

# Phenylephrine-induced elevations in arterial blood pressure are attenuated in heat-stressed humans

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Received 3 April 2002; accepted in final form 12 August 2002

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Phenylephrine-induced elevations in arterial blood pressure are attenuated in heat-stressed humans. *Am J Physiol Regul Integr Comp Physiol* 283: R1221–R1226, 2002. First published August 15, 2002; 10.1152/ajpregu.00195.2002.—To test the hypothesis that phenylephrine-induced elevations in blood pressure are attenuated in heat-stressed humans, blood pressure was elevated via steady-state infusion of three doses of phenylephrine HCl in 10 healthy subjects in both normothermic and heat stress conditions. Whole body heating significantly increased sublingual temperature by  $\sim 0.5^{\circ}\text{C}$ , muscle sympathetic nerve activity (MSNA), heart rate, and cardiac output and decreased total peripheral vascular resistance (TPR; all  $P < 0.005$ ) but did not change mean arterial blood pressure (MAP;  $P > 0.05$ ). At the highest dose of phenylephrine, the increase in MAP and TPR from pre-drug baselines was significantly attenuated during the heat stress [ $\Delta\text{MAP } 8.4 \pm 1.2$  mmHg;  $\Delta\text{TPR } 0.96 \pm 0.85$  peripheral resistance units (PRU)] compared with normothermia ( $\Delta\text{MAP } 15.4 \pm 1.4$  mmHg,  $\Delta\text{TPR } 7.13 \pm 1.18$  PRU; all  $P < 0.001$ ). The sensitivity of baroreflex control of MSNA and heart rate, expressed as the slope of the relationship between MSNA and diastolic blood pressure, as well as the slope of the relationship between heart rate and systolic blood pressure, respectively, was similar between thermal conditions (each  $P > 0.05$ ). These data suggest that phenylephrine-induced elevations in MAP are attenuated in heat-stressed humans without affecting baroreflex control of MSNA or heart rate.

baroreflex sensitivity; vasoconstrictor agents; muscle sympathetic nerve activity; heart rate; whole body heating

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EXPOSURE OF HUMANS to hyperthermic conditions leads to increases in skin blood flow, splanchnic and renal vascular resistances, heart rate, and cardiac output, while decreasing total peripheral resistance (TPR; Refs. 10, 21). These combined responses result in little or no change in mean arterial blood pressure (MAP), accompanied with pronounced decreases in central venous filling pressure (5, 17, 23).

Humans become more susceptible to fainting during orthostatic stress and gravitation acceleration when combined with heat stress (1, 14, 34). A possible mechanism leading to heat-induced reductions in orthostatic tolerance is impaired baroreflex responsiveness.

However, we 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, 35) or during acute changes in arterial blood pressure (7, 36). Moreover, the gain expressing the relationship between blood pressure and muscle sympathetic nerve activity (MSNA) was unaffected by whole body heating (7). In contrast, we reported that whole body heating impairs carotid baroreflex regulation of blood pressure (4), as well as reduces the transfer function gain of the relationship between spontaneous blood pressure and heart rate within the high-frequency range (6). Thus the effects of whole body heating on baroreflex function in humans may depend on the baroreceptor population assessed and/or the method of assessing baroreflex function.

Sympathetic neural outflow plays a pivotal role in blood pressure control via baroreflexes. Sympathetic adrenergic nerves release norepinephrine, which causes vasoconstriction and subsequent increases in blood pressure. In the heated human, observations of a decrease in the maximal gain of carotid-vasomotor responses (4) with no change in the sensitivity of baroreflex control of MSNA (7) suggest that whole body heating may impair vasoconstrictor responses via altered postsynaptic events. In support of this hypothesis, pressor responses and mesenteric vascular resistance to constant and bolus infusions of adrenergic agonists were impaired in heat-stressed anesthetized (12, 15) and conscious (16) rats. Moreover, both whole body heating and local surface heating attenuate cutaneous  $\alpha$ -adrenergic vasoconstriction responsiveness in human nonglabrous skin (33). Taken together, these studies suggest that postsynaptic vascular responses to  $\alpha$ -adrenergic agonists may be impaired by elevations in internal temperature in humans, which could contribute to reduced orthostatic tolerance independent of baroreflex-mediated neural responses. Therefore, the objective of this study was to test the hypothesis that steady-state phenylephrine-induced elevations in blood pressure are attenuated in heat-stressed humans.

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## METHODS

**Subjects.** Ten subjects (7 men and 3 women) participated in this study. The subjects' average age was  $30 \pm 2$  yr, and all were of normal height ( $171.8 \pm 2.4$  cm), weight ( $71.5 \pm 3.3$  kg), and health. A written informed consent from each subject was obtained before participation in this institutionally approved study.

**Instrumentation.** Each subject was instrumented for the measurement of sublingual temperature ( $T_{sl}$ ) with a thermistor placed in the sublingual sulcus. Mean skin temperature ( $T_{sk}$ ) was obtained from the electrical average of six thermocouples attached to the skin (27). The subject was dressed in a tube-lined suit that permitted control of  $T_{sk}$  by changing the temperature of the water perfusing the suit. Heart rate was obtained from the electrocardiogram signal interfaced with a cardiometer (CWE, Ardmore, PA). Arterial blood pressure was measured from the upper arm via electrophygmomanometry (SunTech, Raleigh, NC). This technique involves placing a microphone over the brachial artery to gate Korotkoff sounds to the electrocardiogram. Respiratory excursions were monitored from a piezoelectric respiration transducer (Pneumotrace, Morro Bay, CA). Impedance cardiograph and phonocardiography (models EBI 100C and DA 100, Biopac System, Santa Barbara, CA) were used to measure transthoracic impedance ( $Z_o$ ) and left ventricular ejection time for the estimation of stroke volume. This noninvasive method to measure stroke volume has been widely used under both normothermic and heat stress conditions (3, 11, 13, 19). Forearm skin blood flow was indexed by laser-Doppler flowmetry (Perimed, North Royalton, OH) from an area not covered by the tube-lined suit. Forearm sweat rate was measured via capacitance hygrometry (Visala, Woburn, MA) as previously described (32).

Postganglionic MSNA was recorded from a peroneal nerve. This was accomplished by inserting a tungsten microelectrode with an uninsulated tapered tip of 1–5  $\mu\text{m}$  (FHC, Bowdoinham, ME) into the peroneal nerve, dorsal to the fibular head. A second uninsulated reference electrode was positioned within 3 cm of the recording electrode. The signal was amplified 30,000–70,000 and passed through a band-pass filter (500–5,000 Hz; Iowa Bioengineering, Iowa City, IA). The filtered neurogram was rectified and integrated (0.1-s time constant) and displayed on an oscilloscope. 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 (29). 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) nonresponsive to sound stimulation.

**Protocol.** Under both normothermic and heat-stressed conditions, phenylephrine HCl was infused intravenously at doses of 0.5, 1.0, and 1.5  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ . Each dose was infused for 5 min. Arterial blood pressure was measured during the 3rd and final min of each stage. After normothermic data collection and subsequent return of arterial blood pressure to predrug levels,  $T_{sk}$  was increased to  $\sim 38^\circ\text{C}$  by perfusing the tube-lined suit with  $46^\circ\text{C}$  water. Once  $T_{sl}$  increased  $\sim 0.5$ – $0.7^\circ\text{C}$ , the temperature of the water was reduced to  $44$ – $45^\circ\text{C}$  in an attempt to reduce the rate of rise of internal temperature during drug infusion. The aforementioned phenylephrine dosing regimen was then repeated with the subject in a heat stress condition. The average interval between phenylephrine infusion trials was 42 min.

After the hyperthermic trial, the subject's thermal status was then returned to normothermic conditions by perfusing cool water through the water-perfused suit. A 3-cm-diameter heater element (Perimed, North Royalton, OH), which housed the laser-Doppler flow probe, was then engaged to elevate local skin temperature to  $42^\circ\text{C}$ . Local temperature was held at this level for 30 min to elicit maximal cutaneous vasodilation (28). Skin blood flow was then normalized relative to maximal vasodilation for each site.

**Data analysis.** Data were sampled at 200 Hz via a data-acquisition system (Biopac System). 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 software program that identified bursts based on fixed criteria, including an appropriate latency after the R-wave of the electrocardiogram and a signal-to-noise ratio of  $\geq 3:1$  (7–9). MSNA bursts were counted during the last 2 min of each infusion stage, and the burst rate was calculated both as burst number per minute and as burst number per 100 heart beats. Burst frequency of the MSNA signal was analyzed as opposed to total activity given the long duration between phenylephrine challenges and the occurrence at which the needle needed to be adjusted during this period, thereby making comparisons of MSNA total activity between thermal conditions inappropriate. The averaged value of the two blood pressure measurements for each dose of phenylephrine was used for the statistical analysis. MAP was calculated as diastolic blood pressure plus one-third pulse pressure. Mean beat-by-beat heart rate for the last 2 min of each infusion stage was identified and used for the statistical analysis. Stroke volume was calculated from the change in thoracic impedance using the following equation (13):  $SV = \rho \cdot (L/Z_o)^2 \cdot (dZ/dt) \cdot T$ , where  $\rho$  is a constant,  $L$  is the distance between the two inner pair electrodes,  $Z_o$  is the total impedance of the thorax,  $(dZ/dt)$  is the differential of  $\Delta Z$ , and  $T$  is the left ventricular ejection time obtained from the heart sounds. Average stroke volume during the last 2 min of each infusion stage was calculated. Cardiac output was obtained as the product of stroke volume and heart rate during that 2-min period. TPR was calculated from the ratio of MAP to cardiac output and is expressed in peripheral resistance units (PRU). Total peripheral conductance (TPC) was calculated from the ratio of cardiac output to MAP and is expressed in peripheral conductance units (U). Given the hyperbolic relationship between TPR and TPC (18), coupled with the change in baseline TPR during heating, the effect of phenylephrine administration on both TPR and TPC was analyzed.

The sensitivity of arterial baroreflex control of MSNA was identified from the linear relationship between MSNA burst rate and diastolic pressure during baseline and from data during the last 2 min of each stage of phenylephrine infusion. Diastolic blood pressure was used because MSNA correlates closely with diastolic pressure, but not with systolic pressure (26). If MSNA bursts were absent at higher doses of phenylephrine, those "saturation" data points were not used in the linear regression when calculating baroreflex sensitivity. Baroreflex modulation of heart rate was identified from the slope of the relationship between heart rate and systolic blood pressure during the baseline and the last 2 min of each dose of phenylephrine.

Statistical analyses were performed using commercially available software (SigmaStat 2.03). The effects of heat stress on thermoregulatory parameters and baroreflex gains, compared with normothermia, were analyzed via paired *t*-tests. Differences in phenylephrine-induced responses during normothermic and heat stress trials were evaluated via post

hoc analysis after repeated-measures two-way ANOVA. Differences in hemodynamic responses within normothermic and heat stress trials were evaluated using repeated-measures ANOVA. All values are reported as means  $\pm$  SE. *P* values of  $<0.05$  were considered statistically significant.

## RESULTS

After whole body heating,  $T_{sl}$  increased  $\sim 0.5^{\circ}\text{C}$ . Whole body heating increased heart rate, cardiac output, MSNA, skin blood flow, and sweat rate, while TPR decreased (Table 1). MAP did not change significantly due to whole body heating. Neither  $T_{sk}$  nor  $T_{sl}$  changed significantly during the period of phenylephrine infusion in either normothermic or heat stress conditions (Table 2). Changes in respiratory frequency or depth were not observed during heat stress or drug infusion.

Steady-state infusion of phenylephrine elicited significant and sequential increases in MAP in both thermal conditions (Fig. 1, all  $P < 0.005$ ). However, the elevation in MAP at infusion rates of 1.0 and 1.5  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  during the heat stress was significantly less relative to the elevation in MAP for those doses under normothermic conditions. At the highest dose of phenylephrine, blood pressure increased  $15.4 \pm 1.4$  mmHg under normothermic conditions and  $8.4 \pm 1.2$  mmHg under heat-stressed conditions ( $P < 0.05$  between thermal conditions). The elevation in blood pressure caused a reflex-induced decrease in heart rate (Table 2, all  $P < 0.05$ ) and MSNA (Fig. 2, all  $P < 0.01$ ) relative to baseline in both thermal conditions. The elevation in TPR during drug infusion was significantly greater under normothermic conditions compared with the heat stress condition (Fig. 3,  $P < 0.001$ ). When the data were expressed as TPC, the decrease in TPC during drug infusion under heat stress condition was also significantly attenuated compared with the normothermic conditions ( $P < 0.05$ ). Thus, despite the

Table 2. Hemodynamic and thermal responses during phenylephrine infusion under both thermal conditions

|                               | Baseline       | Phenylephrine, $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ |                  |                  |
|-------------------------------|----------------|---|------------------|------------------|
|                               |                | 0.5   | 1.0              | 1.5              |
| <i>Normothermia</i>           |                |   |                  |                  |
| $T_{sk}$ , $^{\circ}\text{C}$ | $34.1 \pm 0.1$ | $34.1 \pm 0.1$  | $34.0 \pm 0.1$   | $34.0 \pm 0.1$   |
| $T_{sl}$ , $^{\circ}\text{C}$ | $36.6 \pm 0.1$ | $36.6 \pm 0.1$  | $36.5 \pm 0.1$   | $36.6 \pm 0.1$   |
| HR, beats/min                 | $55.8 \pm 1.8$ | $50.1 \pm 1.3^*$  | $46.2 \pm 1.0^*$ | $43.3 \pm 0.9^*$ |
| CO, l/min                     | $5.3 \pm 0.3$  | $4.8 \pm 0.3$   | $4.5 \pm 0.3^*$  | $4.5 \pm 0.3^*$  |
| <i>Heat stress</i>            |                |   |                  |                  |
| $T_{sk}$ , $^{\circ}\text{C}$ | $37.4 \pm 0.1$ | $37.3 \pm 0.2$  | $37.3 \pm 0.2$   | $37.3 \pm 0.1$   |
| $T_{sl}$ , $^{\circ}\text{C}$ | $37.1 \pm 0.1$ | $37.1 \pm 0.1$  | $37.1 \pm 0.1$   | $37.2 \pm 0.1$   |
| HR, beats/min                 | $76.1 \pm 3.0$ | $72.7 \pm 2.5^*$  | $71.5 \pm 2.6^*$ | $69.5 \pm 1.9^*$ |
| CO, l/min                     | $6.3 \pm 0.6$  | $6.3 \pm 0.5$   | $6.4 \pm 0.5$    | $6.4 \pm 0.5$    |

Values are means  $\pm$  SE. CO was estimated using the impedance method. \*Significantly different from baseline ( $P < 0.05$ ).

hyperbolic relationship between TPR and TPC, phenylephrine-induced responses in both TPR and TPC were attenuated under heat stress conditions compared with normothermia. Cardiac output decreased during the infusion of phenylephrine at rates of 1.0 and 1.5  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  in normothermia but did not change at any dose during the heat stress trial (Table 2).

The average slope of the relation between MSNA and diastolic blood pressure during the heat stress ( $-1.77 \pm 0.31$  bursts $\cdot\text{min}^{-1}\cdot\text{mmHg}^{-1}$ ) was not different from that during normothermia ( $-1.26 \pm 0.31$  bursts $\cdot\text{min}^{-1}\cdot\text{mmHg}^{-1}$ ,  $P = 0.10$ ). However, the baroreflex curve was shifted upward before drug delivery by the heat stress as evidenced by a significant increase in MSNA without a change in blood pressure (see Table 1). When MSNA was expressed as bursts per 100 heart beats, the slope of the relationship between diastolic blood pressure and MSNA was also not affected by the heat stress (normothermia:  $-2.12 \pm 0.48$

Table 1. Thermal and hemodynamic responses to the heat stress

|  | Normothermia        | Heat Stress           |
|--|---------------------|-----------------------|
| $T_{sl}$ , $^{\circ}\text{C}$                          | $36.6 \pm 0.1$      | $37.1 \pm 0.1^*$      |
| $T_{sk}$ , $^{\circ}\text{C}$                          | $34.1 \pm 0.1$      | $37.4 \pm 0.1^*$      |
| MAP, mmHg  | $86 \pm 2$          | $82 \pm 2$            |
| HR, beats/min  | $56 \pm 2$          | $76 \pm 3^*$          |
| MSNA, bursts/min                                       | $13 \pm 2$          | $22 \pm 3^*$          |
| CO, l/min  | $5.3 \pm 0.3$       | $6.3 \pm 0.6^*$       |
| TPR, PRU   | $16.8 \pm 1.3$      | $14.2 \pm 1.4^*$      |
| TPC, U   | $0.0619 \pm 0.0038$ | $0.0774 \pm 0.0077^*$ |
| SBF, %max  | $10.5 \pm 1.3$      | $45.8 \pm 4.8^*$      |
| SR, $\text{mg}\cdot\text{cm}^{-2}\cdot\text{min}^{-1}$ | $0.040 \pm 0.004$   | $0.647 \pm 0.142^*$   |

Values are means  $\pm$  SE. Reported data are baseline values before phenylephrine administration. Mean arterial blood pressure (MAP) was calculated as diastolic blood pressure plus one-third pulse pressure. Skin blood flow (SBF) was normalized relative to maximum skin blood flow and is expressed as percentage of maximum (%max). Cardiac output (CO) was estimated using the impedance method.  $T_{sl}$ , sublingual temperature;  $T_{sk}$ , mean skin temperature; HR, heart rate; MSNA, muscle sympathetic nerve activity; TPR, total peripheral vascular resistance; PRU, peripheral resistance unit; TPC, total peripheral vascular conductance; SR, sweat rate. \*Significantly different from normothermia ( $P < 0.05$ ).

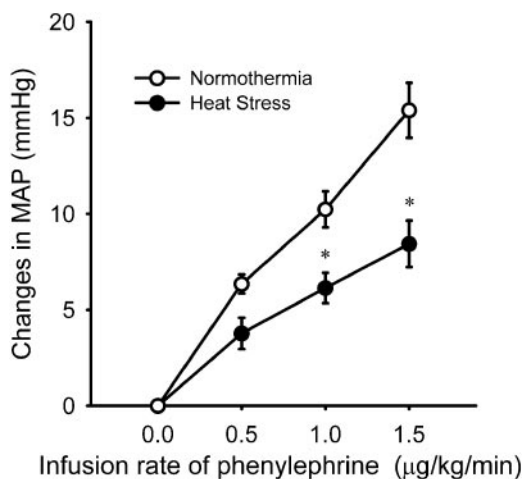


Fig. 1. Effect of whole body heating on changes in mean arterial blood pressure (MAP) in response to steady-state infusion of 0.5, 1.0, and 1.5  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  phenylephrine. Values are reported as a change from baseline during normothermic and heat-stressed conditions. Refer to Table 1 for baseline responses. \* $P < 0.05$  compared with normothermia.

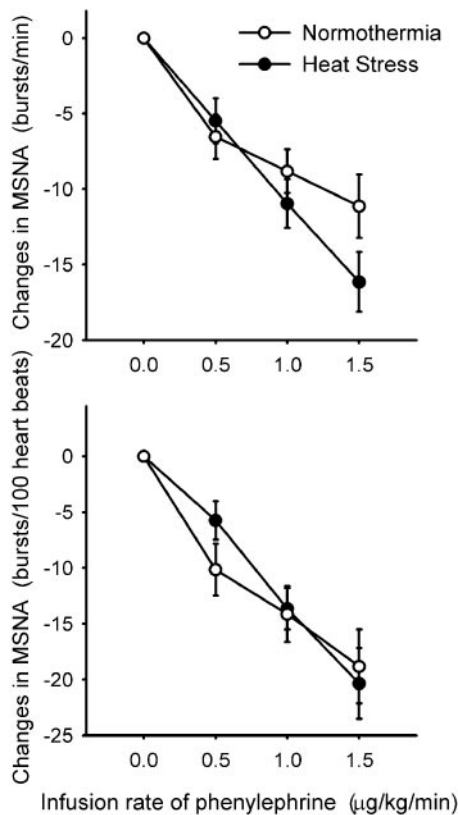


Fig. 2. Effect of whole body heating on changes in muscle sympathetic nerve activity (MSNA) in response to steady-state infusion of 0.5, 1.0, and 1.5  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  phenylephrine. Values are reported as a change from baseline during normothermic and heat-stressed conditions. MSNA is expressed both as bursts per min and bursts per 100 beats. Refer to Table 1 for baseline responses. The elevation in blood pressure due to phenylephrine infusion induced significant decreases in MSNA relative to baselines in both thermal conditions (all  $P < 0.01$ ), while the decrease in MSNA was similar between thermal conditions.

bursts $\cdot$ 100 beats $^{-1}\cdot$ mmHg $^{-1}$ , heat stress:  $-2.46 \pm 0.46$  bursts $\cdot$ 100 beats $^{-1}\cdot$ mmHg $^{-1}$ ,  $P = 0.54$ ). The slope of the change in heart rate relative to the change in systolic blood pressure during the heat stress ( $-0.48 \pm 0.21$  beats $\cdot$ min $^{-1}\cdot$ mmHg $^{-1}$ ) was also not significantly different from that during normothermia ( $-0.55 \pm 0.09$  beats $\cdot$ min $^{-1}\cdot$ mmHg $^{-1}$ ,  $P = 0.71$ ). The curve expressing this relationship was also shifted upward during the heat stress as evidenced by an increase in heart rate without a change in blood pressure (see Table 1).

## DISCUSSION

The purpose of this study was to identify the effects of whole body heating on hemodynamic responses to steady-state phenylephrine infusion in humans. The major finding of this study is that phenylephrine-induced elevations in blood pressure are attenuated in heat-stressed humans. Moreover, whole body heating also reduced phenylephrine-induced elevations in TPR. Although similar findings have been identified in rats (12, 15, 16), to our knowledge these findings have not previously been identified in humans. Similar to our prior findings (7), the gains of baroreflex control of

MSNA and heart rate are not changed after whole body heating. Taken together, these observations support the hypothesis that postsynaptic  $\alpha$ -adrenergic-mediated vasoconstriction is impaired in heat-stressed humans, and this impairment may attenuate the elevation in vascular resistance during orthostasis in this thermal condition, leading to reduced tolerance to orthostatic stress.

Similar to the present findings, the elevation in blood pressure in hyperthermic rats during administration of  $\alpha$ -adrenergic agonists was attenuated compared with when the rats were normothermic (12, 15, 16). However, in those studies attenuated vasoconstrictor responses were observed only after internal temperature of the rats was  $\geq 41^\circ\text{C}$ , which is in contrast to the moderate increase in internal temperature (i.e.,  $\sim 0.5^\circ\text{C}$ ) in the present study. Less consistent are the effects of heating on vasoconstrictor responsiveness in isolated vessels of animals. For example, in isolated dog saphenous veins and isolated rabbit ear veins and arteries, vasoconstrictor responsiveness to  $\alpha$ -adrenergic agents was reduced when the vessels were heated (2, 20, 30, 31). On the other hand, in isolated rat mesenteric arteries, others have shown no effect of

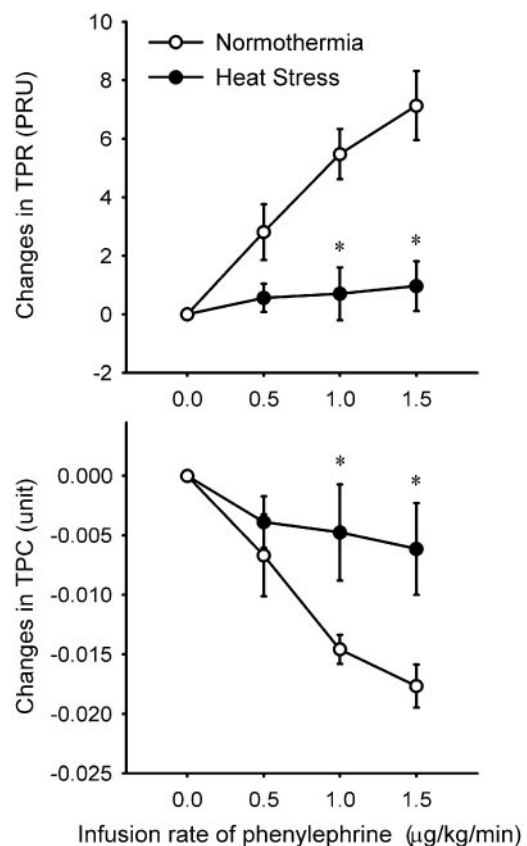


Fig. 3. Effect of whole body heating on changes in total peripheral vascular resistance (TPR) and total peripheral vascular conductance (TPC) in response to steady-state infusion of 0.5, 1.0, and 1.5  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  phenylephrine. Values are reported as a change from baseline during normothermic and heat-stressed conditions. PRU, peripheral resistance unit. Refer to Table 1 for baseline responses. \* $P < 0.05$  compared with normothermia.

heating on vasoconstrictor responsiveness to adrenergic agonists (15, 24). Differences in species and harvested vessels likely contribute to differences seen between these studies.

The vascular bed(s) affected by heating leading to impaired vasoconstrictor responses in humans remains unknown. Previously we (33) reported that vasoconstrictor responses to microdialysis administration of norepinephrine in human skin were significantly attenuated during both local heating and indirect whole body heating (i.e., heating the core but not the area of skin blood flow measurement). Thus it is possible that reduced elevations in vascular resistance and blood pressure to systemic phenylephrine administration in heated subjects may be due to reduced cutaneous vasoconstrictor responsiveness to this drug. Alternatively, because whole body heating increases splanchnic, renal, and muscle vascular resistances (17, 22), increases in vascular resistances of these vascular beds would theoretically reduce the reserve to further vasoconstriction during phenylephrine administration. Thus another possible mechanism for the attenuated elevation in TPR and MAP during phenylephrine administration during the heat stress is an attenuated increase in vascular resistance in the splanchnic, renal, and muscle beds compared with normothermia. Finally, changes in vascular smooth muscle contractility with increasing smooth muscle temperature (2, 30, 31) may lead to blunted hemodynamic response observed in this study.

Maintenance of baroreflex control of MSNA and heart rate during steady-state increases in blood pressure during the heat stress is consistent with our prior study (7) in which blood pressure was acutely decreased and increased via bolus infusions of nitroprusside and phenylephrine, respectively. In that study (7), baroreflex gains were assessed via beat-by-beat analysis, whereas baroreflex gains in the present study were evaluated from steady-state responses. Nevertheless, despite whether pharmacologically induced changes in blood pressure are sustained or acute, whole body heating does not alter baroreflex modulation of MSNA or heart rate. Moreover, these and other studies (4, 7, 36) clearly demonstrate that whole body heating in humans shifts the curves expressing baroreflex modulation of MSNA and heart rate to accommodate heat stress-induced elevations of these variables.

Orthostatic tolerance is reduced in humans when internal temperature is elevated (1, 14, 34). Less clear is the mechanism for this reduction in tolerance. Present and prior findings indicate that baroreflex regulation of heart rate and MSNA is generally preserved during whole body heating in humans (4, 7, 36). Data from the present investigation suggest that impaired postsynaptic responses to adrenergic agents may contribute to reducing orthostatic tolerance in hyperthermic conditions. Thus, despite appropriate MSNA responses (and presumably norepinephrine release) to an orthostatic stress, impaired vasoconstrictor responses to that release of norepinephrine may con-

tribute to reduced orthostatic tolerance observed during a heat stress.

**Study limitations.** Cardiac output, TPR, and TPC were estimated with thoracic impedance using the Kubicek equation (13). This method of estimating cardiac output has previously been used under heat-stressed condition (11, 19). We recognize that this method of cardiac output measurement, and thus the calculation of TPR and TPC, has a number of limitations. Importantly, we feel that the change in cardiac output, and thus the change in TPR, during drug administration can be estimated using thoracic impedance. Nevertheless, potential errors associated with the thoracic impedance method in estimating cardiac output, TPR, and TPC do not affect the primary finding that the elevation in MAP is significantly attenuated when phenylephrine is administered under hyperthermic conditions.

To obtain steady-state blood pressure responses, each dose of phenylephrine was infused for 5 min. Baroreflex gains were evaluated during the last 2 min of each infusion stage. We recognize the potential for baroreceptor resetting during this prolonged period of blood pressure elevation relative to protocols in which phenylephrine is infused via bolus injections (7). Nevertheless, the present observation that heat stress does not cause a significant change in baroreflex gain is consistent with previous findings (4, 7, 36), one of which used bolus injections of phenylephrine (7).

The average interval between phenylephrine infusion trials was 42 min. Blood pressure returned to predrug levels within 5–10 min after the end of phenylephrine infusion. This observation, coupled with findings that there were no differences in the increase in blood pressure in response to repeated phenylephrine challenges separated by 30 min (25), suggests that the first infusion of phenylephrine did not affect the responses of the second infusion. Therefore, the blunted increase in blood pressure during the heat stress phenylephrine challenge was due to factors associated with the heat stress and not due to repeated phenylephrine infusion challenges.

**Conclusion.** The present results show that phenylephrine-induced elevations in MAP and TPR are attenuated in heat-stressed humans without affecting baroreflex control of MSNA or heart rate. Taken together, these data suggest that altered vasoconstrictor responsiveness to  $\alpha$ -adrenergic agents may contribute to reduced orthostatic tolerance observed in heat-stressed humans.

We express appreciation to B. D. Levine and N. Hodges for assistance with this project and to the subjects for willing participation in this project.

This research project was funded in part by National Aeronautics and Space Administration Grant NAG9-1033 and National Heart, Lung, and Blood Institute Grants HL-61388, HL-10488, and HL-67422.

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