

# Cardiopulmonary baroreceptor control of muscle sympathetic nerve activity in heat-stressed humans

C. G. CRANDALL,<sup>1,2</sup> R. A. ETZEL,<sup>1</sup> AND D. B. FARR<sup>1</sup>

<sup>1</sup>Institute for Exercise and Environmental Medicine, Presbyterian Hospital of Dallas, Dallas 75231; and <sup>2</sup>Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas 75235

**Crandall, C. G., R. A. Etzel, and D. B. Farr.** Cardiopulmonary baroreceptor control of muscle sympathetic nerve activity in heat-stressed humans. *Am. J. Physiol.* 277 (*Heart Circ. Physiol.* 46): H2348–H2352, 1999.—Whole body heating decreases central venous pressure (CVP) while increasing muscle sympathetic nerve activity (MSNA). In normothermia, similar decreases in CVP elevate MSNA, presumably via cardiopulmonary baroreceptor unloading. The purpose of this project was to identify whether increases in MSNA during whole body heating could be attributed to cardiopulmonary baroreceptor unloading coincident with the thermal challenge. Seven subjects were exposed to whole body heating while sublingual temperature, skin blood flow, heart rate, arterial blood pressure, and MSNA were monitored. During the heat stress, 15 ml/kg warmed saline was infused intravenously over 7–10 min to increase CVP and load the cardiopulmonary baroreceptors. We reported previously that this amount of saline was sufficient to return CVP to pre-heat stress levels. Whole body heating increased MSNA from  $25 \pm 3$  to  $39 \pm 3$  bursts/min ( $P < 0.05$ ). Central blood volume expansion via rapid saline infusion did not significantly decrease MSNA ( $44 \pm 4$  bursts/min,  $P > 0.05$  relative to heat stress period) and did not alter mean arterial blood pressure (MAP) or pulse pressure. To identify whether arterial baroreceptor loading decreases MSNA during heat stress, in a separate protocol MAP was elevated via steady-state infusion of phenylephrine during whole body heating. Increasing MAP from  $82 \pm 3$  to  $93 \pm 4$  mmHg ( $P < 0.05$ ) caused MSNA to decrease from  $36 \pm 3$  to  $15 \pm 4$  bursts/min ( $P < 0.05$ ). These data suggest that cardiopulmonary baroreceptor unloading during passive heating is not the primary mechanism resulting in elevations in MSNA. Moreover, arterial baroreceptors remain capable of modulating MSNA during heat stress.

whole body heating; sinoaortic baroreceptors; baroreflex; sympathetic nervous system; hyperthermia.

IN HUMANS, elevated internal temperature causes a substantial increase in skin blood flow secondary to increases in cutaneous vascular conductance, increases in cardiac output, and decreases in splanchnic, renal, and muscle vascular conductances (4, 9, 13). These hemodynamic changes are consistent with changes in sympathetic nerve activity measured during heating in both humans and rats (6, 11). For example, Niimi et al.

(11) showed that muscle sympathetic nerve activity (MSNA) in humans is elevated during minimal whole body heating ( $\sim 0.2^\circ\text{C}$  increase in tympanic temperature). Kenney et al. (6) showed that increasing core temperature in rats from  $39.0^\circ\text{C}$  to  $41.0^\circ\text{C}$  causes significant increases in renal, lumbar, and splanchnic sympathetic nerve discharge.

Mechanisms leading to increases in sympathetic nerve activity and accompanying decreases in regional vascular conductance during heating remain unclear. The aforementioned hemodynamic adjustments during whole body heating in humans, coupled with relaxation of the cutaneous veins, result in central venous pressure (CVP) decreasing 2–6 mmHg and mean arterial pressure (MAP) decreasing 5–10 mmHg (1, 14). In normothermia, reductions in CVP and MAP of this magnitude increase MSNA by unloading cardiopulmonary and sinoaortic baroreceptors, respectively (3, 16, 19). To identify whether sinoaortic baroreceptor unloading during whole body heating contributed to the decrease in splanchnic blood flow, Rowell et al. (15) measured splanchnic vascular resistance and blood flow during heating with and without leg elevation followed by thigh occlusion. They found that even though leg elevation followed by 6–10 min of occlusion returned MAP to pre-heat stress levels, splanchnic vascular resistance remained elevated and splanchnic blood flow remained reduced. As a result of these findings, Rowell et al. (15) concluded that the mechanism causing the elevation in splanchnic vascular resistance during whole body heating was not caused by sinoaortic baroreceptor unloading accompanying the heat stress. Thus it is unlikely that the elevation in sympathetic activity during a heat stress is caused by sinoaortic baroreceptor unloading.

In light of the fact that in normothermia unloading cardiopulmonary baroreceptors increase MSNA (3, 16) and of data showing that CVP decreases during a heat stress (1, 9, 14), it may be that the elevation in MSNA during a heat stress is caused by cardiopulmonary baroreceptor unloading associated with the heat stress. Therefore, the purpose of this study was to test the hypothesis that decrease in CVP, and accompanying cardiopulmonary baroreceptor unloading, is the primary mechanism leading to increases in MSNA during whole body heating in humans.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

## METHODS

**Subjects.** For protocol 1, seven subjects (4 female, 3 male) participated in the study. Five subjects participated in protocol 2 (2 female, 3 male). The subjects' average age was  $30 \pm 3$  yr, and all were of normal height ( $169 \pm 4$  cm), weight ( $67 \pm 4$  kg), and health. A written informed consent from each subject was obtained before participation in these institutionally approved studies.

**Instrumentation.** For both protocols, the subject was instrumented for the measurement of sublingual temperature ( $T_{sl}$ ) with a thermocouple and mean skin temperature ( $T_{sk}$ ) from the electrical average of six thermocouples placed on the skin. The subject was then dressed in a tube-lined suit that permitted control of  $T_{sk}$  by changing the temperature of the water perfusing the suit. Arterial blood pressure was obtained by auscultation. MAP was calculated as diastolic blood pressure plus one-third pulse pressure. Heart rate (HR) was obtained from the electrocardiogram signal interfaced with a cardiachometer (CWE, Ardmore, PA). Forearm skin blood flow was indexed by laser-Doppler flowmetry (Perimed, North Royalton, OH). Postganglionic MSNA was recorded from the peroneal nerve. This was accomplished by inserting a tungsten microelectrode with an uninsulated tapered tip of 1–5  $\mu$ m (FHC, Bowdoinham, ME) into the peroneal nerve below the fibular head. A second uninsulated reference electrode was positioned within 3 cm of the recording electrode. A muscle fascicle was identified by observing muscle twitches during intraneural stimulation (0.3–1 V, 1 Hz). The signal was amplified  $\times 1,000$  and passed through a band-pass filter (700–2,000 Hz) having a gain of 60–90 (Iowa Bioengineering, Iowa City, IA). The filtered neurogram was rectified and integrated (0.1-s time constant) and displayed on an oscilloscope with the electrocardiogram. This signal was also routed to an audio amplifier. Minor adjustments were made to the microelectrode until an acceptable MSNA signal was obtained. Verification of MSNA relative to skin sympathetic nerve activity was performed as previously reported (18). After an acceptable MSNA signal was obtained, a venous catheter was placed in an antecubital vein.

**Experimental protocol 1.** With the subject in the supine position, neutral ( $\sim 34^\circ\text{C}$ ) water was perfused through the tube-lined suit. After  $\sim 10$  min, baseline data were collected. After this baseline period,  $T_{sk}$  was increased to  $38.4^\circ\text{C}$  by perfusing the tube-lined suit with warm ( $46^\circ\text{C}$ ) water. After  $T_{sl}$  increased  $\sim 0.6$ – $1^\circ\text{C}$ , 15 ml/kg warmed ( $37^\circ\text{C}$ ) isotonic saline was rapidly administered (7–10 min in duration) through the catheter placed in an antecubital vein. We previously showed that administration of 15 ml/kg saline over this period of time was sufficient to return CVP to pre-heat stress pressures (1). After the infusion,  $T_{sk}$  was returned to pre-heat stress levels by perfusing the suit with cool water.

**Experimental protocol 2.** This protocol was performed to identify whether MSNA can be regulated by sinoaortic baroreceptor loading in heat-stressed humans. This protocol was identical to that previously outlined; however, rather than administering 15 ml/kg warm saline, we administered phenylephrine (60–120  $\mu\text{g}/\text{min}$ ) intravenously to increase MAP by 10–15 mmHg.

**Data collection and statistics.** Data were sampled at 200 Hz through a data acquisition system (Biopac Systems, Santa Barbara, CA) and reduced to the following 3-min periods: immediately before whole body heating (pre-heat stress), immediately before saline infusion or phenylephrine administration (heat stress), and the last 3 min of saline infusion or phenylephrine administration. Because MSNA bursts are coupled with the cardiac cycle and whole body heating causes

Table 1. Responses to passive heating and saline infusion

	Pre-Heat Stress	Heat Stress	Saline Infusion
Sublingual temperature, $^\circ\text{C}$	$36.4 \pm 0.1$	$37.0 \pm 0.1^*$	$37.1 \pm 0.1^*\dagger$
Skin temperature, $^\circ\text{C}$	$34.7 \pm 0.4$	$38.4 \pm 0.1^*$	$38.4 \pm 0.2^*$
Systolic blood pressure, mmHg	$111 \pm 6$	$110 \pm 7$	$110 \pm 7$
Diastolic blood pressure, mmHg	$60 \pm 1$	$57 \pm 2$	$55 \pm 3$
Mean blood pressure, mmHg	$77 \pm 2$	$75 \pm 3$	$73 \pm 4$
Pulse pressure, mmHg	$51 \pm 6$	$54 \pm 7$	$56 \pm 6$
Heart rate, beats/min	$57 \pm 4$	$77 \pm 5^*$	$88 \pm 6^*\dagger$
MSNA, bursts/min	$25 \pm 3$	$39 \pm 3^*$	$44 \pm 4^*$
MSNA (burst/100 heart-beats)	$44 \pm 4$	$53 \pm 3^*$	$50 \pm 4^*$
SBF, perfusion units	$12 \pm 3$	$74 \pm 18^*$	$92 \pm 16^*\dagger$

Values are means  $\pm$  SE. MSNA, muscle sympathetic nerve activity; SBF, skin blood flow. \*Significantly different from pre-heat stress stage ( $P < 0.05$ );  $\dagger$ significantly different from heat stress stage ( $P < 0.05$ ). Each stage represents an average of 3 min of data.

HR to increase, burst frequency was analyzed as both bursts per minute and bursts per 100 heartbeats. All data were statistically analyzed using one-way repeated-measures analysis of variance followed by a Student-Newman-Keuls multiple-comparison test when significant main factor differences were identified. Data for both protocols are expressed as means  $\pm$  SE. The level of statistical significance was set at  $P = 0.05$ .

## RESULTS

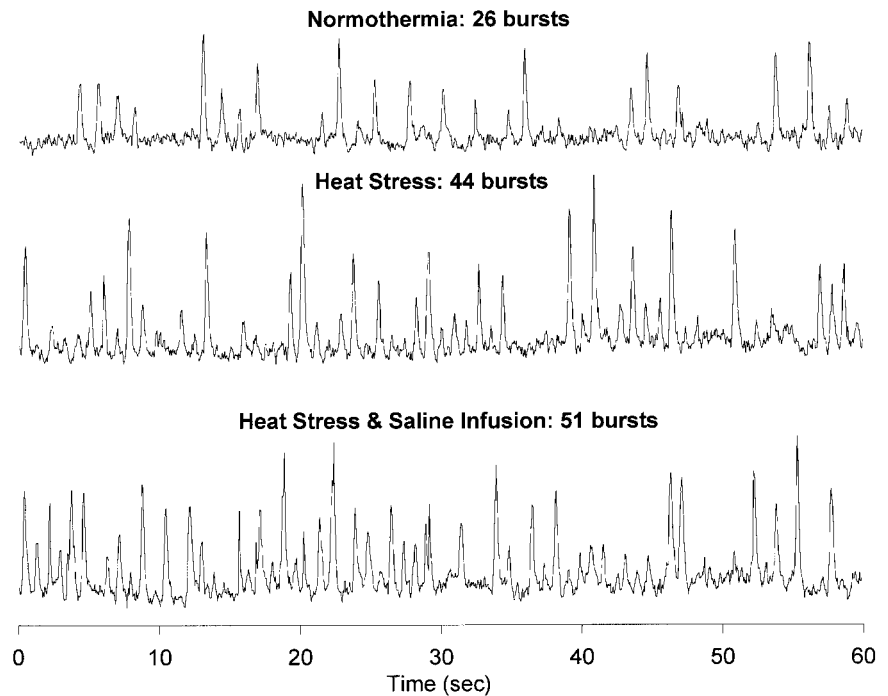
**Protocol 1.** Increasing  $T_{sk}$  to  $38.4^\circ\text{C}$  resulted in significant increases in  $T_{sl}$ , HR, and skin blood flow (Table 1) MAP tended to decrease but was not significantly affected by the heat stress. Although not recorded in the present experiment, we recently reported (1) that this degree and duration of whole body heating significantly decreased CVP from  $7.7 \pm 0.6$  to  $4.9 \pm 0.5$  mmHg. Consistent with the findings of Niimi et al. (11), whole body heating increased MSNA (Tables 1 and 2 and Fig. 1).

Table 2. Responses to passive heating and phenylephrine infusion

	Pre-Heat Stress	Heat Stress	Phenylephrine Infusion
Sublingual temperature, $^\circ\text{C}$	$36.2 \pm 0.2$	$37.0 \pm 0.1^*$	$37.1 \pm 0.1^*$
Skin temperature, $^\circ\text{C}$	$34.5 \pm 0.3$	$38.4 \pm 0.2^*$	$38.5 \pm 0.2^*\dagger$
Systolic blood pressure, mmHg	$124 \pm 6$	$123 \pm 6$	$140 \pm 8^*\dagger$
Diastolic blood pressure, mmHg	$67 \pm 4$	$61 \pm 2^*$	$69 \pm 3^\dagger$
Mean blood pressure, mmHg	$86 \pm 4$	$82 \pm 3^*$	$93 \pm 4^*\dagger$
Pulse pressure, mmHg	$57 \pm 4$	$62 \pm 5$	$71 \pm 6^*\dagger$
Heart rate, beats/min	$59 \pm 4$	$80 \pm 3^*$	$70 \pm 3^*\dagger$
MSNA, bursts/min	$24 \pm 4$	$36 \pm 3^*$	$15 \pm 4^*\dagger$
MSNA, bursts/100 heart-beats	$39 \pm 5$	$45 \pm 3^*$	$20 \pm 5^*\dagger$

Values are means  $\pm$  SE. \*Significantly different from pre-heat stress stage ( $P < 0.05$ );  $\dagger$ significantly different from heat stress stage ( $P < 0.05$ ). Each stage represents an average of 3 min of data.

Fig. 1. Effects of heat stress and heat stress + rapid infusion of 15 ml/kg warmed saline on muscle sympathetic nerve activity (MSNA) for 1 individual. Whole body heating substantially increased MSNA, whereas the administration of saline did not return MSNA to pre-heat stress levels. Original data were sampled at a rate of 200 Hz. For display purposes, data illustrated were resampled at 20 Hz. Vertical scale is the same for each stage.



Rapid infusion of 15 ml/kg saline did not significantly change  $T_{sk}$ , MAP, pulse pressure, or MSNA during the heat stress period. However, as previously reported (1), skin blood flow and HR were significantly elevated by the saline infusion (see Table 1). There was a slight tendency, although not significant, for MSNA to decrease when expressed as bursts per 100 heartbeats during the saline infusion. This was not attributed to decreased MSNA activity, because MSNA expressed as bursts per minute remained elevated (see Fig. 2). Rather, this tendency for a decrease in MSNA expressed as bursts per 100 heartbeats was caused by a significant elevation in HR by the saline infusion without a proportional increase in MSNA burst frequency.

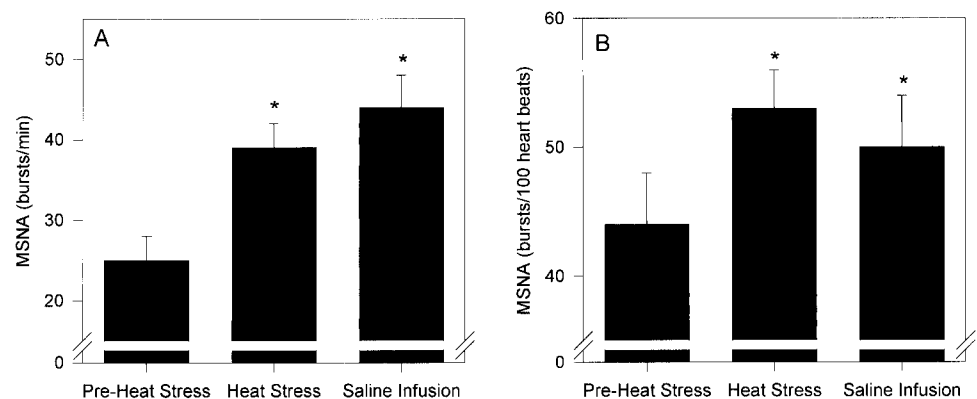
**Protocol 2.** Temperature, hemodynamic, and MSNA responses were similar during passive heating relative to the responses observed in *protocol 1* (see Table 2). Administration of phenylephrine significantly elevated MAP ( $82 \pm 3$  to  $93 \pm 4$  mmHg;  $P < 0.05$ ), systolic blood pressure ( $123 \pm 6$  to  $140 \pm 8$  mmHg;  $P < 0.05$ ), diastolic blood pressure ( $61 \pm 2$  to  $69 \pm 3$  mmHg;  $P < 0.05$ ) and

pulse pressure ( $62 \pm 5$  mmHg to  $71 \pm 6$  mmHg;  $P < 0.05$ ), thereby causing a baroreflex-mediated decrease in MSNA expressed as bursts per minute ( $36 \pm 3$  to  $15 \pm 4$ ;  $P < 0.05$ ) or bursts per 100 heartbeats ( $45 \pm 3$  to  $20 \pm 5$ ,  $P < 0.05$ ; see Fig. 3).

## DISCUSSION

The primary finding of this study was that the elevation in MSNA during passive heating in humans cannot be reversed by expanding central blood volume and loading cardiopulmonary baroreceptors via rapid saline infusion. This conclusion was based on the observation that rapid infusion of 15 ml/kg warm saline during whole body heating did not significantly change MSNA relative to the period immediately before saline infusion. These data suggest that the elevation in MSNA during heat stress was not caused by cardiopulmonary baroreceptor unloading coincident with the thermal challenge. Moreover, loading the sinoaortic baroreceptors via phenylephrine administration during passive heating significantly reduced MSNA,

Fig. 2. Average MSNA responses to heat stress and heat stress + administration of 15 ml/kg warmed saline when expressed as bursts per minute (A) and bursts per 100 heartbeats (B). Heat stress significantly elevated MSNA above pre-heat stress levels. MSNA remained significantly elevated during central blood volume expansion. In both A and B, MSNA during saline infusion stage was not significantly different from that in heat stress state. \*Significantly different from pre-heat stress stage ( $P < 0.05$ ).



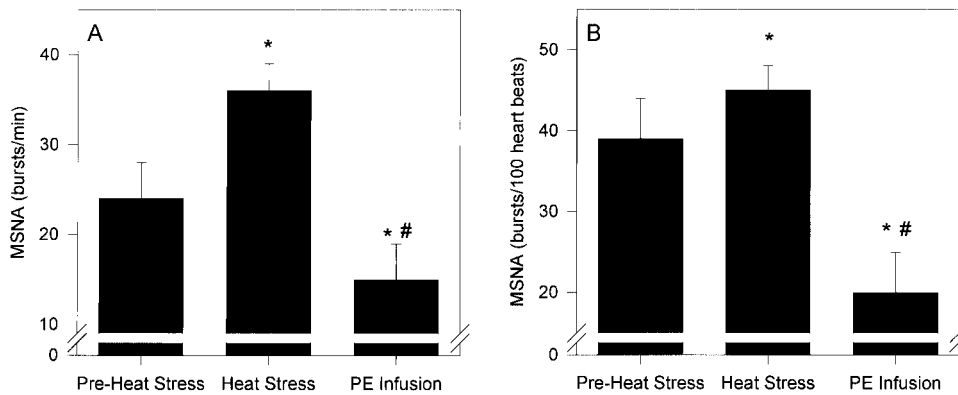


Fig. 3. Average MSNA responses to whole body heating as well as whole body heating + phenylephrine (PE) infusion. Heat stress significantly elevated MSNA relative to pre-heat stress values when expressed as bursts per minute (A) or bursts per 100 heartbeats (B). However, elevating arterial blood pressure via 60–120  $\mu\text{g}/\text{min}$  PE administration during heat stress decreased MSNA to levels below both pre-heat stress and heat stress stages. \*Significantly different from pre-heat stress stage; # significantly different from heat stress stage (both  $P < 0.05$ ).

thereby demonstrating that at least the sinoaortic baroreceptors remain capable of modulating MSNA in this environment.

In normothermia, loading cardiopulmonary baroreceptors via rapid saline infusion (12), water immersion (8), lower-body positive pressure (2), or head-down tilt (10) decreases MSNA, whereas unloading these baroreceptors increases MSNA (3, 16). These findings suggest that the operating point of the cardiopulmonary-MSNA baroreflex curve in normothermia is located somewhere between threshold and saturation. We (1) and others (9, 14) reported that CVP decreases and MSNA increases during whole body heating. If the baroreflex curve depicting cardiopulmonary baroreceptor control of MSNA is not altered by the thermal challenge, i.e., solely a shift in operating point by the heat stress, returning CVP to pre-heat stress levels would cause a baroreflex-mediated decrease in MSNA. However, in the present study, loading cardiopulmonary baroreceptors with rapid saline infusion during the heat stress did not change MSNA. Given this finding, it is possible that either the cardiopulmonary baroreceptors do not modulate MSNA during a heat stress or the cardiopulmonary baroreceptor-MSNA stimulus-response relationship has been dramatically shifted by whole body heating.

To investigate whether arterial baroreceptor modulation of MSNA remains intact during a heat stress, in a separate protocol MAP was elevated via steady-state phenylephrine infusion after heat stress-induced elevations in MSNA were observed. Elevating MAP 10–15 mmHg during the heat stress reduced MSNA to levels less than those observed before the heat stress (Fig. 2). This finding clearly shows that arterial baroreceptor suppression of MSNA remains intact during the heat stress. Nevertheless, these data do not exclude the possibility of an uncoupling of cardiopulmonary baroreceptor control of MSNA during whole body heating.

It is conceivable that the elevation in MSNA during whole body heating is not a baroreflex-mediated response. In support of this hypothesis is the observation that increases in splanchnic sympathetic nerve activity in hyperthermic rats were similar in baroreceptor-innervated and -denervated conditions (6). Moreover, Rowell et al. (15) showed that returning arterial blood pressure during whole body heating to pre-heat stress pressures via leg elevation followed by supersystolic leg

occlusion did not reverse heat-induced elevations in splanchnic vascular resistance.

The observation that phenylephrine-induced elevations in MAP during whole body heating decreased MSNA is insufficient evidence to conclude that the elevations in MSNA in this environment were caused by a reduction in MAP observed during the heat stress. Rather, these data show that sinoaortic baroreceptors are still capable of modulating MSNA during whole body heating. Taken together, these findings suggest that elevations in MSNA during heat stress may occur through central activation of the sympathetic nervous system and are likely independent of heat stress-induced baroreceptor unloading. Nevertheless, we cannot exclude the possibility that some of the increases in MSNA during the heat stress were caused by sinoaortic baroreceptor unloading.

*Potential limitations of interpretation of results.* CVP decreases during passive heating in humans (1, 9, 14). Given our previous finding that administration of 15 ml/kg saline during the heat stress returned CVP to pre-heat stress pressures (1), we felt it unnecessary to have the subjects undergo this invasive procedure in the present experiment. Thus we cannot state conclusively that CVP was returned to pre-heat stress levels by saline infusion. Nevertheless, the similarity of increases in skin blood flow and HR during saline infusion between the present study and our prior study (1), in which CVP was directly measured, support our contention that rapid saline infusion in the present study loaded cardiopulmonary baroreceptors and that this degree of loading was insufficient to decrease MSNA.

Saline infusion during passive heating did not change pulse pressure or MAP. Thus we concluded that this perturbation primarily loaded cardiopulmonary baroreceptors. However, recent studies demonstrate that low levels of lower-body negative pressure, which previously were thought to unload only the cardiopulmonary baroreceptors (5), may also unload sinoaortic baroreceptors (7, 17). Little is known regarding the effects of rapid central blood volume expansion on sinoaortic baroreceptor tension. Thus the possibility cannot be excluded that some degree of sinoaortic baroreceptor loading occurred during saline infusion despite a lack of change in MAP or arterial pulse pressure. However, if

this occurred, the magnitude of sinoaortic baroreceptor loading was insufficient to decrease MSNA.

In normothermia, phenylephrine administration not only increases MAP but also increases CVP. Although it is not confirmed in the present experiment, one may speculate that phenylephrine administration during whole body heating likewise increased CVP and thus cardiopulmonary baroreceptor loading in this environment. However, given that loading cardiopulmonary baroreceptors with saline infusion during heat stress did not change MSNA, the reduction in MSNA during phenylephrine-induced elevations in blood pressure was likely caused by sinoaortic baroreceptor loading.

In conclusion, whole body heating in humans decreases CVP, and presumably cardiopulmonary baroreceptor loading, while at the same time increasing MSNA. The intent of this study was to identify whether this elevation in MSNA was caused by unloading of cardiopulmonary baroreceptors. During the heat stress, cardiopulmonary baroreceptor loading via rapid infusion of warm saline did not affect MSNA. Thus it is unlikely that cardiopulmonary baroreceptor unloading coincident with heat stress is the mechanism leading to elevations in MSNA. In contrast to loading cardiopulmonary baroreceptors, loading sinoaortic baroreceptors during heat stress via steady-state infusion of phenylephrine significantly reduced MSNA to levels below those observed in normothermic and heat stress-alone conditions. It remains unknown whether cardiopulmonary baroreceptor modulation of MSNA is uncoupled by the heat stress or whether the cardiopulmonary baroreceptor-MSNA stimulus-response relationship is altered during whole body heating.

The authors express appreciation to Dr. Benjamin Levine for providing medical support and to the subjects for willing participation in this project. C. G. Crandall expresses appreciation to Drs. Gunnar Wallin, Michael Elam, and Yrsa Sverrisdottir for their time and patience while teaching him microneurography.

This research project was funded in part by the National Heart, Lung, and Blood Institute (HL-61388) and by the National Aeronautics and Space Administration (NAG9-1033).

Address for reprint requests and other correspondence: C. G. Crandall, Inst. of Exercise and Environmental Medicine, Presbyterian Hosp. of Dallas, 7232 Greenville Ave., Dallas, TX 75231 (E-mail: Crandall@email.swmed.edu).

Received 31 March 1999; accepted in final form 12 July 1999.

## REFERENCES

1. **Crandall, C. G., B. D. Levine, and R. A. Etzel.** Effect of increasing central venous pressure during passive heating on skin blood flow. *J. Appl. Physiol.* 86: 605–610, 1999.
2. **Fu, Q., U. Sugiyama, A. Kamiya, A. S. M. Shamsuzzaman, and T. Mano.** Responses of muscle sympathetic nerve activity to lower body positive pressure. *Am. J. Physiol. Heart Circ. Physiol.* 275: H1254–H1259, 1998.
3. **Jacobsen, T. N., B. J. Morgan, U. Scherrer, S. F. Vissing, R. A. Lange, N. Johnson, W. S. Ring, P. S. Rahko, P. Hanson, and R. G. Victor.** Relative contributions of cardiopulmonary and sinoaortic baroreflexes in causing sympathetic activation in the human skeletal muscle circulation during orthostatic stress. *Circ. Res.* 73: 367–378, 1993.
4. **Johnson, J. M., and D. W. Proppe.** Cardiovascular adjustments to heat stress. In: *Handbook of Physiology. Environmental Physiology*. Bethesda, MD: Am. Physiol. Soc., 1996, sect. 4, vol. I, chapt. 11, p. 215–243.
5. **Johnson, J. M., L. B. Rowell, M. Niederberger, and M. M. Eisman.** Human splanchnic and forearm vasoconstrictor responses to reduction of right atrial and aortic pressures. *Circ. Res.* 34: 515–524, 1974.
6. **Kenney, M. J., C. C. Barney, T. Hirai, and C. V. Gisolfi.** Sympathetic nerve responses to hyperthermia in the anesthetized rat. *J. Appl. Physiol.* 78: 881–889, 1995.
7. **Lacolley, P. J., B. M. Pannier, M. A. Slama, J. L. Cucho, A. P. G. Hoeks, S. Laurent, G. M. London, and M. E. Safar.** Carotid arterial haemodynamics after mild degrees of lower-body negative pressure in man. *Clin. Sci.* 83: 535–540, 1992.
8. **Mano, T., S. Iwase, Y. Yamazaki, and M. Saito.** Sympathetic nervous adjustments in man to simulated weightlessness induced by water immersion. *Sangyo Ika Daigaku Zasshi* 7, Suppl.: 215–227, 1985.
9. **Minson, C. T., S. L. Wladkowski, A. F. Cardell, J. A. Pawelczyk, and W. L. Kenney.** Age alters cardiovascular response to direct passive heating. *J. Appl. Physiol.* 84: 1323–1332, 1998.
10. **Nagaya, K., F. Wada, S. Nakamitsu, S. Sagawa, and K. Shiraki.** Responses of the circulatory system and muscle sympathetic nerve activity to head-down tilt in humans. *Am. J. Physiol. Regulatory Integrative Comp. Physiol.* 268: R1289–R1294, 1995.
11. **Niimi, Y., T. Matsukawa, Y. Sugiyama, A. S. M. Shamsuzzaman, H. Ito, G. Sobue, and T. Mano.** Effect of heat stress on muscle sympathetic nerve activity in humans. *J. Auton. Nerv. Syst.* 63: 61–67, 1997.
12. **Pawelczyk, J. A., and B. D. Levine.** Cardiovascular responses to rapid volume infusion, the human Bainbridge reflex (Abstract). *Circulation* 92, Suppl. I: 656, 1995.
13. **Rowell, L. B.** Thermal stress. In: *Human Circulation Regulation During Physical Stress*, New York: Oxford Univ. Press, 1986, p. 174–212.
14. **Rowell, L. B., G. L. Brengelmann, and J. A. Murray.** Cardiovascular responses to sustained high skin temperature in resting man. *J. Appl. Physiol.* 27: 673–680, 1969.
15. **Rowell, L. B., J. R. Detry, G. R. Profant, and C. Wyss.** Splanchnic vasoconstriction in hyperthermic man—role of falling blood pressure. *J. Appl. Physiol.* 31: 864–869, 1971.
16. **Sundlöf, G., and B. G. Wallin.** Effect of lower body negative pressure on human muscle nerve sympathetic activity. *J. Physiol. (Lond.)* 278: 525–556, 1978.
17. **Taylor, J. A., J. R. Halliwill, T. E. Brown, J. Hayano, and D. L. Eckberg.** “Non-hypotensive” hypovolaemia reduces ascending aortic dimensions in humans. *J. Physiol. (Lond.)* 483: 289–298, 1995.
18. **Vallbo, A. B., K. E. Hagbarth, T. E. Torebjork, and B. G. Wallin.** Somatosensory, proprioceptive, and sympathetic activity in human peripheral nerves. *Physiol. Rev.* 59: 919–957, 1979.
19. **Wallin, B. G., and J. Fagius.** Peripheral sympathetic neural activity in conscious humans. *Ann. Rev. Physiol.* 50: 565–576, 1988.