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Sympathetic nerve activity and whole body heat stress in humans

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¹Institute for Exercise and Environmental Medicine, Presbyterian Hospital of Dallas; ²Department of Internal Medicine, University of Texas Southwestern Medical Center at Dallas, Dallas; ³Department of Kinesiology, University of Texas at Arlington, Arlington, Texas; ⁴Department of Kinesiology, University of Alabama, Tuscaloosa, Alabama; and ⁵Department of Kinesiology and Health Education, University of Texas at Austin, Austin, Texas

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Low DA, Keller DM, Wingo JE, Brothers RM, Crandall CG. Sympathetic nerve activity and whole body heat stress in humans. *J Appl Physiol* 111: 1329–1334, 2011. First published August 25, 2011; doi:10.1152/jappphysiol.00498.2011.—We and others have shown that moderate passive whole body heating (i.e., increased internal temperature $\sim 0.7^\circ\text{C}$) increases muscle (MSNA) and skin sympathetic nerve activity (SSNA). It is unknown, however, if MSNA and/or SSNA continue to increase with more severe passive whole body heating or whether these responses plateau following moderate heating. The aim of this investigation was to test the hypothesis that MSNA and SSNA continue to increase from a moderate to a more severe heat stress. Thirteen subjects, dressed in a water-perfused suit, underwent at least one passive heat stress that increased internal temperature $\sim 1.3^\circ\text{C}$, while either MSNA ($n = 8$) or SSNA ($n = 8$) was continuously recorded. Heat stress significantly increased mean skin temperature ($\Delta \sim 5^\circ\text{C}$, $P < 0.001$), internal temperature ($\Delta \sim 1.3^\circ\text{C}$, $P < 0.001$), mean body temperature ($\Delta \sim 2.0^\circ\text{C}$, $P < 0.001$), heart rate ($\Delta \sim 40$ beats/min, $P < 0.001$), and cutaneous vascular conductance [$\Delta \sim 1.1$ arbitrary units (AU)/mmHg, $P < 0.001$]. Mean arterial blood pressure was well maintained ($P = 0.52$). Relative to baseline, MSNA increased midway through heat stress (Δ core temperature $0.63 \pm 0.01^\circ\text{C}$) when expressed as burst frequency (26 ± 14 to 45 ± 16 bursts/min, $P = 0.001$), burst incidence (39 ± 13 to 48 ± 14 bursts/100 cardiac cycles, $P = 0.03$), or total activity (317 ± 170 to 489 ± 150 units/min, $P = 0.02$) and continued to increase until the end of heat stress (burst frequency: 61 ± 15 bursts/min, $P = 0.01$; burst incidence: 56 ± 11 bursts/100 cardiac cycles, $P = 0.04$; total activity: 648 ± 158 units/min, $P = 0.01$) relative to the mid-heating stage. Similarly, SSNA (total activity) increased midway through the heat stress (normothermia; $1,486 \pm 472$ to mid heat stress $6,467 \pm 5,256$ units/min, $P = 0.03$) and continued to increase until the end of heat stress ($11,217 \pm 6,684$ units/min, $P = 0.002$ vs. mid-heat stress). These results indicate that both MSNA and SSNA continue to increase as internal temperature is elevated above previously reported values.

muscle sympathetic nerve activity; neural control; skin sympathetic nerve activity

HEAT STRESS elicits a range of highly coordinated autonomic nervous system responses to maintain both internal temperature and blood pressure within safe limits (32). Heat stress-induced elevations in internal and skin temperatures profoundly increase skin blood flow and sweat rate, which are necessary for heat dissipation (18, 40). At the same time, elevations in cardiac output and vascular resistance of noncutaneous beds ensure the maintenance of arterial blood pressure

(34, 36). Appropriate adjustments of the autonomic nervous system are critical in mediating these cardiovascular and thermoregulatory responses to heat stress. Given that these neural responses are primarily governed by increases in sympathetic nervous system activity, heat stress has been referred to as a “hyperadrenergic” state (33).

Whole body heating causes pronounced increases in skin sympathetic nerve activity (SSNA), which is the neural signal responsible for increasing sudomotor and perhaps cutaneous active vasodilator activity during this exposure (16, 30). Similarly, heat stress elevates sympathetic nerve activity to muscle, i.e., muscle sympathetic nerve activity (MSNA). We and others have shown that moderate passive whole body heating in humans (i.e., increased internal temperature $\sim 0.7^\circ\text{C}$) increases MSNA and SSNA (1, 6–8, 29, 46). We are unaware of any studies in which MSNA or SSNA responses to more severe heat stress were evaluated. It is unknown, therefore, if MSNA and/or SSNA continue to increase with further increases in internal temperature, when even greater demands are placed on the thermoregulatory and cardiovascular systems, or whether these responses plateau following moderate increases in internal temperature.

Progressive increases in renal, lumbar, and splanchnic sympathetic nerve activity during passive heat stress in rats have been recorded over the course of 3°C elevations in core temperature (20, 21, 23). Based upon these observations, it may be that in humans SSNA and MSNA would continue to rise beyond previously reported elevations in core temperature of $\sim 0.7^\circ\text{C}$. Similarly, sympathoexcitation to non-heat-stress interventions, such as hypoxia and exercise, increase in proportion to graded levels of that intervention (37, 39), further supporting the hypothesis of a continued increase in sympathetic nerve activity with increasing severity of a sympathoexcitatory stimulus, as may be the case with passive heating.

Changes in skin blood flow and sweat rate are closely coupled to alterations in internal temperature (18, 40). The skin blood flow/sweat rate to internal temperature relationship is generally not linear throughout heat stress, as the slope of these relationships is often reduced or tends to plateau with further elevations in internal temperature greater than $\sim 0.7^\circ\text{C}$ (17, 40). It is thus possible that SSNA plateaus, or continues to increase, albeit at a reduced rate, beyond relatively minor elevations in internal temperature. In addition, total peripheral resistance and blood flows to renal and splanchnic vascular beds tend to decrease at a lower rate as internal temperature further increases beyond moderate levels of passive heating (28, 35). If MSNA is reflective of sympathetic activity to these regions, these findings suggest that relatively minor increases in MSNA would occur beyond moderate levels of

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passive heating. To address these questions, the aim of this investigation was to test the hypothesis that during passive heating MSNA and SSNA continue to increase while individuals progress from a moderate to a more severe level of heat stress.

METHODOLOGY

Subjects. A total of 13 healthy subjects (8 men, 5 women; mean \pm SD; age 35 ± 9 yr, height 175 ± 10 cm and weight 78 ± 10 kg) underwent one or two passive heat stresses during which successful MSNA ($n = 8$; 5 men) or SSNA ($n = 8$; 4 men) recordings were obtained throughout the heat stress. Three subjects participated in both MSNA and SSNA trials, but on different days. MSNA and SSNA recordings from male and female subjects were not separately analyzed given the low numbers in each group and sex differences not being the primary objective of the evaluation. Subjects were free from cardiovascular, neurological, or metabolic diseases. Subjects were asked to refrain from alcohol and exercise 24 h and caffeine 12 h before the study. Written informed consent was obtained from all participants before they enrolled in the study. All procedures and the consent form were approved by the University of Texas Southwestern Medical Center at Dallas and Texas Health Presbyterian Hospital Dallas.

Instrumentation and measurements. Each subject was placed in a tube-lined suit (Med-Eng, Ottawa, Canada) that permitted the control of skin temperature by changing the temperature of the water perfusing the suit. The suit covered the entire body surface with the exception of the head, one forearm, the hands, the lower leg from which sympathetic recordings were obtained, and the feet. Mean skin temperature was measured via the electrical integration of six thermocouples attached to the skin on the lateral gastrocnemius, anterior quadriceps, lower and upper back, abdomen, and upper chest regions (42). Core temperature was measured from an ingestible telemetry pill (HTI Technologies, Palmetto, FL) that was swallowed at least 2 h before data collection began. Heart rate was obtained from an electrocardiogram (SpaceLabs, Redmond, WA) interfaced with a cardiotelemetry (CWE, Ardmore, PA). Intermittent arterial blood pressure was measured from the brachial artery by electrophygmomanometry (SunTech, Raleigh, NC). Cutaneous blood flow was indexed using a multifiber laser-Doppler probe (Perimed, North Royalton, OH) placed on a dorsal forearm not covered by the suit.

Multifiber recordings of MSNA and SSNA were obtained using a tungsten microelectrode positioned in the common peroneal nerve. A reference electrode was placed subcutaneously ~ 2 – 3 cm from the recording electrode. The position of the recording electrode was adjusted until a site was attained in which bursts of MSNA or SSNA were identified using previously established criteria (13, 43). The main criteria for the identification and differentiation of MSNA relative to SSNA recordings were 1) synchronicity of discharges with pulse rate, 2) increases in (or lack of) activity during inspiratory apnea, and 3) responsiveness to mental or somatosensory stimulation (e.g., loud sound and light stroking of the innervated region). Needle adjustments were made for recordings that contained evidence of both MSNA and SSNA, until just MSNA or just SSNA recordings were evident. Nerve signals were amplified, passed through a bandpass filter with a band width of 700–2,000 Hz, and integrated with a time constant of 0.1 s (Iowa Bioengineering, Iowa City, IA). Mean voltage neurograms were displayed on a chart recorder. Nerve signals were also routed to an oscilloscope and a loudspeaker for monitoring throughout the study. If evidence of a position change in the recording electrode was identified, which occurred in a few subjects, the protocol was immediately ended and these data were not analyzed. Subjects in whom this occurred are not included in the aforementioned subject numbers.

Experimental protocols. Experiments were performed in a temperature-controlled laboratory ($26 \pm 1^\circ\text{C}$) in the morning or early

afternoon at least 2 h postprandial. After instrumentation, subjects rested in the supine position while 34°C water was perfused through the tube-lined suit for ~ 15 min. Thereafter, subjects were heat stressed by perfusing 48°C water through the suit. Subjects were also covered with blankets during this heating protocol. The heat stress ended once subjects had reached the target internal temperature increase (~ 1.3 – 1.5°C). This temperature was chosen given our experience that at temperatures much past this level subjects are often agitated making it difficult to maintain sympathetic nerve recordings.

Data analysis. Data were sampled at 200 Hz via a data-acquisition system (Biopac System, Santa Barbara, CA) and analyzed using a statistical software package (SPSS v17, Chicago, IL). Mean arterial blood pressure (MAP) was calculated as one-third pulse pressure + diastolic blood pressure. Cutaneous vascular conductance (CVC) was calculated from the ratio of skin blood flux to MAP. Mean body temperature (T_b) was calculated as $(0.9 \times T_c) + (0.1 \times T_{sk})$, where T_{sk} is mean skin temperature. MSNA data were evaluated using LabView software (National Instruments, Austin, TX) that identified bursts on a beat-by-beat basis from the integrated neurogram established by fixed criteria, including an appropriate latency after the R-wave of the ECG and signal-to-noise ratio (7, 10). MSNA was expressed as burst frequency (bursts/min), burst incidence (number of bursts per 100 cardiac cycles), and total activity (identified from burst area of the integrated neurogram). To assess SSNA (expressed as total activity), a period of normothermic baseline in the absence of SSNA bursts was identified. The area of the integrated bursts above this baseline was measured at each stage of the heat stress. This approach was required given that for some subjects during more severe heating sequential SSNA bursts did not consistently return to baseline, and thus the area of individual bursts could not be identified. Segments of the digitized MSNA and SSNA records from normothermia (4–6 min), from the middle level (2–3 min) of heating, and the end of the heat stress (2–3 min) were selected for analysis. A shorter duration was used for heat stress periods to avoid substantial increases in T_c over the evaluation period. MSNA data were expressed relative to the increase in T_c whereas the SSNA data were expressed relative to the increases in mean T_b and T_c , given the recognized influence of skin temperature on cutaneous vasodilator and sudomotor responses (44, 46). For the MSNA recordings, the middle of heat stress was defined as half of the magnitude of the increase in T_c . For SSNA recordings, the middle of the heat stress was defined as half of the magnitude of the increase in both T_c and T_b . Thermoregulatory, MSNA, and SSNA responses during normothermia, at the mid-point of the heat stress, and the end of heat stress were statistically compared using a 1-way repeated-measures ANOVA followed by post hoc comparisons, where necessary. All values are reported as means \pm SD unless otherwise indicated. P values of <0.05 were considered statistically significant.

RESULTS

Thermoregulatory and cardiovascular responses to heat stress. Thermoregulatory and cardiovascular responses to passive heating, during the periods when SSNA and MSNA were analyzed, are summarized in Tables 1 and 2, respectively. Heat stress significantly increased T_c , T_{sk} , and T_b at the middle level and at the end of heating. Similarly, heart rate and cutaneous vascular conductance increased at both stages of heating (both $P < 0.05$). Mean arterial blood pressure was maintained throughout heating ($P > 0.05$).

SSNA responses to heat stress ($N = 8$). Compared with normothermia, when expressed against mean body temperature, SSNA increased midway through the heat stress (ΔT_b $1.01 \pm 0.10^\circ\text{C}$; baseline $1,486 \pm 472$ to mid heat stress $6,467 \pm 5,256$ units/min, $P = 0.03$, Fig. 1A) and continued to increase until the end of heating (ΔT_b $1.95 \pm 0.19^\circ\text{C}$, $11,217 \pm 6,684$ units/min, $P = 0.01$ vs. baseline and $P = 0.002$ vs. mid-heat

Table 1. Mean thermoregulatory and cardiovascular responses to normothermia and heat stress when SSNA was recorded

	Normothermia	Mid Heat Stress (T _b)	Mid Heat Stress (T _c)	End Heat Stress
Core temperature, °C	37.10 ± 0.18	37.37 ± 0.29*	37.70 ± 0.22*‡	38.35 ± 0.30*‡
Mean skin temperature, °C	34.6 ± 0.7	38.5 ± 0.5*	38.7 ± 0.6*	39.3 ± 0.5*‡
Mean body temperature, °C	36.6 ± 0.2	37.6 ± 0.2*	37.9 ± 0.2*	38.6 ± 0.3*†
Heart rate, beats/min	55 ± 10	73 ± 14*	80 ± 13*	94 ± 16*†
Systolic blood pressure, mmHg	112 ± 14	114 ± 11	115 ± 10	120 ± 16
Diastolic blood pressure, mmHg	68 ± 6	65 ± 4	65 ± 6	66 ± 10
Mean arterial blood pressure, mmHg	82 ± 8	81 ± 5	81 ± 6	84 ± 11
Forearm CVC, AU/mmHg	0.41 ± 0.35	1.05 ± 0.67*	1.19 ± 0.61*	1.51 ± 0.59*‡

Values are means ± SD; n = 8. SSNA, skin sympathetic nerve activity; T_b, mean body temperature; T_c, mean core temperature; CVC, cutaneous vascular conductance; AU, arbitrary units. *P < 0.05 vs. normothermia; †P < 0.05 vs. mid heat stress (T_b and T_c); ‡P < 0.05 vs. mid heat stress (T_b only).

stress). Similar responses were identified when changes in SSNA were expressed against the elevation in T_c (Fig. 1B). The change in SSNA for the latter half of heating (e.g., moderate to severe heating) was not different from the first half of heating (e.g., normothermia to moderate heating; 4,795 ± 4,435 vs. 5,075 ± 2476 units·min⁻¹·°C⁻¹, P > 0.05).

MSNA responses to heat stress (n = 8). Relative to normothermic conditions, MSNA increased midway through the heat stress (ΔT_c 0.63 ± 0.05°C, see Fig. 2) when expressed as burst frequency (26 ± 14 to 45 ± 16 bursts/min, P = 0.001), burst incidence (39 ± 13 to 48 ± 14 bursts/100 cardiac cycles, P = 0.03), or total activity (317 ± 170 to 489 ± 150 units/min, P = 0.02). Relative to mid-heat stress, MSNA was further elevated at the end of heating when expressed as burst frequency (61 ± 15 bursts/min, P = 0.01), burst incidence (56 ± 11 bursts/100 cardiac cycles, P = 0.04), and total activity (648 ± 158 units/min, P = 0.01). The change in MSNA for the latter half of heating (e.g., moderate to severe heating) was not different from the first half of heating (e.g., normothermia to moderate heating) regardless of the expression of MSNA, e.g., frequency (30 ± 12 vs. 19 ± 21 bursts·min⁻¹·°C⁻¹, P > 0.05), incidence (14 ± 15 vs. 10 ± 19 bursts·100 cardiac cycles⁻¹·°C⁻¹, P > 0.05), or total activity (276 ± 210 vs. 202 ± 217 units·min⁻¹·°C⁻¹, P > 0.05).

DISCUSSION

The aim of this investigation was to test the hypothesis that MSNA and SSNA continue to increase during more severe passive heating relative to that employed in previous studies. MSNA or SSNA were continuously recorded while subjects, dressed in a water-perfused suit, underwent whole body heating that increased internal temperature ~1.3°C. The main findings of this study are that, relative to the mid-point of heating (e.g., moderate passive heating), MSNA (regardless of whether it was expressed as frequency, incidence, or total

activity) and SSNA continued to increase with further heating. These results indicate that MSNA and SSNA do not plateau after an elevation of internal temperature of ~0.7°C but continue to increase as internal/mean body temperature increase above these previously reported values. These findings are consistent with progressive elevations in sympathetic nerve activity across a wider range of increases in core temperature during passive heating in the rodent model (20, 21, 23).

Appropriate alterations in sympathetic nerve activity are vital for the effective regulation of internal body temperature. Whole body heating causes pronounced increases in SSNA, which presumably cause elevations in skin blood flow and sweating to facilitate heat dissipation (16, 18, 30, 40). The neural signal contained within the SSNA signal includes both vasoconstrictor and vasodilator components (43). Transitioning from normothermic conditions to slight heating initially withdraws vasoconstrictor activity, which is evident by reductions in SSNA (1). More pronounced heating increases the sudomotor, and perhaps the vasodilator component, considerably, resulting in large increases in SSNA that are well above normothermic baseline. Consistent with these changes, in previous studies, which increased internal temperature by no more than ~0.7°C, we and others have shown that this moderate level of passive whole body heating increases SSNA (1, 6–8, 29, 46). The relationship between skin blood flow/sweat rate and internal temperature is not generally linear during heat stress, as the rate of increase in skin blood flow and sweat rate are often attenuated with further elevations in internal temperature beyond ~0.7°C (17, 40). It therefore seemed reasonable that SSNA responses may likewise be attenuated during more severe passive heating.

In the present study, more severe passive whole body heating was utilized to almost double the internal temperature increase previously employed, resulting in further increases in SSNA above the midpoint of heating (i.e., increased internal

Table 2. Mean thermoregulatory and cardiovascular responses to normothermia and heat stress when MSNA was recorded

	Normothermia	Mid Heat Stress	End Heat Stress
Core temperature, °C	37.01 ± 0.22	37.64 ± 0.22*	38.37 ± 0.22*†
Mean skin temperature, °C	34.6 ± 0.6	38.7 ± 0.7*	39.2 ± 0.6*†
Mean body temperature, °C	36.6 ± 0.2	37.9 ± 0.2*	38.6 ± 0.2*†
Heart rate, beats/min	63 ± 11	92 ± 11*	105 ± 10*†
Systolic blood pressure, mmHg	122 ± 16	125 ± 12	130 ± 14
Diastolic blood pressure, mmHg	77 ± 6	68 ± 5*	68 ± 9
Mean arterial blood pressure, mmHg	92 ± 10	87 ± 6	89 ± 7
Forearm CVC, AU/mmHg	0.34 ± 0.40	1.45 ± 0.66*	1.52 ± 0.69*

Values are means ± SD; n = 8. MSNA, muscle sympathetic nerve activity. *P < 0.05 vs. normothermia; †P < 0.05 vs. mid heat stress.

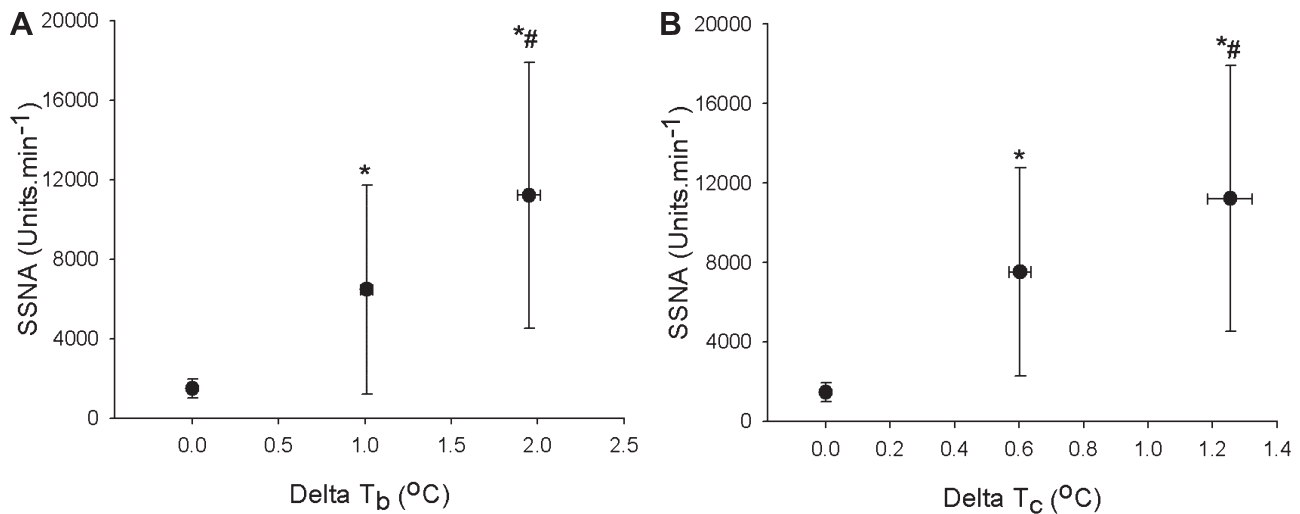


Fig. 1. Group (\pm SD) averaged skin sympathetic nerve activity (SSNA) data during normothermia, and mid and end of heat stress, expressed as total activity (arbitrary units) against increases in mean body temperature (T_b ; A) or increases in core temperature (T_c ; B). Regardless of how it is expressed, SSNA continues to increase throughout heat stress with no evidence of a plateau following the midlevel of heating. * $P < 0.05$ vs. normothermia, # $P < 0.05$ vs. mid-heat stress ($n = 8$).

temperature of $\sim 0.7^\circ\text{C}$; Fig. 1B). This finding indicates that SSNA continues to increase with more severe whole body heating relative to that previously reported and likely mediates continued elevations in sweat rate and skin blood flow with increasing internal temperature. SSNA, as well as skin blood flow and sweat rate, are very sensitive to changes in mean skin temperature (44, 46). In the present study, there was a significant increase in mean skin temperature between mid- and final heating stages. To account for these changes in mean skin temperature, SSNA responses were also evaluated against mean body temperature (Fig. 1B), which resulted in similar findings relative to that observed when analyzed against intestinal temperature (Fig. 1A).

One could speculate that cardiopulmonary baroreceptor unloading coincident with passive heating, which attenuates heat stress-induced elevations in skin blood flow (5), may alter the elevation in SSNA during both moderate and more severe heat stress. If this were the case, then such unloading would limit the extent to which SSNA increases during heat stress. However, prior findings strongly suggest that baroreceptor unloading with lower body negative pressure or upright tilt does not alter SSNA in heat-stressed humans (9, 46). That said, it remains unknown whether preventing the reduction in cardiopulmonary baroreceptor unloading during passive heating would augment SSNA responses to that heat stress.

Others have shown a reduced rate in the decrease in splanchnic and renal blood flows, as well as total peripheral resistance, as passive heat stress progressed from moderate to more severe heating (28, 35). Based upon these observations, it may be that the increase in MSNA upon progressing from moderate to more severe heat stress would likewise be attenuated, recognizing the limitation that MSNA responses are not necessarily representative of the sympathetic response to splanchnic and renal vascular beds. Counter to that hypothesis, MSNA responses continued to increase throughout the heat stress at a rate comparable to the early phase of the heat stress. The specific mechanism(s) responsible for increases in MSNA during heat stress are unclear. MSNA can be modulated by baroreceptor loading status, where baroreceptor unloading increases MSNA

and baroreceptor loading reduces MSNA. Previously we showed that during moderate heat stress reductions in central venous pressure, and presumably cardiopulmonary baroreceptor unloading, were not responsible for accompanying increases in MSNA (4). However, in the cited study the elevation in internal temperature was moderate, and thus it remains unknown whether cardiopulmonary baroreceptor unloading contributes to the elevations in MSNA during more severe heat stress. In contrast, sympathetically mediated elevations in splanchnic vascular resistance during whole body heat stress are not caused by baroreceptor unloading (36), and increases in splanchnic sympathetic nerve activity in hyperthermic rats occur in both baroreceptor-denervated conditions (20). Furthermore, arterial baroreceptor modulation of MSNA remains intact during heat stress (3, 19), suggesting a preserved coupling of arterial baroreceptor control of MSNA.

Heat stress-induced elevations in core temperature cause increases in ventilation that may aid in heat loss (45). Sympathetic nerve activity is subject to respiratory modulation through a within-breath pattern as a result of an inhibitory pulmonary stretch reflex (14, 38) and central (medullary) respiratory oscillators, e.g., central respiratory drive (11), suggesting that thermal hyperpnea could contribute to heat stress-induced sympathoexcitation. There are, however, a number of factors that do not support this hypothesis. First, the profile of the change in respiratory rate with heating does not match the temporal profile of the MSNA response. The change in ventilation during hyperthermia displays an exponential increase in which the majority of the elevation in ventilation occurs later during heat stress; i.e., after a core temperature increase of $\sim 1^\circ\text{C}$ (45) and well after large increases in MSNA have occurred (see Fig. 2). Second, although the within-breath pattern of MSNA is potentiated during hyperpneic conditions (38) and is reflected in a reduction in MSNA during inspiration and an increase in MSNA during expiration, increases in tidal volume produce no or small decreases in steady-state total MSNA (38, 41). Although ventilation was not measured in the present study, it is unlikely that relatively subtle changes in ventilation in the progression from moderate to more severe heat is responsible for further increases in MSNA. Finally, interventions that exclusively manipulated central respiratory drive (i.e., those that do not induce

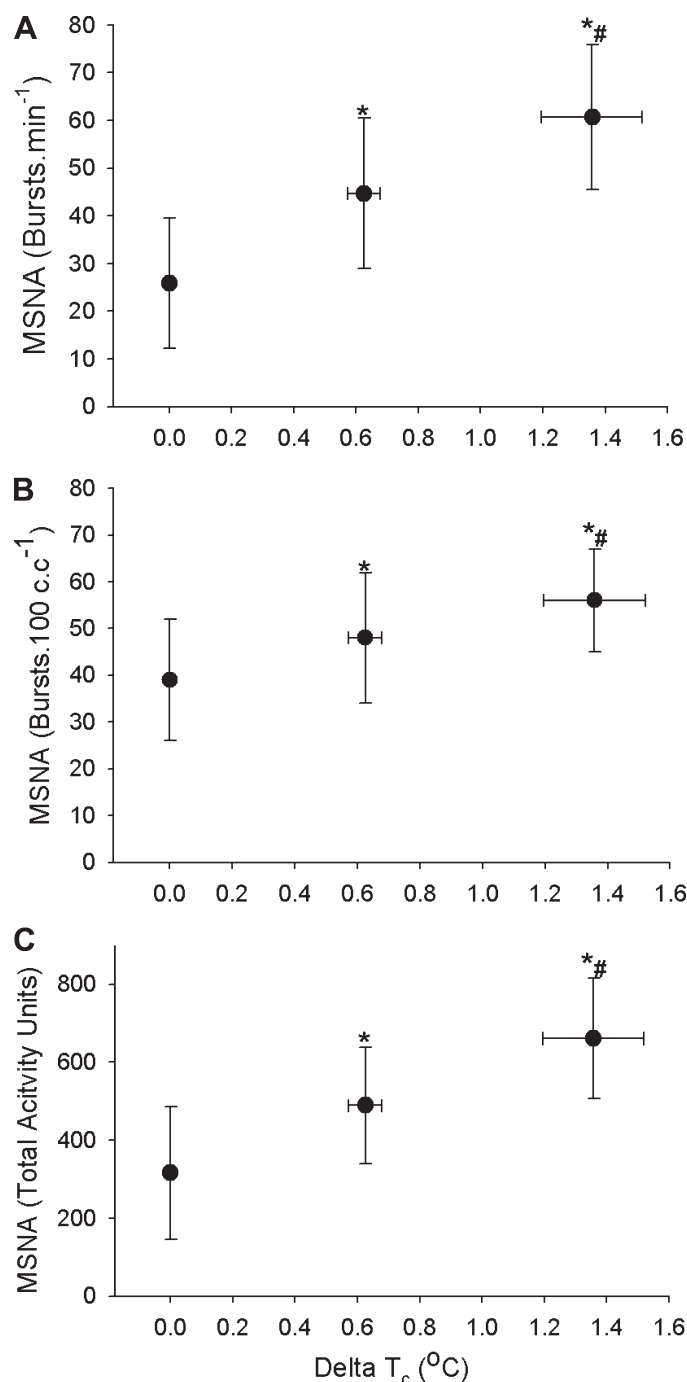


Fig. 2. Group (\pm SD) averaged muscle sympathetic nerve activity (MSNA) data, expressed as burst incidence (A), bursts per 100 cardiac cycles (B), and total activity (C), during normothermia (first data point) and at mid (second data point) and end (last data point) of heat stress. Regardless of how it is expressed, MSNA continues to increase throughout heat stress with no evidence of a plateau following the mid-level of heating. Delta T_c: Increase in core temperature measured from telemetry pill in the intestines. * $P < 0.05$ vs. normothermia, # $P < 0.05$ vs. mid heat stress ($n = 8$).

chemoreceptor activation) do not change MSNA (14, 38). These data suggest that even if central respiratory drive increased with heating at and above elevations in core temperature of $\sim 1^\circ\text{C}$, this response is unlikely to contribute to the elevation in MSNA.

One hypothesis for heat stress-induced elevations in MSNA, and likely SSNA, is a central activation of the sympathetic

nervous system. Central regulation of sympathetic outflow occurs primarily within the brain stem (medulla), pons, and hypothalamus, which integrate inputs from many different peripheral and central sources and provide major sources of supraspinal sympathoexcitatory outflow to sympathetic preganglionic neurons in the intermediolateral cell column of the spinal cord (11). The role of the central nervous system in mediating sympathetic nerve responses to heat stress is complex. Previous studies in rodents suggest that hypothalamic, brain stem, and spinal cord sites are involved (22–25). In those models sympathoexcitation is not specifically dependent on intact neural connections between the forebrain and brain stem, while brain stem neural circuits play a key role (25), in particular the rostral ventral lateral medulla (24). Nevertheless, the mechanism(s) that might contribute to the heat stress-related sympathetic activation in the human are unclear.

A central mechanism that may contribute to sympathoexcitation associated with heat stress in humans might revolve around changes in body water content. Sweating is a critical heat loss mechanism during hyperthermic conditions, but it is accompanied with dehydration (40). Dehydration increases MSNA without alterations in blood pressure, presumably via activation of the renin-angiotensin system (31). Increases in renin and angiotensin II occur during whole body hyperthermia (15, 26), supporting the possibility that factors associated with dehydration and the renin-angiotensin system could explain heat stress-induced sympathetic nerve activity and reductions in renal blood flow in rats (2, 27). Further research is warranted to investigate this hypothesis.

Limitations. In the present study, heat stress induced an average increase in internal temperature of $\sim 1.3^\circ\text{C}$, which was approximately double that of previous studies that have assessed sympathetic nerve activity responses to this challenge. Despite this extension of previous investigations, the findings of the present study are only applicable to the temperature range studied. It is thus unknown if MSNA and SSNA would continue to increase or plateau beyond the internal temperature studied in the present investigation.

Vasoconstrictor, sudomotor, and perhaps vasodilator components are contained within the SSNA signal, and it is not possible to separate primary sources of elevations in SSNA among these components. The primary responses observed in the integrative SSNA recording is likely related to the neural signal that is closest, and has the greatest neural fiber recruitment, relative to the recording electrode. It is therefore possible that the magnitude of the elevation in SSNA to the heat stress at a site (i.e., in a given subject) that primarily records from sudomotor fibers may be different from a site whose recording has significant contributions from cutaneous vasoconstrictor fibers. This would result in an increased variability in the elevation in integrative SSNA between subjects during the heat stress (see Fig. 1). However, every subject increased SSNA from normothermic to moderate heat stress as well as from moderate to severe heat stress as sudomotor and perhaps vasodilator fibers were activated.

In conclusion, relative to a moderate level of passive heating, MSNA and SSNA continue to increase during more profound passive heat stress sufficient to elevate internal temperature $\sim 1.3^\circ\text{C}$. These results indicate that MSNA and SSNA do not plateau but continue to increase as internal/mean body temperatures increase above previously reported values. The

mechanisms causing heat stress-induced elevations in MSNA and SSNA remain to be determined.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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