

Muscle sympathetic nerve activity during lower body negative pressure is accentuated in heat-stressed humans

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Submitted 10 July 2003; accepted in final form 9 February 2004

Cui, Jian, Thad E. Wilson, and Craig G. Crandall. Muscle sympathetic nerve activity during lower body negative pressure is accentuated in heat-stressed humans. *J Appl Physiol* 96: 2103–2108, 2004. First published February 20, 2004; 10.1152/jappphysiol.00717.2003.—The purpose of this project was to test the hypothesis that increases in muscle sympathetic nerve activity (MSNA) during an orthostatic challenge is attenuated in heat-stressed individuals. To accomplish this objective, MSNA was measured during graded lower body negative pressure (LBNP) in nine subjects under normothermic and heat-stressed conditions. Progressive LBNP was applied at -3 , -6 , -9 , -12 , -15 , -18 , -21 , and -40 mmHg for 2 min per stage. Whole body heating caused significant increases in sublingual temperature, skin blood flow, sweat rate, heart rate, and MSNA (all $P < 0.05$) but not in mean arterial blood pressure ($P > 0.05$). Progressive LBNP induced significant increases in MSNA in both thermal conditions. However, during the heat stress trial, increases in MSNA at LBNP levels higher than -9 mmHg were greater compared with during the same LBNP levels in normothermia (all $P < 0.05$). These data suggest that the increase in MSNA to orthostatic stress is not attenuated but rather accentuated in heat-stressed humans.

autonomic nervous system; baroreflexes; vasomotor; hyperthermia; orthostasis

HUMANS ARE MORE SUSCEPTIBLE to fainting during orthostatic stress and gravitation acceleration when combined with heat stress (1, 18, 33), the mechanisms of which remain unclear. Our laboratory and others have shown that whole body heating does not alter the maximal gain of baroreflex control of heart rate during carotid baroreceptor perturbations (4, 34) or during acute changes in arterial blood pressure (6, 35). Moreover, whole body heating did not affect the gain of arterial baroreflex control of muscle sympathetic nerve activity (MSNA) during rapid unloading and loading of arterial baroreceptors (6) or during sustained elevations in blood pressure (7).

In contrast, primarily loading cardiopulmonary baroreceptors via rapid saline infusion (15 ml/kg) did not alter MSNA in heat-stressed humans (3), despite findings in which MSNA decreases in normothermia during cardiopulmonary baroreceptor loading via rapid saline infusion, water immersion, head-down tilt, or lower body positive pressure (13, 19, 20, 22). A possible explanation for differing MSNA responses between thermal conditions may be that cardiopulmonary baroreceptor control of MSNA is impaired or uncoupled by whole body heating. If such were the case, impaired cardiopulmonary baroreceptor control of MSNA during heat stress could con-

tribute to reduced orthostatic tolerance in this thermal condition. Although it is recognized that arterial baroreceptors may compensate for possible heat stress impairment of cardiopulmonary baroreceptors, functioning arterial and cardiopulmonary baroreceptor are likely required for appropriate maintenance of orthostatic tolerance. However, the combined effects of heat stress and an orthostatic challenge on MSNA responses have not been investigated. Thus the purpose of this project was to test the hypothesis that MSNA responses to an orthostatic challenge are attenuated in heat-stressed individuals. If whole body heating selectively impairs or uncouples cardiopulmonary baroreceptor control of MSNA, this functional impairment would be identified via attenuated MSNA responses during lower levels of orthostatic stress.

METHODS

Nine subjects (5 men, 4 women) participated in this study. The subjects' average age was 33 ± 3 (SE) yr, and all were of normal height (168 ± 3 cm) and weight (72 ± 4 kg). Subjects were normotensive (supine blood pressures of $<140/90$ mmHg), were not taking medications, and were free of any known cardiovascular, metabolic, or neurological diseases. Subjects refrained from caffeine, alcohol, and heavy exercise for 24 h before the study. Each subject signed an informed consent that was approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas.

Instrumentation and measurements. Internal temperature [sublingual temperature (T_{sl})] was measured from a thermistor placed in the sublingual sulcus. Mean skin temperature (T_{sk}) was measured via the weighted average of six thermocouples attached to the skin (28). Each subject was dressed in a tube-lined suit that permitted the control of T_{sk} by changing the temperature of the water perfusing the suit. Subjects were placed in a Plexiglas box, which was sealed at the level of the iliac crests. The water-perfused suit consisting of an upper and lower garment, and thus the (LBNP) device was sealed directly to the subject's skin, which minimizes cooling during LBNP. Suction was provided by a vacuum pump and controlled with a variable transformer. The pressure difference between the LBNP chamber and atmosphere was measured with a digital manometer.

Multifiber recordings of MSNA were obtained with a tungsten microelectrode inserted in the common peroneal nerve. A reference electrode was placed subcutaneously 2–3 cm from the recording electrode. The recording electrode was adjusted until a site was found in which MSNA bursts were clearly identified by using previously established criteria (10, 11, 30). The main criteria for identification of MSNA relative to skin sympathetic nerve recordings were 1) pulse-synchronous efferent burst discharges, 2) increases in MSNA during inspiratory apnea, and 3) nonresponsiveness to sound and light tactile stimulation. The nerve signal was amplified, passed through a band-

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pass filter with a bandwidth of 500–5,000 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. The nerve signal was also routed to an oscilloscope and a loudspeaker for monitoring throughout the study.

Heart rate was obtained from the electrocardiogram signal (SpaceLabs, Redmond, WA) interfaced with a cardiometer (1,000-Hz sampling rate; CWE, Ardmore, PA). Blood pressure was recorded by auscultation of the brachial artery (SunTech, Medical Instruments Raleigh, NC). Mean arterial blood pressure (MAP) was calculated as diastolic blood pressure plus one-third pulse pressure. Arterial blood pressure was also monitored by a Finapres device. Respiratory frequency was monitored using piezoelectric pneumography. Impedance cardiograph (model EBI 100C, Biopac System, Santa Barbara, CA) was used to measure transthoracic impedance as an index of thoracic fluid shifts (2, 23). Skin blood flow was measured from the dorsal forearm skin via laser-Doppler flowmetry by using integrating flow probes (Perimed, North Royalton, OH). After the entire procedure, a 3-cm-diameter heater element (Perimed, North Royalton, OH), which housed the laser-Doppler flow probe, was engaged to elevate local T_{sk} to 42°C. Local temperature was held at this level for 30 min to elicit maximal cutaneous vasodilation (29). Skin blood flow was then normalized relative to maximal vasodilation for each site. Sweat rate was measured from dorsal forearm skin via capacitance hygrometry (Viasala, Woburn, MA) by perfusing 100% nitrogen at a flow rate of 300 ml/min through a ventilated capsule (surface area = 2.83 cm²) attached to the surface of the skin.

Protocol. Under both normothermic and heat-stressed conditions, progressive LBNP at -3, -6, -9, -12, -15, -18, -21, and -40 mmHg was applied at 2 min per stage. Water at 34°C was perfused through the suit throughout the normothermic trial. After normothermic data collection and subsequent return of arterial blood pressure to pre-LBNP levels, T_{sk} was increased to ~38°C by perfusing the tube-lined suit with 46°C water. Once T_{sl} increased ~0.5–0.7°C, the temperature of the water was reduced to 44–45°C in an attempt to reduce the rate of rise of internal temperature during progressive LBNP. The aforementioned LBNP protocol was repeated with the subject in this heat-stressed condition.

LBNP was terminated if the subject developed signs and/or symptoms of presyncope, such as sudden onset of nausea, sweating, light headedness, bradycardia, or hypotension (sustained systolic blood pressure of <80 mmHg). In the present study, all subjects completed the protocol under normothermic conditions, whereas, in the heat-stressed condition, LBNP was terminated in two individuals at -40 mmHg because of presyncopal symptoms.

Data analysis. Data were sampled at 200 Hz via a commercial data acquisition system (Biopac System, Santa Barbara, CA) and analyzed by using LabView software (National Instruments, Austin, TX). MSNA bursts were first identified in real time by visual inspection of data plotted on a chart recorder, coupled with the burst sound from the audio amplifier. These bursts were further evaluated from a computer program that identified bursts on the basis of fixed criteria, including an appropriate latency after the R wave of the electrocardiogram and a signal-to-noise ratio of >3:1 (5–9). The integrated MSNA was normalized by assigning a value of 100 to the mean amplitude of the largest sympathetic bursts (the top 10% of all identified bursts) during the 5-min baseline period before LBNP during normothermic condition. Subsequent bursts for that subject were then normalized against that value. The burst area of the integrated neurogram was measured on a beat-by-beat basis. Total MSNA of a burst was defined as the burst area of the rectified and integrated neurogram. With use of this method, total MSNA expressed as units per minute during each thermal baseline and the second minute of each LBNP stage was quantified (5, 6, 8). The number of identified MSNA bursts during these periods was also identified. Mean heart rate, blood pressure (via auscultation), and thoracic impedance during the second minute of each LBNP stage were obtained and statistically analyzed.

Statistical analyses were performed by using a commercial software package (SigmaStat 2.03, Chicago, IL). Differences between normothermic and heat stress baseline values (i.e., pre-LBNP) were evaluated by paired *t*-tests. Differences in LBNP-induced responses between normothermic and heat stress trials were evaluated via post hoc analysis after repeated-measures two-way ANOVA. Main factors of that ANOVA were thermal conditions and LBNP stage. Differences in hemodynamic responses within normothermic and heat stress trials were evaluated by using one-way repeated-measures ANOVA. All values are reported as means ± SE. *P* values of <0.05 were considered statistically significant.

RESULTS

After whole body heating, T_{sl} increased 0.6 to 0.7°C. Whole body heating increased heart rate, skin blood flow, sweat rate, and MSNA (Table 1). Whole body heating did not change MAP. During the period of progressive LBNP, although mean T_{sk} decreased slightly during the heat stress trial, T_{sl} did not change in either normothermic or heat-stressed conditions (Table 2).

Application of LBNP from -3 to -15 mmHg did not alter heart rate or MAP regardless of the thermal condition, whereas increases in heart rate were observed around LBNP levels of -18 to -21 during the heat stress trial (Fig. 1). At -40 mmHg LBNP, MAP decreased and heart rate increased in both normothermic and heat-stressed conditions (Fig. 1).

Progressive LBNP caused gradual increases in MSNA in both normothermic and heat-stressed conditions (Figs. 2 and 3). However, the increase in MSNA induced by LBNP at -12 through -40 mmHg during the heat stress was significantly greater relative to normothermia (Fig. 3). As depicted in Fig. 4, a significant correlation existed between the increase in MSNA and the increase in thoracic impedance for both normothermic ($r = 0.86 \pm 0.14$, $n = 9$) and heat-stressed ($r = 0.83 \pm 0.11$, $n = 9$) conditions. The slope of the relationship between the change in MSNA and the change in thoracic impedance induced by progressive LBNP up to -21 mmHg LBNP in the heat-stressed condition (523 ± 230 units/Ω, $n = 9$) was significantly greater relative to the normothermic condition (235 ± 103 units/Ω, $n = 9$, $P < 0.01$).

Table 1. Thermal and hemodynamic responses to the heat stress

	Normothermia	Heat Stress
T_{sl} , °C	36.5 ± 0.1	37.2 ± 0.1*
T_{sk} , °C	34.5 ± 0.2	37.9 ± 0.3*
MAP, mmHg	84 ± 2	81 ± 2
HR, beats/min	56 ± 1	79 ± 3*
Total MSNA, units/min	286 ± 43	531 ± 112*
MSNA, bursts/min	16 ± 3	30 ± 3*
Thoracic impedance, Ω	22.48 ± 0.54	22.72 ± 0.69
Forearm SkBF, % maximum	10.5 ± 2.5	46.8 ± 6.1*
Forearm SR, mg·cm ⁻² ·min ⁻¹		0.55 ± 0.07*

Values are means ± SE. Data show baseline values before lower body negative pressure (LBNP). Mean arterial blood pressure (MAP) was calculated as diastolic blood pressure plus one-third pulse pressure. Skin blood flow (SkBF) was normalized relative to maximum skin blood flow and is expressed as percentage of maximum. T_{sl} , sublingual temperature; T_{sk} , mean skin temperature; HR: heart rate; MSNA, muscle sympathetic nerve activity; SR, sweat rate. *Significantly different from normothermia, $P < 0.05$.

Table 2. Skin and sublingual temperatures and the change in thoracic impedance during progressive LBNP in both thermal conditions

	LBNP, mmHg								
	Baseline	-3	-6	-9	-12	-15	-18	-21	-40
<i>Normothermic</i>									
\bar{T}_{sk} , °C	34.5±0.2	34.4±0.2	34.4±0.2	34.4±0.1	34.4±0.1	34.4±0.1	34.4±0.1	34.4±0.1	34.4±0.1
T_{sl} , °C	36.5±0.1	36.6±0.1	36.6±0.1	36.6±0.1	36.6±0.1	36.6±0.1	36.6±0.1	36.6±0.1	36.6±0.1
ΔTI , Ω	0	0.15±0.08	0.31±0.07*	0.50±0.08*	0.66±0.10*	0.85±0.12*	1.07±0.15*	1.31±0.20*	1.96±0.32*
<i>Heat stress</i>									
\bar{T}_{sk} , °C	37.9±0.3†	37.9±0.3†	37.8±0.3†	37.7±0.3*†	37.6±0.3*†	37.6±0.2*†	37.6±0.3*†	37.6±0.2*†	37.4±0.2*†
T_{sl} , °C	37.2±0.1†	37.2±0.2†	37.2±0.2†	37.2±0.1†	37.2±0.1†	37.2±0.1†	37.2±0.1†	37.2±0.1†	37.2±0.1†
ΔTI , Ω	0	0.28±0.09	0.42±0.04*	0.62±0.12*	0.73±0.09*	0.91±0.08*	1.00±0.10*	1.18±0.18*	1.67±0.19*

Values means ± SE. ΔTI , change in thoracic impedance from baseline; $n = 9$ subjects, except $n = 7$ for -40 mmHg LBNP in heat-stressed condition
*Significantly different from baseline, $P < 0.05$. †Significantly different from normothermic condition, $P < 0.05$.

DISCUSSION

The major finding of present study is that the elevation in MSNA in heat-stressed subjects is accentuated, not attenuated, during an orthostatic challenge. This observation is evident both from a greater increase in MSNA for a given level of LBNP and from a greater slope of the relationship between the elevation in MSNA relative to the decrease in central blood volume during the heat stress orthostatic challenge.

Previously, our laboratory showed that primarily loading the cardiopulmonary baroreceptors via rapid saline infusion did

not alter MSNA in heat-stressed humans (3), which is in contrast to perturbations that decrease MSNA during loading of primarily cardiopulmonary baroreceptors in normothermia (13, 19, 20, 22). In a heat stress study (3), our laboratory speculated that a possible explanation for an absence of a reduction in MSNA during baroreceptor loading was an uncoupling of cardiopulmonary baroreceptor control of MSNA by the heat stress. However, data from the present experiment do not support this hypothesis.

Decreases in central venous pressure with low levels of LBNP are similar between normothermic and heat-stressed conditions (24). Although we did not measure central venous pressure in the present experiment, we observed similar decreases in the index of central blood volume during LBNP between thermal conditions (Table 2). Moreover, up to -21 mmHg LBNP, we observed that the increase in MSNA relative to the reduction in central blood volume was greater during the heat-stressed compared with the normothermic condition. Together, these data suggest that cardiopulmonary baroreceptors remain capable of modulating MSNA in heat-stressed subjects during an unloading stimulus, although we recognize that we cannot exclude the possibility that arterial baroreceptor unloading contributed in part to some of the increases in MSNA during LBNP (27).

Prior findings indicate that arterial baroreflex regulation of MSNA is generally preserved during whole body heating in humans (6, 7), whereas the present data show a greater increase in MSNA for a given level of LBNP or a reduction in central blood volume. Differences in these observations may be related to the magnitude of orthostatic stress and associated differences in the population of baroreceptors unloaded. For example, previously we demonstrated that whole body heating did not alter the gain of arterial baroreceptor control of MSNA, which was accessed by sequentially unloading and loading arterial baroreceptors via bolus infusions of nitroprusside followed by phenylephrine (6). However, that perturbation may not alter cardiopulmonary baroreceptors, because central venous pressure was unaffected by these rapid changes in blood pressure (12). Thus, in contrast to the present protocol, our prior protocol (6) could not address the effects of combined cardiopulmonary and arterial baroreceptor unloading on MSNA responses in heat-stressed individuals. In a subsequent study, we administered varying doses of phenylephrine in both normothermic and heat-stressed conditions to increase arterial

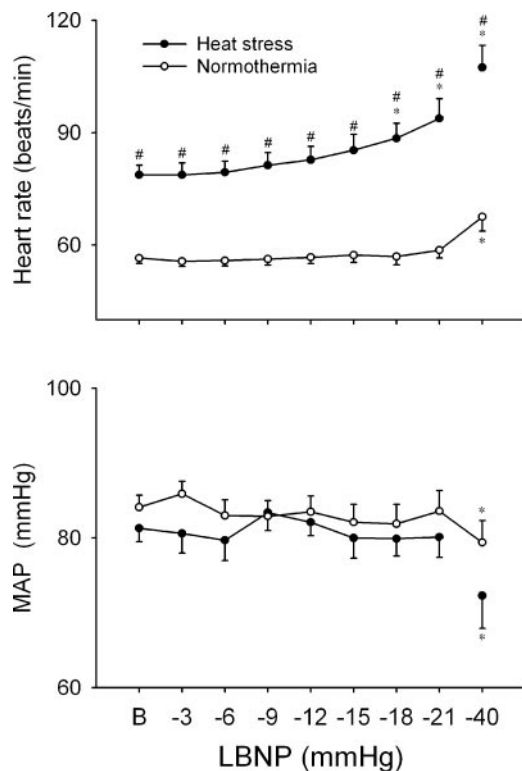
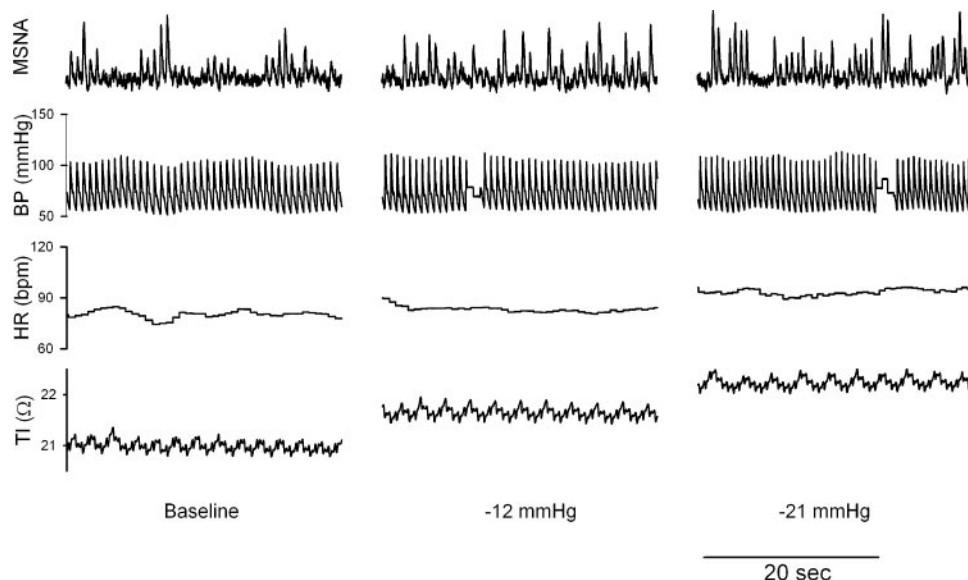


Fig. 1. Effects of heat stress on heart rate and mean arterial blood pressure (MAP) in response to progressive lower body negative pressure (LBNP). Values are means ± SE; $n = 9$ subjects for baseline (B) through -21 mmHg, $n = 7$ for -40 mmHg for the heat stress trial because of presyncopal symptoms of 2 subjects, and $n = 9$ for all stages of LBNP during the normothermic trial. * $P < 0.05$ compared with baseline before LBNP. # $P < 0.05$ compared with normothermia.

Fig. 2. Effects of LBNP at baseline, -12, and -21 mmHg on muscle sympathetic nerve activity (MSNA), blood pressure (BP, by Finapres), heart rate (HR), and thoracic impedance (TI) in 1 representative subject during whole body heat stress.



and central venous pressures (7), thereby loading both arterial and cardiopulmonary baroreceptors (26). Similar to the bolus infusion study, arterial baroreflex gain, identified from the slope of the relationship between the reduction in MSNA and the elevation in arterial blood pressure, was not altered by heating.

The present findings suggest that, in the heat-stressed condition for a given orthostatic challenge (i.e., LBNP stage or reduction in central blood volume), MSNA is greater relative

to that same orthostatic challenge under normothermic conditions. The mechanism resulting in this observation is unclear and can only be speculated on at this time. The simplest explanation is that progressive LBNP in the heat-stressed condition causes greater unloading of the baroreceptors. In support of this argument, at -40 mmHg LBNP, the reduction in arterial blood pressure was significantly greater during the heat stress trial (Fig. 1). However, a few observations suggest that this may not be the sole explanation for augmented increases in MSNA during LBNP in the heat. For example, large differences in MSNA responses between thermal conditions are observed before differences in arterial blood pressure or heart rate (see Figs. 1 and 3). Second, a previous study showed that the central venous pressures were similar during -10 through -60 mmHg LBNP between normothermic and heat-stressed conditions (24). This observation is consistent

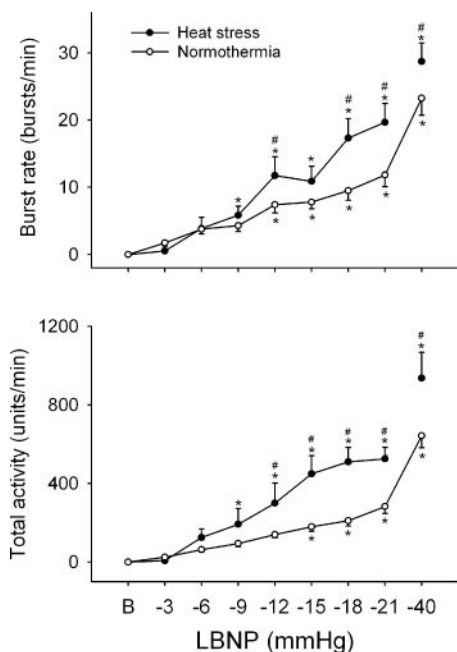


Fig. 3. Effects of heat stress on changes in MSNA in response to progressive LBNP. For a given level of orthostatic stress (i.e., LBNP stage), the increase in MSNA was greater in the heat-stressed condition relative to normothermia. Values are means ± SE reported as a change from baseline (B) during normothermic and heat-stressed conditions. Refer to Table 1 for baseline values. The number of subjects per LBNP stage is as given in the legend of Fig. 1. **P* < 0.05 compared with baseline. #*P* < 0.05 compared with normothermia.

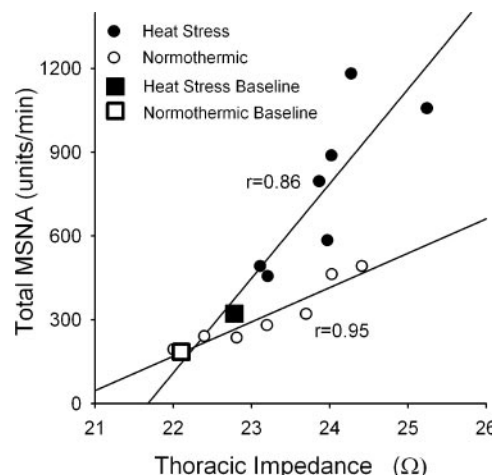


Fig. 4. An example of the linear regression between MSNA and thoracic impedance induced by progressive LBNP from baseline to -21 mmHg for a representative subject. Squares depict baseline MSNA and thoracic impedance before LBNP. For this subject, the slope of this relationship was elevated by the heat stress (123-338 units·min⁻¹·Ω⁻¹), which is consistent with the observed significant increase in the average slope. *r*, Correlation coefficients for this subject's data.

with the present findings that the reduction in central blood volume, as indexed by thoracic impedance, during LBNP is similar between thermal conditions. Finally, we observed that the slope of the relationship between the increase in thoracic impedance and increases in MSNA was greater in the heat-stressed condition (Fig. 4). This result indicates that, for a given fluid shift (i.e., reduction in central blood volume and accompanied cardiopulmonary and arterial baroreceptor unloading), there was a greater increase in MSNA during the heat-stressed condition relative to normothermia. If a greater elevation in MSNA during the heat stress LBNP trial was solely due to enhanced orthostatic stress, then the slope of this relationship should not be different between thermal trials. Together, these findings suggest that differences in the elevation in MSNA during LBNP between thermal conditions is not simply due to greater baroreceptor unloading during the heat stress trial.

Regardless of the mechanism, accentuated MSNA responses to LBNP in the heat-stressed condition should be beneficial in maintaining blood pressure during the orthostatic challenge. However, postsynaptic vasoconstrictor responses to exogenous α -adrenoceptor agonists are impaired by whole body heating in human skin (32) and rats (17). Although the postsynaptic response has not been verified in other vascular beds, systemic vasoconstrictor responsiveness to α -adrenergic agents are impaired in humans (7). Therefore, it may be that greater levels of sympathetic activation are required to maintain blood pressure during an orthostatic challenge because postsynaptic vasoconstrictor responsiveness is attenuated by whole body heating. On the other hand, heat stress itself increases MSNA, and the present findings suggest that, for any level of orthostatic stress (to -40 mmHg LBNP), MSNA is greater in heat-stressed conditions. The combination of these factors may result in a reduced reserve to increase MSNA during greater levels of orthostatic stress. Such a response could contribute to orthostatic intolerance.

Study limitations. Central venous pressure decreases during LBNP in both normothermic (16, 25, 31) and heat-stressed conditions (24). In the present study, low levels of LBNP did not cause measurable changes in arterial blood pressure or heart rate. We recognize that low levels of LBNP, especially during the heat stress, may cause some degree of arterial baroreceptor unloading despite the absence of a noticeable corresponding efferent response (14, 15, 21, 27). Therefore, a contribution of arterial baroreceptors in mediating some of the responses observed during low levels of LBNP cannot be excluded. Nevertheless, the present data show that MSNA will increase during low levels of LBNP, and, for a given level of orthostatic stress, MSNA responses are enhanced when individuals are heat stressed.

LBNP trials between thermal conditions were not randomized. Such randomization would require LBNP challenges to be performed on separate days, because it would be inappropriate to first conduct a heat stress LBNP trial followed by a normothermic LBNP trial on the same day, especially for those subjects who experienced presyncope during the heat stress trial. To account for this limitation, ample time elapsed between the normothermic and heat stress LBNP trials. After the normothermic LBNP trial, the subjects rested for 30 min or more, during which time heart rate, blood pressure, respiration rate, and MSNA burst rate returned to pre-LBNP levels. After

this period, whole body heating took 40–60 min to cause the targeted increase in sublingual temperature (0.5 – 0.7°C). Thus LBNP protocols were separated by a minimum of 70 min. We believe this interval was long enough to minimize any effects of the first LBNP challenge on the second LBNP trial, although it is recognized that this possibility cannot be completely excluded.

In conclusion, the present findings demonstrate that, in a heat-stressed condition, MSNA remains capable of increasing during low and moderate levels of LBNP. This observation is in contrast to prior findings in which loading primarily cardiopulmonary baroreceptors with rapid saline infusion did not alter MSNA in heat-stressed individuals. Moreover, the increase in MSNA for a given level of orthostatic stress (i.e., LBNP level or central blood volume) was greater during the heat stress trial relative to the normothermic trial. These data suggest that the increase in MSNA to orthostatic stress is not attenuated but rather accentuated in heat-stressed humans.

GRANTS

This research project was funded in part by National Heart, Lung, and Blood Institute Grants HL-61388 and HL-10488 and by American Heart Association Grant 0225036Y.

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