) weak electrical stimulation through the electrode elicited paraesthesia on the dorsal foot without any involuntary muscle contraction, 2) spontaneous bursts were not synchronous with the cardiac cycle, and 3) a burst was evoked by a deep breath, sudden arousal (noise), or gentle touch within the innervated area but not evoked by a Valsalva maneuver. During data analysis, two individuals identified each SSNA burst while listening for the characteristic burst sound from the loudspeaker (33).

Responses of thermal effector organs. Skin blood flow was measured by laser-Doppler velocimetry (LDV; moorLAB, Moor Instruments, Devon, UK) with a time constant of 0.1 s on an area on the dorsal foot that was innervated by the peroneal nerve and devoid of any superficial cutaneous veins. Two pairs of optic probes (model DP7a, Moor Instruments) were used for measurement of skin blood flow at bretylium-treated and untreated skin sites within the innervated area. LDV flux measurements were normalized to a voltage between 0 and 10 V by using a ratio of the maximal full-scale setting to the full-scale level used for each probe (range 10–1,000). Cutaneous vascular conductance (CVC) was calculated by dividing LDV flux in vols by mean arterial blood pressure (MAP) (V/mmHg).

A sweat capsule with a capacitance hygrometer (HHH-3.610, Honeywell, Freeport, IL) was placed on the dorsal foot (0.7-cm² area) beside the LDV probes to detect sweat expulsions. Dry nitrogen gas was ventilated through the capsule at 120 ml/min. To assist in the detection of sweat expulsion rate, the sweat glands in the area of interest were primed by local iontophoresis of pilocarpine. The priming of sweat glands allows for a strong coupling between sudomotor activity and the sweat expulsion at the skin (22). The sweat capsule covered an area that included on average ~130 sweat glands, which is a similar sweat gland density as the forearm (14). Approximate sweat gland density was determined by the method of Kuno et al. (15).

Body temperature. Esophageal temperature (Tes) was measured with a copper-constantan thermocouple inserted through a nostril into the esophagus to the approximate level of the heart. Insertion depth was calculated as one-fourth of subject’s standing height. Tes was measured with thermocouples at seven sites and calculated according to the following equation (4):

\[
\overline{T_{es}} = 0.10 \times T_1 + 0.21 \times T_2 + 0.28 \times T_3 + 0.12 \times T_4
+ 0.06 \times T_5 + 0.15 \times T_6 + 0.08 \times T_7
\]

where the subscripts refer to the temperature of the following areas: 1, chest; 2, forehead; 3, abdomen; 4, lateral upper arm; 5, dorsal surface of forearm; 6, anterior thigh; and 7, lateral calf. Weighting of each site is based on the product of regional area and local relative thermal
sensitivity (19). $T_{\text{foot}}$ was also monitored from a single thermocouple placed beside the LDV probe.

**Cardiovascular and respiratory variables.** Beat-by-beat measures of HR were obtained from an electrocardiogram (model 1500B, Hewlett-Packard, Palo Alto, CA). Continuous beat-by-beat arterial blood pressure was obtained noninvasively from the middle digit of the left hand by the Peñaz method (Finapres 2300, Ohmeda, Louisville, CO). Simultaneously, systolic (SBP) and diastolic arterial blood pressure (DBP) were also assessed from the right arm every 2 min by automated brachial auscultation (STBP model 780B, Colin, Komaki, Japan). SBP and DBP measurements obtained from the Finapres were used to calculate MAP ($=\frac{1}{3}\text{DBP} + \frac{2}{3}\text{SBP}$). Respiratory movement was continuously monitored using a respiratory belt transducer (MLTI132, ADInstruments, Colorado Springs, CO).

**Data Acquisition and Analysis**

Mean voltage neurogram of SSNA, electrocardiogram, arterial blood pressure from Finapres, skin blood flow, and respiratory movement were collected with a 16-channel computerized data-acquisition system at a sampling rate of 400 Hz (PowerLab/16SP, ADInstruments) and stored in files on a computer. $T_{\text{es}}$, skin temperature, and $T_{\text{foot}}$ were recorded continuously and averaged every 20 s on a personal computer.

We counted the number of the SSNA bursts and calculated the area under each burst from the mean neurogram during each stage. The area under the burst was integrated in each stage (total SSNA) and then normalized to the value at baseline (stage I). CVC was also presented as a percentage of the value in the first stage of the experiment. We used the number of sweat gland expulsions per 10-min period as our index of sudomotor activity.

One-way ANOVA with repeated measures was applied for comparison of all values between stages. We did not apply a two-way ANOVA with repeated measures to compare CVC between untreated sites (CVC Con) and bretylium sites (CVC BT), because the values of CVC were relative values based on the baseline value (stage I). Subsequent post hoc tests to determine significant differences in various pairwise comparisons were performed by Fisher’s least significant difference test. Statistical significance was accepted at $P < 0.05$.

**RESULTS**

Effectiveness of bretylium for blockade of skin sympathetic vasoconstrictor system was evaluated by the magnitude of reduction in CVC during skin cooling. At the start of the experiment, skin cooling caused a 41.0 ± 4.6% decrease ($P < 0.05$) in CVC Con and a small 9.8 ± 1.6% ($P < 0.05$) reduction in CVC BT. At the end of the experimental period, skin cooling induced a 36.6 ± 10.0% ($P < 0.05$) decrease in CVC Con but no reduction in CVC BT (+5.2 ± 11.1%; $P > 0.05$), thereby confirming effective and persistent blockade of skin sympathetic vasoconstrictor activity.

Mild graded heat stress produced a significant increase in $T_{sk}$ from 34.8 ± 0.2°C at stage I to 35.2 ± 0.2 at stage II ($P < 0.01$), 35.5 ± 0.1 at stage III ($P < 0.01$), and 35.7 ± 0.1°C at stage IV ($P < 0.01$) (Table 1). $T_{es}$ and $T_{foot}$ averaged 36.9 ± 0.1 and 33.3 ± 0.4°C, respectively, at stage I and did not change through stage III. However, $T_{es}$ and $T_{foot}$ increased by 0.17 ± 0.04°C and 0.4 ± 0.1°C, respectively, at stage IV compared with stage I ($P < 0.01$). HR, SBP, and DBP averaged 66 ± 4 beats/min, 111 ± 4 mmHg, and 65 ± 3 mmHg, respectively, at stage I and did not change during the mild graded heat stress.

The increase in CVC BT, expressed as a percentage change from stage I ($\Delta$CVC BT), plotted as a function of $T_{sk}$ is shown in Fig. 1. The $\Delta$CVC BT rose during stages III and IV compared with stage I ($P < 0.05$) (Fig. 1A), whereas change in CVC Con ($\Delta$CVC Con) did not change during the mild graded heat stress (Fig. 1B). The number of sweat gland expulsions did not change during the first two stages of heating but increased during stage III and stage IV compared with stage I ($P < 0.01$; Fig. 1C). The response of sudomotor activity was similar to that of CVC BT.

SSNA burst number did not change from 115 ± 17 at stage I to III, but it increased significantly to 170 ± 30 at stage IV compared with stages I ($P < 0.05$) and II ($P < 0.05$) (Fig. 2A). Total SSNA showed a similar trend as SSNA burst number (Fig. 2B) and increased significantly by ~80% from stage II to IV ($P < 0.05$). The SSNA burst number and total SSNA did not change during the first three stages; however, this pattern of response for all stages was similar to that of $\Delta$CVC BT or the number of sweat gland expulsions.

The characteristics of the measured SSNA activity changed when moving from stage II to stage III (Fig. 3). SSNA burst amplitude, normalized to the average value at stage I, showed a significant increase at stage III compared with stage I or II (Fig. 3A; $P < 0.05$). SSNA burst amplitude remained elevated throughout stage IV of the heating protocol. The average width of the SSNA bursts decreased after the transition from stage II to stage III (Fig. 3B; $P < 0.05$). The change in the characteristics of the SSNA burst activity corresponded to the observed significant changes in CVC BT and the number of sweat gland expulsions during the heating protocol.

Figure 4 shows the typical SSNA mean voltage neurogram by 10.220.33.6 on July 12, 2017 http://jap.physiology.org/ Downloaded from

**DISCUSSION**

The present data provide unique support for the hypothesis that the active cutaneous vasodilator system does participate in

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Table 1. Effect of a mild heat stress on body temperature and cardiovascular values

<table>
<thead>
<tr>
<th>Stage</th>
<th>Stage I (34°C)</th>
<th>Stage II (36°C)</th>
<th>Stage III (38°C)</th>
<th>Stage IV (40°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{sk}$, °C</td>
<td>34.8 ± 0.2</td>
<td>35.2 ± 0.2*</td>
<td>35.5 ± 0.1**</td>
<td>35.7 ± 0.1**</td>
</tr>
<tr>
<td>$T_{es}$, °C</td>
<td>36.9 ± 0.1</td>
<td>36.9 ± 0.1</td>
<td>37.0 ± 0.1</td>
<td>37.1 ± 0.1*</td>
</tr>
<tr>
<td>$T_{foot}$, °C</td>
<td>33.3 ± 0.4</td>
<td>33.5 ± 0.4</td>
<td>33.5 ± 0.4</td>
<td>33.7 ± 0.4*</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>64 ± 2</td>
<td>64 ± 2</td>
<td>67 ± 4</td>
<td>68 ± 3</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>111 ± 2</td>
<td>110 ± 5</td>
<td>114 ± 5</td>
<td>113 ± 5</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>65 ± 3</td>
<td>66 ± 3</td>
<td>66 ± 4</td>
<td>66 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SE for 6 subjects. $T_{sk}$, mean skin temperature; $T_{es}$, esophageal temperature; $T_{foot}$, foot temperature; HR, heart rate; SBP and DBP, systolic and diastolic arterial blood pressure, respectively. *Significantly different from baseline (34°C, stage I), $P < 0.05$. †Significantly different from previous stage, $P < 0.05$.
thermoregulatory reflexes initiated by changes in Tsk when body core temperature is normothermic (37.0°C). Furthermore, the present data illustrate the neural competition between sympathetic vasoconstrictor and active vasodilator activities in the regulation of skin blood flow when Tsk varied between 34 and 36°C (Fig. 1). Specifically, CVC was normalized with the value at stage I (34°C, baseline). Values are means ± SE for 6 subjects. *Significantly different from stage I, P < 0.05.

Our present model is dependent on our assumption that the SSNA recorded from the peroneal nerve is associated with the thermoregulatory effector organ responses (CVC and sweat) on the dorsal foot where the nerve innervates. The pattern of skin blood flow from different skin sites is synchronous during 60% of total data collection period (26), and SSNA bursts patterns are similar for different hairy skin sites (2). These observations indicate that vasmotion in the skin is regulated by a uniform central drive, via changes in SSNA. As such, we believe that the pattern of the end-organ responses (CVC and number of sweat glands activity) on the dorsal foot would reflect reasonably well the pattern of SSNA measured at the peroneal nerve. In addition, we examined the consistency of the evoked SSNA bursts elicited before and after each data collection period. Consistency in the evoked SSNA burst provided confidence that the microelectrode tip had not moved in any significant manner over the course of the experiment.

Fig. 1. Change (Δ) in cutaneous vascular conductance at bretylium tosylate-treated site (ΔCVCBT, A) and untreated (control) skin sites (ΔCVCCon, B) and number of sweat gland expulsions (C) as a function of mean skin temperature (Tsk). ΔCVC was normalized with the value at stage I (34°C, baseline). Values are means ± SE for 6 subjects. *Significantly different from stage I, P < 0.05.

Our present model is dependent on our assumption that the SSNA recorded from the peroneal nerve is associated with the thermoregulatory effector organ responses (CVC and sweat) on the dorsal foot where the nerve innervates. The pattern of skin blood flow from different skin sites is synchronous during 60% of total data collection period (26), and SSNA bursts patterns are similar for different hairy skin sites (2). These observations indicate that vasmotion in the skin is regulated by a uniform central drive, via changes in SSNA. As such, we believe that the pattern of the end-organ responses (CVC and number of sweat glands activity) on the dorsal foot would reflect reasonably well the pattern of SSNA measured at the peroneal nerve. In addition, we examined the consistency of the evoked SSNA bursts elicited before and after each data collection period. Consistency in the evoked SSNA burst provided confidence that the microelectrode tip had not moved in any significant manner over the course of the experiment.

Fig. 2. Number of skin sympathetic nerve activity (SSNA) bursts (A) and Δtotal SSNA (B) during each stage plotted as a function of Tsk. Values are means ± SE for 6 subjects. *Significantly different from stage I (34°C, baseline), P < 0.05. $ Significantly different from stage II (36°C), P < 0.05.
increase in CVCCon during mild heat stress, it is clear that the increase in active vasodilator activity observed in the CVCBT site is insufficient to overcome the vasoconstrictor bias normally present at the level of Tsk. By abolishing the sympathetic vasoconstrictor system, we were able to unmask this effect.

We attribute part of our success to our experimental design because we set our lower Tsk level at the upper end of the thermoneutral zone. As such, increases in Tsk above this level did not produce paradoxical reductions in body core temperature that might have impacted cutaneous dilation (8, 23, 25). The increase in Tsk might stimulate the peripheral warm-sensitive neurons that mainly belong to unmyelinated C-fiber afferents. The discharge frequency of the warm-sensitive neurons rises rapidly after increasing temperature followed by transient attenuation and shows a steady-state activity after a few minutes of warming (24). The steady-state activity of the warm neurons begins at ~30°C and shows a maximal activity between 40 and 45°C in monkey forearm skin (24). Therefore, in our model, the range of Tsk from 34 to 36°C in the present study corresponded to the period of marked increase in the warm-neuron discharge. The input of this sensory information to the hypothalamic temperature-regulating centers would contribute to the initiation of active cutaneous vasodilation.

Our data at first appear in conflict with previous data showing that an increase in Tsk produced only withdrawal of vasoconstrictor activity when body core temperature was ~37°C. Pergola et al. (23) showed that, at rest, increasing Tsk from 32 to 36°C produced a small reflex increase in CVCCon but no change in CVCBT. During exercise when Tes was elevated, raising Tsk a similar amount produced an increase in CVCCon and CVCBT. Johnson and Park (8) showed that a rapid increase in Tsk from 32 to 37°C resulted in little change in forearm blood flow at rest but a marked change in forearm blood flow during exercise accompanying the rise in Tsk. Both previous studies suggested that an increase in Tsk would only induce a withdrawal of vasoconstrictor activity when Tes was close to thermoneutral levels (37°C). The major differences between the previous work and the present study reside in the site of skin blood flow measurement (forearm vs. dorsal foot) and the heating protocol. Our present data indicate that cutaneous vasoconstrictor activity is quite strong on the dorsal foot, presumably due to a higher density of vasoconstrictor nerves. This stronger vasoconstrictor activity would explain the limited increase in CVCCon during the mild heat stress. The heating protocol of Pergola et al. (23) started at a lower initial Tsk, i.e., 32°C, than the present study. In our heating protocol, we reach an initial thermoregulatory equilibrium by perfusing 34°C water through the suit for at least 1 h before control measurements were made. Another important point is that the skin vasoconstrictor tone would be greater at a Tsk of 32°C than 34°C. An increase in skin temperature, starting from a Tsk of 32°C, will favor vasoconstrictor withdrawal rather than active cutaneous vasodilation.

Earlier studies monitored the CVC responses to an increase in Tsk across the thermoneutral zone. This type of heating protocol elevated Tsk at a rate of ~1.0°C/min for the first few minutes and resulted in a large increase in CVC at rest (23). However, this heating protocol also produced a transient decrease in Tes by 0.2–0.3°C for the first few minutes at rest (23). The transient decrease in Tes is related to a redistribution of body heat from core to skin as reported by Savage and Brengelmann (25). These authors showed that, if Tsk were
cycled between 33 and 35°C every 15 min, skin blood flow would vary linearly with \( T_{sk} \), but \( T_{es} \) would exhibit an inverse pattern. The range of the change in \( T_{es} \) during the 2°C \( T_{sk} \) cycling was \(-0.1–0.2°C\) (25). On the basis of these data, we can estimate the “central drive” for thermoregulatory function using weighting factors of 10 and 1 for core and skin temperatures (19, 31, 32). In doing so, we note that variations in \( T_{sk} \) within the thermoneutral zone produced changes in skin blood flow without a significant change in central thermoregulatory drive. As such, dilation can only be explained by withdrawal of vasoconstrictor tone. In the present study, we evaluated the steady-state thermoregulatory responses to graded heat stress resulting from an increase in the water temperature from the thermoneutral zone (34°C) by 2°C. A 20-min waiting period followed by 10 min of data collection allowed the thermoregulatory responses to reach steady state.

The existence of an active cutaneous vasodilator system in hairy skin, e.g., forearm, in humans has been reported previously (5, 12). However, it is not clear whether the magnitude and/or sensitivity to heat stress is similar in the dorsal foot as in the forearm. Johnson et al. (9) reported the existence of the active cutaneous vasodilator system in the dorsal aspect of the hand with a vasodilator response similar to that in the forearm. Preliminary studies in our laboratory (3) showed \(-200\%\) increase in a magnitude of vasodilation from baseline on the dorsal foot similar to the forearm at both control and bretylium-treated skin sites during passive heating (increase in \( T_{es} \) of 0.5–0.7°C) induced by immersion of the opposite leg in 44°C for 45 min (unpublished data). Thus we are confident that dorsal foot skin possesses an active vasodilator system that is at least as responsive to thermal stress as forearm skin.

**Change in the Magnitude of SSNA and the Type of the Bursts During the Mild Heat Stress**

Previous microneurographers reported that SSNA from nerves innervating hairy skin areas is low or almost nil at normal room temperature (25–27°C) and increased at room temperature due to the peripheral warming (25°C)."
temperature increases, primarily because of enhanced sudomotor activity (1). Our data are consistent with these observations, although SSNA did not increase significantly during the first three stages of our mild heat stress. The main reason for the nonstatistical increment during the first three stages is possibly that the vasoconstrictor activity present at stage I (34°C) decreased as vasodilator and sudomotor activities increased. Based upon the shape of the curve shown in Fig. 2, we speculate that the decrease in vasoconstrictor activity was smaller than the increase in combined sudomotor and vasodilator activity. The net effect is a small decline in SSNA at stage II before it begins to rise in later stages of heating. Overall, this means that, over the entire range of Tsk tested, the magnitude of the change in SSNA response does not correspond directly with the changes in active vasodilator and/or sudomotor activities. However, above stage II we do find that the increase in SSNA tends to vary in direct proportion to the change in effector organ responses, such as an active vasodilation or number of sweat gland expulsions.

As shown in Fig. 3, A and B, the SSNA burst duration and amplitude change from a low-amplitude, wide-duration burst at stages I and II to a high-amplitude, narrow-duration bursts at stages II and IV. It has been reported that the SSNA burst amplitude-to-duration ratio differs with respect to vasoconstrictor and sudomotor components of SSNA. Specifically, Bini et al. (2) reported that the SSNA burst amplitude-to-duration ratio was higher for sudomotor bursts than vasoconstrictor bursts recorded from median nerve. Sugenoja et al. (27) reported similar findings from the peroneal nerve. As such, the vasoconstrictor activity is reflected by the presence of low and wide bursts that disappear as mild heat stress is applied. On the basis of the data in Figs. 2 and 3, we suggest that the onset of significant active cutaneous vasodilation and sweating corresponds to the appearance of high-amplitude, short-duration SSNA bursts.

Relationship Between SSNA and Active Cutaneous Vasodilation

Although the present data and earlier work show a close relationship between sudomotor and vasodilator activity in the skin (18, 29), evidence indicates that the two processes are not always linked (3, 21). It is clear that an unknown cotransmitter released by a sympathetic cholinergic nerve regulates active cutaneous vasodilation (13). What is unclear is whether an independent vasodilator nerve regulates the active cutaneous vasodilator system. Blumberg et al. (3) reported that a painful intraneural stimulation at anterior ankle induces an increase in skin blood flow on the same side of the dorsal foot with the strength of the stimulation but that local anesthesia at a proximal site abolished the increase in skin blood flow and pain, suggesting that local nociceptors may have mediated the cutaneous vasodilation associated with intraneural stimulation. They also showed that the increase in skin blood flow due to the intraneural stimulation remained after intravenous injection of atropine, which suppressed sudomotor activity (3). Noll et al. (21) observed a marked increase in skin blood flow on the dorsal foot with short periods of increasing SSNA bursts.
during non-rapid eye movement sleep in humans, whereas skin resistance on the dorsal foot remained constant. Furthermore, Lundberg et al. (16) showed that an intraneural stimulation at lumbar sympathetic chain (L2–L4) after epidural block at the level of T6 initiates a transient vasodilation on the dorsal foot followed by a vasoconstriction during surgical operations in humans. These results indicate that neural vasomotor activity is independent of sudomotor activity and the enhancement of vasodilator activity could shift the balance between vasodilator and vasoconstrictor activity toward that of dilation. Our study was unable to provide any direct evidence of the presence of vasodilator nerves independent from sudomotor nerves.

Limitation of This Study

One limitation of our study is our assumption that the SSNA recorded from the peroneal nerve is associated with the thermoregulatory effector organ responses (CVC and sweat) on the dorsal foot. We made measurements of skin blood flow and sweating from skin sites located within the innervation zone of the peroneal nerve. We assume that, within this skin area, the response patterns are similar and can be representative of the entire dorsal foot. In support of our assumption, Schechner and Braverman (26) observed synchronized patterns of skin blood flow from different skin sites (within a 20-mm radius) on the ipsilateral forearm and on comparable skin sites on the contralateral forearm. These authors noted that the pattern of skin blood flow was synchronous for ~60% of the total sampling time (940 min). Such a high degree of synchrony at different sites suggested that the vasomotion is regulated by a uniform central drive, via changes in SSNA. In addition, Bini et al. (2) showed that SSNA burst patterns were similar for the antibrachial and superficial radial nerves, both of which innervate hairy skin. As such, we believe that the pattern of the end-organ responses (CVCBT and number of sweat gland expulsion) on the dorsal foot should reflect reasonably well the pattern of SSNA measured at the peroneal nerve.

Multunit SSNA signal involves sudomotor, vasoconstrictor, and vasodilator activity (28, 30) and in some cases may include pilomotor activity (7). The involvement of the multiple components makes an interpretation of changes in SSNA activity complicated. The interpretations are guided by the corresponding skin blood flow responses, especially in skin sites that have the vasoconstrictor component removed by the application of bretylium tosylate. As such, we interpret an increase in SSNA when associated with a rise in CVCBT to reflect an increase in vasodilator activity. However, the rise in SSNA could be the result of an increase in sudomotor activity. Finally, we do not know the contribution or responsiveness of pilomotor and lipomotor activity to multunit SSNA recordings during mild heat stress.

It is possible that the tip of the microelectrode moved during the course of the experiment and thereby impacted the pattern of recorded SSNA, especially because the present protocol took at least 2 h to complete. However, we examined the consistency of the evoked SSNA bursts elicited before and after each data collection period. Consistency in the evoked SSNA burst provided confidence that the microelectrode tip had not moved in any significant manner over the course of the experiment.

Local skin temperature can influence the vasodilator responses to heat stress. In this study, $T_{\text{foot}}$ was unchanged during the first three stages of heating when active cutaneous vasodilation occurred. Although $T_{\text{foot}}$ did increase by stage IV, this increase occurred in response to the dilation in the foot. The change in $T_{\text{foot}}$ during the present study was very small ($\Delta 0.4°C$) and likely had little impact on the change in cutaneous vasodilation or sweat expulsion number (19).

In summary, our data demonstrate that, during mild heat stress, the increase in skin temperature alone (with no change in core temperature) evoked active cutaneous vasodilation. These data provide insight into the interaction and unique competition between the active cutaneous vasodilator and vasoconstrictor systems in regulating skin blood flow at rest and during mild heat stress. Furthermore, the active cutaneous vasodilator system is responsive to changes in both skin and body core temperature. Within the range of $T_{k}$ studied we noted that vasoconstrictor activity is the main component regulating skin blood flow. However, as heat stress increases and $T_{k}$ exceeds 35°C, the sudomotor and vasoconstrictor components are activated. The increase in activity of the active vasodilator and sudomotor response is proportional to the increase in $T_{k}$. The enhancement of active vasodilator system was associated with the appearance of the higher and narrower SSNA bursts. Despite the rise in active vasodilator activity during the later stages of mild heating, it was insufficient to overcome the background level of skin sympathetic vasoconstrictor tone.

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GRANTS

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