Forearm cutaneous vascular and sudomotor responses to whole body passive heat stress in young smokers

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Moyen NE, Anderson HM, Burchfield JM, Tucker MA, Gonzalez MA, Robinson FB, Ganio MS. Forearm cutaneous vascular and sudomotor responses to whole body passive heat stress in young smokers. Am J Physiol Regul Integr Comp Physiol 309: R36–R42, 2015. First published April 29, 2015; doi:10.1152/ajpregu.00079.2015.—The purpose of this study was to compare smokers and nonsmokers’ sudomotor and cutaneous vascular responses to whole body passive heat stress. Nine regularly smoking (SMK; 29 ± 9 yr; 10 ± 6 cigarettes/day) and 13 nonsmoking (N-SMK; 27 ± 8 yr) males were passively heated until core temperature (Tc) increased 1.5°C from baseline. Forearm local sweat rate (LSR) via ventilated capsule, sweat gland activation (SGA), sweat gland output (SGO), and cutaneous vasomotor activity via laser-Doppler flowmetry (CVC) were measured as mean body temperature increased (ΔTc) during passive heating using a water-perfused suit. Compared with N-SMK, SMK had a smaller ΔTc at the onset of sweating (0.52 ± 0.19 vs. 0.35 ± 0.14°C, respectively; P = 0.03) and cutaneous vasodilation (0.61 ± 0.21 vs. 0.31 ± 0.12°C, respectively; P < 0.01). Increases in LSR and CVC per °C ΔTc (i.e., sensitivity) were similar in N-SMK and SMK (LSR: 0.63 ± 0.21 vs. 0.60 ± 0.40 amg/cm²/min/°C ΔTc, respectively; P = 0.81; CVC: 82.5 ± 46.2 vs. 58.9 ± 23.3 Δ%max/°C ΔTc, respectively; P = 0.19). However, the plateau in LSR during whole body heating was higher in N-SMK vs. SMK (1.00 ± 0.13 vs. 0.79 ± 0.26 amg/cm²−min−1; P = 0.03), which was likely a result of higher SGO (8.94 ± 3.99 vs. 5.94 ± 3.49 μg gland−1·min−1, respectively; P = 0.08) and not number of SGA (104 ± 7 vs. 121 ± 9 glands/cm², respectively; P = 0.58). During whole body passive heat stress, smokers had an earlier onset for forearm sweating and cutaneous vasodilation, but a lower local sweat rate that was likely due to lower sweat output per gland. These data provide insight into local (i.e., forearm) thermoregulatory responses of young smokers during uncompensatory whole body passive heat stress.

Cigarette; nicotine; thermoregulation; skin blood flow; sweating

THERMOREGULATION CAN BE AFFECTED by various factors such as age (23) and drug use [e.g., cocaine (8)]. In the absence of heat stress, chronic smokers have increased sympathetic nervous system activity (24) and greater cardiovascular strain as a result of high nicotine consumption and structural/functional changes in the blood vessels, respectively (13, 34). These chronic changes in smokers may exacerbate the cardiovascular and thermoregulatory strain experienced during heat stress, especially because heat stress increases cardiovascular strain and sympathetic nervous system activity in nonsmokers (44).

More specifically, chronic smoking alters the microvasculature of the skin (24, 34), which could modulate cutaneous vasodilatory responses to whole body passive heat stress (i.e., reflex vasodilation). Although we are unaware of any studies examining vasodilation during whole body heating in smokers, several studies show smokers have impairments to local stimuli [e.g., iontophoresis (10, 14, 19), microdialysis (15), and local heating (43)]. Smokers have impaired postsynaptic endothelial nitric oxide synthase (eNOS)-dependent and eNOS-independent maximal vasodilation (1, 10, 14, 15, 19, 28, 43). These local vasodilatory impairments in smokers suggest that vasodilation occurring during whole body heat stress may also be attenuated. However, it should be recognized that increases in cutaneous vasodilation during whole body heat stress are an integration of presynaptic and postsynaptic activity (5) and are dependent on different neurotransmitters than local heating. For example, local heating used to elicit maximal vasodilation is largely nitric oxide-dependent (~60%: Ref. 29), while during whole body heat stress, nitric oxide only contributes ~30% to cutaneous vasodilation (5). Thus, as previous studies have only explored smokers’ postsynaptic cutaneous vascular activity, it is unclear whether smokers’ cutaneous vascular responses during whole body heat stress are impaired. Vasodilation may be enhanced because nicotine causes the release of ACh (24), an endothelium-dependent vasodilator (18). However, vasoconstriction may also be increased because nicotine leads to increased vasopressin and endothelin-1 (24), well-known vasoconstrictors (42). Last, it is possible that vasodilation during whole body heat stress is impaired in smokers because of reduced endothelial nitric oxide production secondary to decreased nitric oxide synthase (24). However, cutaneous vasodilation during whole body heat stress is largely dependent on neuronal nitric oxide synthase (nNOS; Ref. 21), which may or may not be attenuated in smokers. Regardless of the mechanism(s) for modulated skin blood flow responses, it is important to first identify whether cutaneous vascular responses during whole body heat stress do, in fact, differ between smokers and nonsmokers.

Chronic smoking may also alter the sweat glands’ sensitivity to the neurotransmitters that increase sweat rate through the axon reflex (17, 32), which could subsequently affect sudomotor responses to whole body passive heat stress. It is plausible that smokers have heightened sudomotor sensitivity during heat stress, given that one study observed a lower dose of nicotine (4 × 10−7 M vs. 6 × 10−7 M) injected into volar forearm skin was required to initiate sweating when skin temperature was >35°C vs. <35°C (32). Smoking also increases skin sympathetic nerve activity (30), which might lead to a higher sweat rate because sweat expulsions follow sympathetic bursts (33). On the other hand, sudomotor responses may be attenuated in smokers because of chronically lower nitric oxide synthase production, a known augmenter of sweating during...
heat stress in young adults (39, 45). Similar to skin blood flow, before mechanisms are investigated, it is important to first determine whether the sudomotor responses to heat stress differ between smokers and nonsmokers.

The overall purpose of this study was to examine forearm cutaneous vascular and sudomotor responses to whole body passive heat stress in smokers vs. nonsmokers. We used a passive heating model because it isolates the effects of heat stress on thermoregulatory responses independent of exercise, as exercise can separately alter sweating and vasodilatory parameters (9). It was hypothesized that during whole body passive heat stress, compared with nonsmokers, smokers would have (1) a similar onset but decreased forearm cutaneous vasodilation, and (2) an earlier sweat onset and, therefore, higher forearm sweat rate for a given mean body temperature.

METHODS

Nine male chronic smokers (SMK: age = 29 ± 9 yr, height = 176.9 ± 6.8 cm, mass = 80.6 ± 22.9 kg) and 13 nonsmokers (N-SMK: age = 27 ± 8 yr, height = 177.4 ± 7.0 cm, mass = 76.6 ± 8.3 kg) matched (P > 0.05) for age, height, body mass, and exercise habits (7) participated. Chronic smokers were defined as those who smoked at least two packs of cigarettes per week for the last 5 years. Smokers in the present study smoked 10 ± 6 cigarettes per day for the last 11.8 ± 9.5 (median = 8.0) yr. Individuals with previous heat illness, serious medical conditions, or taking medications altering cardiovascular or thermoregulatory function were excluded. In frequent exposure to heat stress prior to testing inferred subjects were not heat-acclimatized. Before participating, subjects read and signed informed consent documents approved by the University of Arkansas’s Institutional Review Board.

Experimental controls. Prior to each visit, subjects refrained from exercise and alcohol for 24 h and caffeine for 8 h. To aid in euhydration, subjects drank ~1,000 ml of extra water the night before and ~500 ml of water the morning of testing. Subjects refrained from food at least 4 h prior to the trial. Gastrointestinal (GI) temperature was used to measure core temperature via an ingestible telemetric pill (HQ, Palmetto, FL) that was swallowed at least 5 h prior to each trial. GI temperature is a valid measurement of core temperature compared with other accepted methods, such as esophageal temperature (4). Despite reported slight delays in detecting fast changes in body temperature (compared to esophageal temperature (25)), when lying supine (as in our study), esophageal and GI temperatures have the same rate of temperature change and time to threshold (27). Furthermore, possible differences between groups were detectable because all subjects used the same method of measuring core temperature (Tc) for both trials (i.e., GI temperature), and values are expressed as a change in mean body temperature.

Upon arrival to the laboratory, subjects filled out a 24-h history form to verify adherence to all experimental controls. Nude body mass was obtained (Health-o-meter digital scale, model 349KLX; Pelstar LLC, Alsip, IL), and urine specific gravity was measured (clinical refractometer 30005, SPER Scientific, Scottsdale, AZ) from a urine sample that subjects provided prior to the trial start. Subjects started each trial in a euhydration state and were not provided any fluids during the trial.

There was concern that during the long protocol (~4 h) in which the smokers had to abstain from smoking, possible physiological withdrawal symptoms would confound any observed findings (e.g., decreased heart rate and hypothalamic pituitary adrenal axis dysregulation; (11)). This is especially true since the smokers in the present study smoked one cigarette every ~2 h. Therefore, smokers were instructed to smoke one cigarette immediately prior to arrival at the laboratory. Any acute cardiovascular effects of smoking subsided after ~45 min (13), so baseline measures in the present study occurred ~1 h after the last cigarette was smoked. Thus, any alterations in thermoregulation were due to the acute effects of smoking in chronic smokers, but not as a result of changes in cardiovascular function (2, 13). Furthermore, a control trial in which body temperature remained normothermic was completed on a separate day (in a counter-balanced randomized fashion) at least 48 h apart, where subjects laid supine for 110 min while skin temperature water (~34°C) perfused through the suit. Core and skin temperatures, along with cutaneous vasomotor activity, were measured to confirm that cutaneous vasomotor activity did not change over time independent of heating (see RESULTS).

Experimental procedures. To assess thermoregulatory responses (sweating and cutaneous vascular conductance) during whole body passive heat stress, SMK and N-SMK completed one trial where core temperature was increased 1.5°C from baseline. After instrumentation (see below), subjects were dressed in a tube-lined, water-perfused suit (Allen Vanguard, Ottawa, ON, Canada) that covered the entire body except the face, hands, feet, and right forearm. Subjects also wore a waterproof jacket and pants over the water-perfused suit to facilitate heating. Subjects laid supine for the entire trial. After a 30-min equilibration period where 34°C water perfused through the suit, all baseline measures were taken. Subjects were then passively heated by perfusing 49°C water through the suit until reaching a 1.5°C increase in core temperature, and unless otherwise noted, measures were taken at each 0.5°C Tc increase (i.e., 0.5, 1.0, and 1.5°C).

Experimental measures. Blood pressure (Tango+; SunTech Medical, Morrisville, NC) was measured at the left brachial artery via electrophysiomonometer, and heart rate (HR) was measured using a standard Polar Heart Rate monitor (Polar Electro, Lake Success, NY). Mean arterial pressure (MAP; mmHg) was calculated as MAP = (1/3-systolic blood pressure) + (2/3-diastolic blood pressure).

Skin temperature (Tsk) was measured with thermistors (Omega Engineering, Stamford, CT) placed on the right anterior thigh (midway between the greater trochanter and lateral condyle), chest (midway between the axilla and areola), lateral calf (midway between the tibial condyle and malleolus), and upper arm. Mean-weighted Tsk was calculated with the following formula (35): Tsk = 0.3(chest) + 0.3(arm) + 0.2(thigh) + 0.2(calf).

Given that both skin and core temperature significantly contribute to thermoregulatory responses (44) and they both significantly increased throughout the trials (see RESULTS), thermoregulatory outcome measures (i.e., sweating and skin blood flow) are expressed as a change in mean body temperature from baseline (ΔTsk,°C) using the following formula (40): Tsk = 0.10(Tsk) + 0.90(Tc).

Red blood cell flux, an index of skin blood flow, was assessed by laser-Doppler flowmetry (31) on the right dorsal forearm with a probe (laser-Doppler perfusion monitor and Probe 2b; Moor Instruments, Wilmington, DE) held in place by a local heater (Periflux System 5000; Perimed, Armdor, PA). Changes in cutaneous vasomotor activity, expressed as cutaneous vascular conductance (CVC), were calculated by dividing red blood cell flux by MAP and reported as a percentage of maximal CVC (%max). Maximal CVC was determined at the end of the trial by locally heating the skin at 42°C for at least 30 min [i.e., until a plateau occurred (3)].

Adjacent to the laser-Doppler probe, local sweat rate was measured by a 2.85 cm² ventilated capsule held on the skin by adhesive tape. Dry nitrogen gas was supplied through the capsule at a rate of 0.3 l/min. The absolute humidity (g/m³) and ambient temperature from the effluent air of the capsule were monitored by a humidity and temperature sensor (HMT333; Vaisala, Woburn, MA), and local sweat rate (LSR; mg·cm⁻²·min⁻¹) was calculated as LSR = [(flow rate in mg·min⁻¹·absolute humidity in g/m³) / (capsule surface area in cm²)]·1,000.

At the onset of LSR and CVC were determined by two separate investigators blinded to the subject classification (i.e., SMK vs. N-SMK); results were compared, and if a discrepancy was found between the investigators, a third investigator evaluated the data. In the same manner, the same two investigators identified where CVC

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and LSR plateaued (i.e., highest CVC and LSR during whole body passive heat stress) and noted the corresponding Tb. These plateaus were used along with the onsets to derive cutaneous and sudomotor sensitivities: Sensitivity = (LSR or CVC at plateau − LSR or CVC at onset) / (Tb at plateau − Tb at onset).

Sweat gland activation (SGA) was measured by wiping the skin dry and then lightly applying a 2.85 cm² circular piece of iodine impregnated paper to a site immediately adjacent to the local sweat rate capsule for ~5 s (16). Two consecutive samples were collected at each 0.5°C Tc increase. All images were immediately scanned into a computer, and ImageJ software (set at a pixel size of ~100-1,000) was used to count the number of active sweat glands in each circular area. Relative SGA (glands/cm²) was determined by dividing the number of active sweat glands by 2.85 cm².

Sweat output per gland (SGO; µg-gland⁻¹-min⁻¹) was calculated by dividing LSR at the time of measurement by the corresponding number of SGA. Methodologically, it is not possible to collect SGA underneath the sweat capsule at the end of heating (after the adjacent site (where SGA was measured throughout heating), SGA number of sweat glands was activated underneath the sweat capsule as % of maximal CVC) as mean body temperature increased (Tb at plateau). Tb at onset).

Throughout the heat stress trial, independent of the increase in core temperature, HR was significantly higher overall in SMK (99 ± 3 beats/min) vs. N-SMK (88 ± 3 beats/min; P = 0.03). In SMK and N-SMK, HR significantly increased (P < 0.01) from baseline (66 ± 11 and 58 ± 9 beats/min, respectively) to 1.5°C ΔTc (120 ± 17 and 109 ± 15 beats/min, respectively). MAP was not different between groups (P = 0.86) and did not change from baseline (SMK = 83 ± 10 and N-SMK = 82 ± 7 mmHg) to 1.5°C ΔTc (SMK = 83 ± 12 and N-SMK = 84 ± 12 mmHg; P = 0.06). Smokers’ urge to smoke did not change from baseline to 1.5°C ΔTc [22.42 ± 31.33 to 25.11 ± 33.76 arbitrary units (AU); P > 0.05].

Baseline core temperature (SMK = 37.00 ± 0.18°C vs. N-SMK = 36.95 ± 0.25°C), mean skin temperature (SMK = 34.20 ± 0.64°C vs. N-SMK = 34.18 ± 0.45°C), and mean body temperature (SMK = 36.73 ± 0.17°C vs. N-SMK = 36.67 ± 0.24°C) were not different between groups (all P > 0.05). During whole body passive heat stress, the mean change of Tb from baseline for each 0.5°C Tc increase (when measurements were taken) was not different between groups (grand mean ± SD = 0.46 ± 0.16°C, 0.99 ± 0.11°C, and 1.47 ± 0.10°C). Likewise, Tb and Tn did not differ between groups during heating (P > 0.05), and increased with each 0.5°C Tc increase from baseline to 1.5°C ΔTc (grand mean ± SD: Tb = 34.17 ± 0.57°C, 39.03 ± 0.52°C; 39.77 ± 0.51°C; 40.07 ± 0.56°C; Tn = 36.69 ± 0.17°C, 37.66 ± 0.23°C, 38.15 ± 0.22°C, 38.61 ± 0.21°C, respectively; all P < 0.01).

Total body sweat rate was similar between SMK and N-SMK (1.14 ± 0.60 vs. 1.02 ± 0.38 l/h, respectively; P = 0.53), and subsequently, there were no differences in percent body mass loss with heating between SMK and N-SMK (~1.54 ± 0.40 vs. ~1.50 ± 0.51%, respectively; P = 0.85). Total time required to reach a 1.5°C Tc increase was also similar between SMK and N-SMK (1.2 ± 0.3 vs. 1.2 ± 0.2 h, respectively; P = 0.73).

Baseline CVC (%max) was not different between SMK and N-SMK (33.5 ± 17.0 vs. 36.4 ± 15.3%; P = 0.64) and did not differ between SMK and N-SMK with each 0.5°C ΔTc (grand mean ± SD: 57.0 ± 23.9 vs. 56.3 ± 17.8%; P = 0.10). During heat stress, CVC increased from baseline until reaching a 1.0°C ΔTc (P < 0.01), with no significant increases thereafter. CVC onset occurred at a smaller ΔTc from baseline in SMK vs. N-SMK (P < 0.01; Table 1 and Fig. 1). CVC sensitivity was
similar between SMK and N-SMK (P = 0.19). SMK and N-SMK had similar CVC (%max) at plateau (i.e., highest CVC during whole body passive heat stress; Table 1 and Fig. 1; P = 0.99) and maximal absolute CVC during local heating (90.6 ± 39.1 vs. 115.7 ± 42.6 AU; P = 0.13).

Sweat onset occurred at a smaller ΔTb from baseline in SMK vs. N-SMK (P = 0.03; Table 1 and Fig. 2). Sweat sensitivity was similar between groups (P = 0.81). LSR plateau during whole body passive heat stress (i.e., highest LSR during heating) was significantly lower in SMK than N-SMK (P = 0.03; Table 1 and Fig. 2).

LSR (i.e., values at each 0.5°C ΔTc) did not differ between groups with heating (P = 0.41), but independent of group, LSR was significantly greater at 1.5°C ΔTc compared with 0.5°C and 1.0°C ΔTc (0.80 ± 0.41, 0.57 ± 0.33, and 0.72 ± 0.39 mg·cm⁻²·min⁻¹, respectively; P < 0.01). SGA did not differ between groups with heating (P = 0.58; Fig. 3) and did not change after the 0.5°C Tc time point (P = 0.66). SGO tended to be lower overall in SMK (5.9 ± 3.5 µg·gland⁻¹·min⁻¹) vs. N-SMK (8.9 ± 4.0 µg·gland⁻¹·min⁻¹; P = 0.08; Fig. 3). Independent of group, SGO increased from 0.5°C to 1.0°C ΔTc (P < 0.01), with no further increases at 1.5°C ΔTc.

DISCUSSION

The purpose of this study was to compare cutaneous vascular and sudomotor responses to whole body passive heat stress in smokers vs. nonsmokers. The main findings from this study are that forearm LSR and CVC onset occurred at a lower change in mean body temperature in SMK vs. N-SMK, but forearm LSR and CVC sensitivity did not differ between groups. The plateau of forearm LSR during heating was lower in SMK vs. N-SMK, likely as a result of lower sweat output per gland and not number of glands activated. Taken together, these results indicate some local thermoregulatory responses during whole body passive heat stress are impaired in smokers, while some are not.

To our knowledge, no previous research has examined sweating responses in smokers during whole body passive heat stress. We found that smokers had an earlier onset for sweating at the forearm compared with nonsmokers (Table 1 and Fig. 2). Although the exact mechanism for this response is unknown, a few possibilities exist. Nicotine may initiate sweating through the axon reflex, leading to an earlier onset of sweating in smokers than nonsmokers (41). It is also possible that local heating enhances the sensitivity of the sweat gland to nicotine, leading to earlier onset of sweating (32). Regardless of the exact mechanism, the present data support the notion that elevated skin/body temperatures in the presence of nicotine (i.e., smokers) lead to an earlier onset of sweating relative to

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Table 1. Values for cutaneous vascular conductance and local sweat rate for smokers and nonsmokers during whole body passive heat stress

<table>
<thead>
<tr>
<th>Measurement</th>
<th>SMK</th>
<th>N-SMK</th>
</tr>
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<tbody>
<tr>
<td>CVC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset, ΔTb from baseline, °C</td>
<td>0.31 ± 0.12</td>
<td>0.61 ± 0.21*</td>
</tr>
<tr>
<td>Sensitivity, change in %max per °C ΔTb</td>
<td>82.5 ± 46.2</td>
<td>58.9 ± 23.3</td>
</tr>
<tr>
<td>Plateau, %max</td>
<td>68.4 ± 27.4</td>
<td>68.4 ± 21.6</td>
</tr>
<tr>
<td>LSR</td>
<td></td>
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<tr>
<td>Onset, ΔTb from baseline, °C</td>
<td>0.35 ± 0.14</td>
<td>0.52 ± 0.19*</td>
</tr>
<tr>
<td>Sensitivity, mg·cm⁻²·min⁻¹ per °C ΔTb</td>
<td>0.60 ± 0.40</td>
<td>0.63 ± 0.21</td>
</tr>
<tr>
<td>Plateau, mg·cm⁻²·min⁻¹</td>
<td>0.79 ± 0.26</td>
<td>1.00 ± 0.13*</td>
</tr>
</tbody>
</table>

Values are presented as means ± SD. CVC, cutaneous vascular conductance (expressed as % maximal CVC); LSR, local sweat rate; Tb, mean body temperature; SMK, smokers; N-SMK, nonsmokers. *Significant difference between groups (P < 0.05).

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Fig. 2. Changes in forearm local sweat rate (LSR) as mean body temperature increased (ΔTb) with whole body passive heat stress. Drawn from data in Table 1.

Fig. 3. Number of sweat glands activated (SGA; top) and output per sweat gland (SGO; bottom) as mean body temperature increased (ΔTc) with whole body passive heat stress. All values are expressed as means ± SD. SGO, independent of body temperature, tended to be higher in nonsmokers than smokers (P = 0.08; see RESULTS). *Significant main effect of time (P < 0.05).
those that have elevated skin/body temperature without nicotine (i.e., nonsmokers).

Although SMK had an earlier onset for sweating, LSR sensitivity did not differ between groups (Table 1 and Fig. 2). Similar LSR sensitivity between groups suggests that chronic smoking does not alter increases in sweat rate driven by afferent feedback to the hypothalamus or the effferent signals to the sweat gland thereafter.

Interestingly, LSR plateau was lower in SMK (Table 1 and Fig. 2). The mechanism causing the lower LSR plateau in SMK vs. N-SMK is unclear; however, our data indicate this is likely a result of lower SGO and not alterations in SGA (Fig. 3). In nonsmokers, initial increases in sweat rate are caused by combined increases in sweat gland activation and output; after maximal SGA, further increases in sweat rate are from increased SGO (26). Our data show a similar response occurred for SMK (Fig. 3). Furthermore, there were no differences between groups in SGA at any time point during heat stress. This is not too surprising given that smokers have a similar number of sweat ducts and coils (17). However, smokers’ SGO tended to be lower than nonsmokers at the 1.0 and 1.5°C ΔTc time points (P = 0.06). This could be a result of impairments presynaptically or postsynaptically. Smokers have less nicotinic ACh receptors on the sweat glands than nonsmokers (17), which could lead to an overall attenuated sweating response during heat stress. However, if the number of receptors is playing a role in smokers’ sweating responses during heat stress, it is only evident during maximal sweating (i.e., plateau) and does not affect sweat sensitivity or the onset of sweating. Future research should aim to determine the exact mechanisms by which chronic smoking may affect sweating.

SMK had an earlier onset for cutaneous vasodilation at the forearm than N-SMK (Table 1 and Fig. 1). It is unknown what mechanism(s) caused the earlier onset for cutaneous vasodilation in SMK; however, it could be that similar to sweating, vasodilation was initiated by the combination of whole body heat stress and nicotine (43). More mechanistic studies are required to determine the exact pathways mediating these responses.

Forearm CVC sensitivity and plateau were similar between SMK and N-SMK (Table 1 and Fig. 1). This was contrary to our hypothesis that smokers would have attenuated CVC responses during whole body heat stress because of the reported endothelial damage and decreased endothelial nitric oxide synthase production (24, 34). The similar CVC sensitivity between groups is likely a result of using whole body heat stress to elicit increases in reflex vasodilation (CVC), compared with previous literature that used local stimuli [e.g., iontophoresis (10, 14, 19), microdialysis (15), and local heating (43)] to invoke postsynaptic increases in CVC. Prior research (10, 14, 15, 19, 43) showing that smokers have impaired maximal skin blood flow isolated postsynaptic activity, which is typically indicative of eNOS-dependent vasodilation (21). However, cutaneous vasodilation that occurs during whole body heat stress is an integration of presynaptic and postsynaptic activity, and is largely reliant on eNOS-independent pathways (21, 22). Since smokers’ eNOS-dependent pathways are attenuated, similar CVC responses between SMK and N-SMK during whole body heat stress would indicate that other sources of nitric oxide, such as nNOS, might remain intact in smokers and produce similar (or greater) nitric oxide levels to invoke similar CVC (Fig. 1 and Ref. 46). This theory is further supported by research demonstrating that populations with eNOS-dependent impairments do not necessarily exhibit dysfunction in endothelium-independent pathways (12, 20). Moreover, other metabolites such as endothelial-derived hyperpolarizing factors (EDHFs) might also be contributing to smokers’ similar vasodilatory responses, especially since smokers do not have impairments (at least postsynaptically) in EDHF-induced vasodilation (15). Overall, the similar CVC responses in SMK and N-SMK suggest that chronic smokers’ eNOS-independent pathways might still be intact to sufficiently increase reflex CVC during whole body passive heat stress [as it largely requires eNOS-independent pathways to increase vasodilation (21, 22)].

Limitations and considerations. Time since the last cigarette smoked has the potential to confound cardiovascular and thermoregulatory responses; therefore, we standardized the time period between the last cigarette smoked and the beginning of data collection (~1 h). This methodological control minimized the potential that our findings were confounded by physiological withdrawal symptoms that would have otherwise occurred during the long protocol (~4 h (11)). The control trial, during which skin and core temperatures remained normothermic, provides evidence that SMK did not exhibit physiological withdrawal symptoms because CVC over time was not different between groups (see RESULTS). Furthermore, using a validated urge-to-smoke questionnaire, we observed that SMK urge to smoke a cigarette did not change from baseline to 1.5°C ΔTc. Although it appears that smoking one cigarette ~1 h before the trial was sufficient to avoid physiological and psychological withdrawal symptoms, we recognize the findings of this study are within the context of chronic smokers who smoked a cigarette 1 h prior to heat stress. Future studies will need to examine whether similar changes are observed in nonsmokers who acutely smoke one cigarette. However, given the well-known changes that occur with chronic smoking, it is hypothesized that the present findings are a result of the long-term modulations of the microvascular and sudomotor systems that occur with chronic smoking.

Laser-Doppler flowmetry and local heating were used as the standard methodology for measurement and analysis of CVC (29, 31). However, making between-group comparisons using this methodology and expressing the data as % of maximal CVC assumes that absolute maximal blood flow with local heating is similar between groups (29). Chronic smoking may reduce nitric oxide production and subsequently maximal CVC (1, 10, 14, 15, 19, 28, 43). However, in the present study there were no significant differences in absolute maximal CVC during local heating between groups (see RESULTS), and thus expressing values during passive heating as % of maximal CVC is founded. Nonetheless, between-group comparisons using this methodology can be limiting, and future studies should employ additional measures, such as venous occlusion plethysmography.

We also acknowledge the limitations of measuring only the forearm site for CVC and LSR. Similar to regional variations in sweating and cutaneous vasomotor activity (36, 37), there are regional variations in the isoforms (e.g., eNOS vs. nNOS) that produce NO and increase CVC during heat stress (38). However, by using the same site for both SMK and N-SMK, it allowed us to make proper between-group
comparisons. Still, these findings only apply to the forearm site, and regional variations in LSR and CVC might result in different whole body heat loss responses when core and skin temperatures are not controlled (e.g., during exercise heat stress). Thus, future research should examine regional differences in sweating and skin blood flow between smokers and nonsmokers.

**Perspectives and Significance**

We used whole body passive heat stress to examine forearm cutaneous vascular and sudomotor responses between chronic smokers and nonsmokers. These data, although specifically applicable to the forearm site, suggest that chronic smokers’ thermoregulatory responses are both enhanced (i.e., earlier onset of sweating and cutaneous vasodilation) and attenuated (i.e., lower local sweat rate plateau) during whole body passive heating.

These findings provide groundwork for future research and suggest that chronic smoking alters some thermoregulatory responses during heat stress. However, it is important to note that we examined local (i.e., forearm) responses under uncompensatory heat stress conditions. The current study was not designed to examine whole body heat loss responses or smokers’ ability to dissipate heat during active heat stress (e.g., exercise). Still, it is interesting to note that total body sweat rate was similar between groups. Future studies should examine whole body heat transfer in smokers and nonsmokers (e.g., during exercise heat stress). This could provide insight as to whether the local alterations in smokers’ thermoregulatory responses found in the present study translate to differences in whole body heat gain and heat loss.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**


**REFERENCES**