Combined heat and mental stress alters neurovascular control in humans

Jenna C. Klein,1 Craig G. Crandall,2 R. Matthew Brothers,2 and Jason R. Carter1

1Department of Exercise Science, Health and Physical Education, Michigan Technological University, Houghton, Michigan; and 2Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital, Dallas, and Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas

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Klein JC, Crandall CG, Brothers RM, Carter JR. Combined heat and mental stress alters neurovascular control in humans. J Appl Physiol 109: 1880–1886, 2010. —This study examined the effect of combined heat and mental stress on neurovascular control. We hypothesized that muscle sympathetic nerve activity (MSNA) and forearm vascular responses to mental stress would be augmented during heat stress. Thirteen subjects performed 5 min of mental stress during normothermia (Tcore; 37 ± 0°C) and heat stress (38 ± 0°C). Heart rate, mean arterial pressure (MAP), MSNA, forearm vascular conductance (FVC; venous occlusion plethysmography), and forearm skin vascular conductance (SKVcf; via laser-Doppler) were analyzed. Heat stress increased heart rate, MSNA, SKVcf, and FVC at rest but did not change MAP. Mental stress increased MSNA and MAP during both thermal conditions; however, the increase in MAP during heat stress was blunted, whereas the increase in MSNA was accentuated, compared with normothermia (time × condition; P < 0.05 for both). Mental stress decreased SKVcf during heat stress but not during normothermia (time × condition, P < 0.01). Mental stress elicited similar increases in heart rate and FVC during both conditions. In one subject combined heat and mental stress induced presyncopal coupling with atypical blood pressure and cutaneous vascular responses. In conclusion, these findings indicate that mental stress elicits a blunted increase of MAP during heat stress, despite greater increases in total MSNA and cutaneous vasoconstriction. The neurovascular responses to combined heat and mental stress may be clinically relevant to individuals frequently exposed to mentally demanding tasks in hyperthermic environmental conditions (i.e., soldiers, firefighters, and athletes).

sympathetic nerve activity; arterial blood pressure; blood flow; vascular conductance; hyperthermia; mental arithmetic

SEVERAL POPULATIONS are at heightened risk to experience mental stress during hyperthermic conditions, including soldiers, firefighters, and athletes. It is unclear if the autonomic adjustments that occur independently during heat stress and mental stress are altered during combined exposure. Separately, both of these physiological stressors increase the prevalence of orthostatic intolerance (16, 20); thus examining neurovascular responses to combined heat and mental stress is clinically relevant. To date, neural and cardiovascular responses to mental stress and heat stress have been studied independently but not collectively.

The mechanism(s) underlying both mental and heat stress-induced orthostatic intolerance remain equivocal, but altered autonomic activity, and subsequent vascular responses, are believed to be primary contributors. Heat stress induces cutaneous vasoconstriction, which substantially decreases total peripheral resistance (25). However, increases in heart rate and accompanying increases in cardiac output during heat stress offset the reduction of total peripheral resistance (25). As a result, arterial blood pressure remains relatively constant during heat stress. A failure to adequately increase cardiac output during heat stress can result in reduced arterial blood pressure and compromised orthostatic tolerance.

In contrast to heat stress, mental stress elicits prompt and sustained increases in arterial blood pressure. This hypertensive response is accompanied by consistent increases in heart rate, vasodilation of the forearm muscle bed (2, 4), and variable muscle sympathetic nerve activity (MSNA) responses (10). The level of forearm vasodilation during mental stress appears to be dependent on the intensity of stress, with greater vasodilation during high levels of perceived stress (24). It is suspected that this paradoxical peripheral vasodilation may contribute to the syncpe associated with high levels of stress. Moreover, rapid reductions in heart rate are observed during presyncopal episodes associated with dramatic forearm vasodilation (3), suggesting neural and cardiovascular dysfunction may also contribute to mental stress-induced syncpe.

Therefore, the purpose of the present study was to examine neural and cardiovascular responses to combined heat and mental stress in humans. We hypothesize that combined heat and mental stress will elicit greater increases in MSNA and forearm vascular conductance than mental stress in normothermic conditions. An augmentation of forearm vasodilation during combined heat and mental stress would potentially render individuals more susceptible to syncopal episodes, whereas an augmentation of MSNA could have an opposite, or counteracting, influence. Such findings could be of particular interest to individuals exposed to mentally demanding tasks in hyperthermic environmental conditions.

METHODS

Subjects. Thirteen young, healthy subjects (6 men and 7 women; age 21 ± 1 yr, height 173 ± 3 cm, weight 74 ± 3 kg) participated in this study. All subjects were nonsmokers and had no history of asthma, diabetes, or cardiovascular disease. Female subjects were not taking oral contraceptives or other hormonal supplementation. Testing sessions for female subjects were not limited to a specific menstrual phase as recent work reports similar MSNA responses to mental stress during altered phases of the menstrual cycle (9). Subjects were asked to abstain from caffeine, alcohol, and exercise for 12 h before testing. All subjects signed an informed consent that was approved by the Michigan Technological University Institutional Review Board and conformed to the provisions of the Declaration of Helsinki.

Experimental design. Each subject participated in two trials: 1) a normothermic trial and 2) a heat stress trial. Trials were performed on the same day and were not randomized. The normothermic trial was always conducted first to ensure true normothermic readings as body temperature is slow to return to baseline after heat stress. Trials were
performed with the subject in the supine position and each consisted of a 5-min baseline, 5 min of mental arithmetic, and 5-min recovery. Mental arithmetic required subjects to subtract the number 6 or 7 from two- and three-digit numbers. The number being subtracted was randomized for the normothermic trial (i.e., number 6 or 7), and the remaining number was used during the heat stress trial. Body temperature was controlled by manipulating the temperature of water perfusing a tube-lined suit worn by the subject. Following the normothermic trial, the heating process was initialized. The water temperature was controlled by manipulating the temperature of water remaining in the suit. The number of cycles performed with the subject in the supine position and each consisted of a 5-min baseline, 5 min of mental arithmetic, and 5-min recovery. 

Measurements. Heart rate was recorded continuously via a three-lead electrocardiogram. Arterial blood pressures were obtained using two separate techniques. Three consecutive readings of supine arterial blood pressure were taken with an automated sphygmomanometer immediately before the normothermic and heat stress trials (Omron HEM-907XL, Omron Health Care, Vernon Hills, IL). In addition, beat-to-beat arterial blood pressure was monitored continuously throughout the experiment using a Finometer (Finapres Medical Systems, Amsterdam, The Netherlands). Baseline arterial blood pressure measured via the Finometer during both normothermia and heat stress was corrected using the respective supine blood pressure readings taken from the automated sphygmomanometer. Arterial blood pressures are expressed as systolic (SAP), diastolic (DAP), and mean (MAP) arterial pressures.

Direct recordings of MSNA were obtained using microneurography. Briefly, a tungsten microelectrode (Frederick Haer, Bowdoinham, ME) was inserted into the peroneal nerve located in the popliteal region behind the right knee, while a reference electrode was inserted subcutaneously 2–3 cm from the microneurography electrode. Quality MSNA recordings were considered to be spontaneous, pulse-synchronous bursts that remained unchanged when stimulated by auditory arousal or stroking of the skin.

Forearm blood flow (FBF) was measured using venous occlusion plethysmography (Hokanson, Bellevue, WA), while forearm skin blood flow (SkBFf) was measured using laser-Doppler flowmetry (MoorLAB Laser-Doppler Perfusion Monitor, Moor Instruments, Wilmington, DE). FBF and SkBFf were measured on opposite arms, with SkBFf being measured on the arm with continuous recordings of the microelectrode. MSNA was expressed as bursts per minute and total MSNA (i.e., the sum of the normalized burst areas). SkBFf can be meaningfully compared between thermal conditions, which were separated by ~45 min and often required slight readjustment of the microelectrode. MSNA was expressed as bursts per minute and total MSNA (i.e., the sum of the normalized burst areas).

Statistical analysis. All data were analyzed statistically using commercial software (SPSS 16.0, SPSS, Chicago, IL). A two-way repeated-measures ANOVA was used to determine if changes in heart rate, MAP, MSNA, FVC, and SkVCf occurred during mental stress (baseline vs. each minute of mental stress) and across trials (normothermia vs. heat stress). Post hoc analyses were performed using the least significant differences test. Paired t-tests were used to compare baseline and recovery. Pearson correlations were utilized to probe relations between the changes in MSNA and hemodynamic/vascular responses to mental stress. Quality recordings of MSNA were obtained throughout both the normothermic and heat stress trials in eight subjects. All other variables were determined from 12 subjects (one subject became presyncopal during combined heat and mental stress and thus was excluded given the repeated-measures design). However, data from the presyncopal subject are relevant and presented separately. Thermal and hemodynamic variables during normothermic and heat stress baselines were compared using paired t-tests. Means were considered significantly different when $P < 0.05$. Data are expressed as 5-min average in RESULTS and minute-by-minute averages in figures. Results are expressed as means ± SE.

RESULTS

Mean baseline values during normothermia and heat stress are presented in Table 1. Diastolic blood pressure decreased in response to whole body heating, while MAP did not change. All other baseline values were significantly elevated during heat stress compared with normothermia. Core body temperature remained stable at 38.3°C throughout all 5 min of the combined heat and mental stress trial.

Figure 1 demonstrates that mental stress significantly increased MAP during both normothermic ($\Delta$14 ± 2 mmHg; $P < 0.001$) and heat stress ($\Delta$10 ± 2 mmHg; $P < 0.001$) trials.

### Table 1. Baseline values during heat stress and normothermia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normo</th>
<th>Heat</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP, mmHg</td>
<td>104 ± 3</td>
<td>113 ± 4*</td>
<td>0.003</td>
</tr>
<tr>
<td>DAP, mmHg</td>
<td>53 ± 2</td>
<td>47 ± 2*</td>
<td>0.002</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>70 ± 2</td>
<td>69 ± 2</td>
<td>0.457</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>66 ± 3</td>
<td>96 ± 4*</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>11 ± 3</td>
<td>31 ± 6*</td>
<td>0.005</td>
</tr>
<tr>
<td>MSNA, bursts/100 hb</td>
<td>18 ± 5</td>
<td>32 ± 5*</td>
<td>0.021</td>
</tr>
<tr>
<td>SkBFf, units</td>
<td>14 ± 2</td>
<td>101 ± 5*</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>SkVCf, units/mmHg</td>
<td>0.20 ± 0.02</td>
<td>1.46 ± 0.07*</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>FBF, units</td>
<td>3 ± 0</td>
<td>11 ± 1*</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>FVC, units/mmHg</td>
<td>0.04 ± 0.00</td>
<td>0.17 ± 0.02*</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>STTemp, °C</td>
<td>34.4 ± 0.2</td>
<td>38.7 ± 0.1*</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Core temp, °C</td>
<td>37.3 ± 0.0</td>
<td>36.3 ± 0.0*</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
</table>

Values are mean ± SE; $n = 12$ unless noted otherwise. SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial blood pressure; HR, heart rate; MSNA, muscle sympathetic nerve activity ($n = 10$); SkBFf, forearm skin blood flow; SkVCf, forearm skin vascular conductance; FBF, forearm blood flow (venous occlusion plethysmography); FVC, forearm vascular conductance; STTemp, skin temperature; Core temp, core body temperature; Normo, normothermia; Heat, heat stress; hb, heart beats. *Significantly different from corresponding normothermia value.
but MAP increases were blunted in the heat compared with normothermia (time × condition, $P < 0.02; n = 12$). Mental stress elicited similar increases in heart rate during both thermal conditions. Figure 2 demonstrates that mental stress increased total MSNA during both normothermia ($\Delta 1,025 \pm 549$ units; $P < 0.05$) and heat stress ($\Delta 4,668 \pm 1,224$ units; $P < 0.01$), but total MSNA increases were augmented during heat stress relative to normothermia (time × condition, $P < 0.01; n = 8$). Conversely, increases in MSNA burst frequency (bursts/min) were similar between conditions (Fig. 2). Perceived stress levels were significantly greater during combined heat and mental stress compared with mental stress during normothermia ($2.8 \pm 0.2$ vs. $2.2 \pm 0.2$ units; $P < 0.04$).

As expected, heat stress increased cutaneous blood flow and vascular conductance to the forearm (Fig. 3). Mental stress reduced SkVCF during heat stress ($\Delta -0.14 \pm 0.02$ units/mmHg; $P < 0.001$) but not normothermia ($\Delta -0.02 \pm 0.02$ units/mmHg; time × condition, $P > 0.05; n = 12$). Figure 4 demonstrates that heat stress also increased FBF and FVC measured via venous occlusion plethysmography. In contrast to the cutaneous vascular responses depicted in Fig. 3 (i.e., cutaneous vasoconstriction), mental stress increased FVC during both thermal conditions (i.e., forearm vasodilation). The magnitude of the mental stress-induced forearm vasodilatory responses was not different between heat stress and normothermia (time × condition, $P = 0.20$). The four subjects without MSNA data demonstrated similar hemodynamic and vascular responses to the eight subjects with complete MSNA data.

During normothermia, changes in total MSNA during mental stress were not correlated to changes in diastolic arterial pressure (DAP; $r = 0.01; P = 0.97$), SkVCF ($r = 0.11; P = 0.76$), or FVC ($r = -0.20; P = 0.57$). Likewise, changes in total MSNA during combined heat and mental stress were not correlated to changes in DAP ($r = 0.44; P = 0.27$), SkVCF ($r = 0.01; P = 0.98$), or FVC ($r = -0.32; P = 0.44$). Similar to total MSNA results, MSNA burst frequency responses to mental stress were not correlated to changes in DAP, SkVCF, or FVC regardless of thermal condition.

Figure 5 illustrates SkVCF for each subject during baseline and mental stress of normothermia and heat stress. The dashed line represents the subject who became presyncopal at the end of the mental stress period in the heat. Note that SkVCF increased during mental stress while heat stressed in this subject, while SkVCF decreased or remained unchanged in all other subjects. Additionally, this subject demonstrated a substantial reduction of baseline SAP during heat stress (120 to 92 mmHg), while the 12 nonpresyncopal subjects demonstrated a consistent increase of baseline SAP during heat stress (120 to 92 mmHg), whereas baseline MAP did not significantly change across thermal conditions in the 12 nonpresyncopal subjects (Table 1).

**DISCUSSION**

The present study examined neurovascular responses to combined heat and mental stress in healthy humans. The
results reveal two novel findings. First, heat stress blunted the typical increase of arterial blood pressure during mental stress. Second, this blunted pressor response was present despite cutaneous vasoconstriction of the forearm, a response not observed during normothermic conditions, and an augmented increase in total MSNA during mental stress. Additionally, one subject became presyncopal during combined heat and mental stress, and this individual was the only subject to demonstrate compromised resting arterial blood pressure and a mental stress-induced cutaneous vasodilation during heat stress. The altered neural and cardiovascular responses reported in the present study may render individuals more susceptible to syncopal episodes during combined mental and heat stress.

Fig. 3. Skin blood flow (SkBF) and vascular conductance (SkVC) to the forearm during 5 min of mental stress in normothermic and heat stress conditions \((n = 12)\). Heat stress increased absolute levels of SkBF and SkVC (top and middle panels, respectively). Mental stress elicited cutaneous vasoconstriction in the forearm during heat stress, but not during normothermia (bottom panel). \(\ast P < 0.05\) vs. corresponding normothermic value.

Fig. 4. Forearm blood flow (FBF) and vascular conductance (FVC) via venous occlusion plethysmography during 5 min of mental stress in normothermic and heat stress conditions \((n = 10)\). Heat stress increased absolute levels of FBF and FVC (top and middle panels, respectively). Mental stress elicited forearm vasodilation during both thermal conditions, and these responses were not statistically different from one another (bottom panel).
The present study reveals a blunted MAP response to mental stress during heat stress conditions. Because MAP is the product of cardiac output and total peripheral resistance, the blunted MAP response observed during combined heat and mental stress must be due to blunted increases in cardiac output and/or total peripheral resistance. We did not assess cardiac output, so we cannot rule out altered cardiac output as a contributing factor. However, it appears unlikely that a blunted cardiac output response is responsible for the blunted MAP response mainly because the subjects demonstrated similar increases in heart rate during mental stress in both thermal conditions; although this assumes similar stroke volume responses between trials.

In contrast, vascular data demonstrate patterns of vasoconstriction and vasodilation during combined heat and mental stress that may ultimately lead to a blunted increase of total peripheral resistance. Specifically, passive heat stress elicited profound forearm vasodilatation whether measured using venous occlusion plethysmography or in the cutaneous circulation using laser-Doppler. Interestingly, mental stress elicited cutaneous vasoconstriction of the forearm (measured via laser-Doppler) during heat stress, but not normothermia. In contrast, mental stress induced similar forearm vasodilation during both thermal conditions when examined using venous occlusion plethysmography. It is important to note that laser-Doppler flowmetry isolates the cutaneous vasculature, whereas venous occlusion plethysmography does not discriminate between cutaneous and muscular beds. Therefore, cutaneous vasoconstriction during combined heat and mental stress, together with similar whole forearm vasodilation, suggests that mental stress-induced forearm muscle vasodilation may be augmented during heat stress. We are careful not to overemphasize this interpretation as we recognize the limitations of venous occlusion plethysmography in a study in which there were pronounced vascular responses in both the skin and muscle beds. Nevertheless, the combined acquisition of laser-Doppler flowmetry and venous occlusion plethysmography warrants some inference regarding forearm muscle vasodilation during mental stress, which is well documented and suspected to be a primary contributor to stress-induced syncpe during normothermic conditions (2, 24).

In the present study, one subject became presyncopal during combined heat and mental stress. To our knowledge, this is the first documented hypotensive episode during combined heat and mental stress. Of interest, this individual was the only subject to demonstrate 1) forearm cutaneous vasodilation during mental stress in the heat stress trial and 2) a substantial drop in baseline systolic blood pressure during passive heat stress. In contrast, the nonpresyncopal subjects demonstrated a decrease (10 subjects) or no change (2 subjects) in forearm cutaneous vascular conductance during combined heat and mental stress, and an increase in baseline systolic blood pressure during passive heat stress. We recognize limitations associated with the presentation of this presyncopal subject. The abnormal cutaneous vasodilation response to mental stress and drop in systolic blood pressure at rest could be due to several factors not assessed, including a greater decrease in plasma volume, impaired cardiac function, decreased release of vasoconstricting hormones, etc. Nevertheless, regardless of the mechanism, it remains that combined heat and mental stress elicited a hypotensive episode in a subject with an abnormal systolic blood pressure response to heat stress and an abnormal cutaneous vasodilatory response to combined heat and mental stress. Perhaps cutaneous vasoconstriction during mental stress in the heat and/or a rise in baseline systolic blood pressure during heat stress are important in preserving central blood volume and preventing a precipitous drop in arterial blood pressure.

Mental stress elicits a variable MSNA response (10). Most studies report an increase in leg MSNA during mental stress, but some report no change or a decrease (1, 8, 10, 15). Furthermore, some report that mental stress increases or does not change MSNA depending on whether it is reported as burst frequency or total MSNA (17, 19, 27). The results from the present study also demonstrate differences in MSNA responses to mental stress when expressed as burst frequency or total MSNA. Specifically, mental stress elicited similar increases in MSNA burst frequency during each thermal condition, while total MSNA responses to mental stress were significantly augmented during heat stress compared with normothermia. The physiological significance of this augmented total MSNA is unclear, but it did not augment arterial blood pressure responses to mental stress. In fact, arterial blood pressure was blunted despite an augmented MSNA response, suggesting that the complex vascular responses to combined heat and mental stress are negating any potential enhancement of MSNA-mediated vasoconstriction. Alternatively, it is possible that without this augmented total MSNA response, the blunted MAP response to combined heat and mental stress would have been more dramatic.

The variable MSNA response to mental stress observed in the present study was further probed by examining relations between MSNA and hemodynamic/vascular responses. Our results demonstrate that regardless of thermal condition, no relations existed between changes in MSNA and changes in DAP, SkVCF, and FVC. Thus, despite an augmented total MSNA response to combined heat and mental stress, there
appears to be a disassociation between total MSNA and arterial blood pressure responses to mental stress during normothermia or heat. This suggests humans are capable of regulating arterial blood pressure via a variety of sympathetic neural and cardio-vascular strategies during heat and mental stress. These find-ings complement recent work focusing on the importance of interindividulal MSNA variability on both short- and long-term regulation of arterial blood pressure (18). Moreover, a recent study has demonstrated a variety of sympathetic neural re-sponses to orthostatically induced presyncope (12). Under-standing different “sympathetic” strategies could lend valuable insight into better understanding diseases such as hypertension and orthostatic hypotension.

Perceived stress levels were higher during combined heat and mental stress compared with the normothermic trial. We have previously demonstrated that perceived stress levels do not appear to influence MSNA responses to mental stress (7, 10), and thus the augmented total MSNA response during the combined trial is unlikely related to augmented perceived stress. However, perceived stress levels do appear to influence forearm vascular responses (24), suggesting that it is possible the altered vascular responses reported in this study were influenced by the increased perception of stress. It is important to note that previous studies have reported that multiple mental arithmetic trials within one study produce similar perceived stress levels (9, 11). In other words, there does not appear to be a noticeable learning effect, which is probably related to the randomization of the subtraction number. Therefore, the greater perceived stress levels during combined heat and mental stress is unlikely related to trial order (i.e., normothermic followed by heat stress). Moreover, previous heat stress studies have successfully employed the nonrandomized experimental approach used in the present study (5, 6, 14, 21, 22, 26, 28).

We recognize three limitations. First, the present study did not assess cardiac output. It was originally anticipated that the Finometer model flow technique would provide an index of cardiac output, but recent evidence has revealed this method of estimating cardiac output is compromised during heat stress (13). Second, we did not examine arm MSNA. Although this would have been a valuable addition, obtaining arm MSNA is technically challenging and success rates are substantially reduced compared with leg MSNA. Moreover, recent evidence suggests similar arm and leg MSNA responses to mental stress (8), although this remains debatable (1). Third, whereas the widely variable MSNA responses to mental stress between subjects (i.e., interindividul variability) are well documented (7, 8, 10), MSNA variability during mental stress within a subject (i.e., intraindividual variability) has not been specifically addressed. We cannot exclude the potential influence of intraindividual MSNA variability on our findings, but recent evidence demonstrates similar MSNA responses to mental stress separated by an 8-wk control period (23).

In conclusion, the present study demonstrates blunted MAP responses and variable vascular patterns during combined heat and mental stress. These findings could be of significant importance for individuals exposed to mental stress in hyper-thermic environments (i.e., firefighters, soldiers, athletes). If these individuals are unable to maintain MAP during heat stress to the same extent as in normothermic conditions, they may be at increased risk of experiencing orthostatic intolerance when faced with mentally taxing situations in heat-stressed conditions. The altered neurovascular responses during combined heat and mental stress demonstrated in the present study may provide mechanistic insight into this relationship.

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DISCLOSURES

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

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