Neurovascular responses to mental stress in the supine and upright postures

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Submitted 5 December 2007; accepted in final form 17 January 2008

Kuipers NT, Sauder CL, Carter JR, Ray CA. Neurovascular responses to mental stress in the supine and upright postures. J Appl Physiol 104: 1129–1136, 2008.—The purpose of this study was to determine neurovascular responses to mental stress (MS) in the supine and upright postures. MS was elicited in 23 subjects (26 ± 1 yr) by 5 min of mental arithmetic. In study 1 (n = 9), Doppler ultrasound was used to measure mean blood flow velocity in the renal (RBFV) and superior mesenteric arteries (SMBFV), and venous occlusion plethysmography was used to measure forearm blood flow (FBF). In study 2 (n = 14), leg blood flow (LBF; n = 9) was measured by Doppler ultrasound, and muscle sympathetic nerve activity (MSNA; n = 5) was measured by microneurography. At rest, upright posture increased heart rate and MSNA and decreased LBF, FBF, RBFV, and SMBFV and their respective conductances. MS elicited similar increases in mean arterial blood pressure (~12 mmHg) and heart rate (~17 beats/min), regardless of posture. MS in both postures elicited a decrease in RBFV, SMBFV, and their conductances and an increase in LBF, FBF, and their conductances. Changes in blood flow were blunted in the upright posture in all vascular beds examined, but the pattern of the vascular response was the same as the supine posture. MS did not change MSNA in either posture (change: ~1 ± 3 and ~3 ± 3 bursts/min, respectively). In conclusion, the augmented sympathetic activity of the upright posture does not alter heart rate, mean arterial blood pressure, or MSNA responses to MS. MS elicits divergent vascular responses in the visceral and peripheral vasculature. These results indicate that, although the upright posture attenuates vascular responses to MS, the pattern of neurovascular responses does not differ between postures.

visceral blood flow; sympathetic; orthostatic; vascular conductance; renal; forearm

COMMON, EVERYDAY STRESSORS, such as public speaking and mental challenges, have a significant influence on the cardiovascular system. Furthermore, these mental stressors are linked to the development of a variety of cardiovascular disorders. For example, mental stress is associated with development of myocardial ischemia (11, 27, 37), hypertension (44), and endothelial dysfunction (17, 38). The vast majority of studies investigating the physiological responses to mental stress, simulated in laboratories by color word tests, mental arithmetic, and public speaking, have been performed in the supine posture. However, humans often experience mental stress during orthostatic challenge. Similar to mental stress, maintaining the upright posture is associated with a variety of pathological conditions, and it is estimated that 1–6% of emergency room visits a year are related to orthostasis (39). The upright posture has been linked to the same physiological phenomena as mental stress, including the development of myocardial ische-

mia (27, 37), changes in endothelial function (18, 19), and abnormal blood pressures (16, 31). Currently, little is known about how mental stress and the upright posture interact with respect to cardiovascular hemodynamics. An understanding of this general interaction in healthy individuals may help us understand if the stressors are additive with each other and exacerbate the cardiovascular diseases associated with each.

The cardiovascular responses to mental stress in the supine posture and the upright posture have similarities and differences. Cardiovascular responses to mental stress in the supine posture include the following: 1) increases in heart rate, blood pressure, and forearm blood flow (FBF) (4, 5, 20); 2) vasoconstriction in the visceral arteries (22, 40); and 3) increases or no change in muscle sympathetic nerve activity (MSNA) (2, 8). The physiological responses to the upright posture include increases in heart rate, vasoconstriction in the limbs and viscera, and increases in sympathetic outflow (26, 34, 42). How cardiovascular hemodynamics will be altered by the combined challenge of the upright posture and mental stress and how these responses will be regulated remain unclear.

An understanding of the pattern of responses to combined mental stress and orthostatic challenge is important because it has been speculated that vasodilation in the forearm elicited by mental stress may compromise cerebral perfusion and contribute to syncope (7, 32), even though increases in FBF are blunted during combined mental stress and orthostatic challenge (21, 36). Therefore, the present study was designed to examine whether posture influences neurovascular responses to mental stress. We compared renal artery, superior mesenteric artery, forearm, and leg blood flows (LBF) during mental stress in the supine and upright postures. Furthermore, MSNA responses to mental stress in the supine and upright postures were examined. It was hypothesized that the upright posture would diminish neurovascular responses to mental stress because of elevated MSNA, total peripheral resistance, and heart rate, but that the pattern of the responses would remain the same.

METHODS

Twenty-three subjects (age 26 ± 1 yr; height 175 ± 3 cm; weight 73 ± 4 kg; body mass index, 24 ± 1 kg/m2; 9 women and 14 men) participated in the study. All subjects were normotensive, nonobese, nonsmokers, not taking any medications, and had no autonomic dysfunction or cardiovascular diseases. Subjects arrived at the laboratory fasted and having abstained from caffeine, alcohol, and exercise for 12 h. The experimental protocol was approved by the Institutional Review Board at the Pennsylvania State University College of Medicine, and all subjects gave written, informed consent before participating.

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1129

Experimental Protocol

Study 1. Renal and superior mesenteric artery mean blood velocities (RBFV and SMBFV, respectively) and FBF were recorded in the supine and upright postures during mental stress \( (n = 9) \). During the upright trials, subjects were strapped to a table and tilted to 80°. The order of the supine and upright trials and the renal and superior mesenteric trials were counterbalanced. A 5-min baseline was recorded in each respective posture followed by 5 min of mental stress and a 5-min recovery. RBFV and SMBFV were recorded on the same laboratory visit. We were unable to obtain renal blood flow in one subject; thus, our RBFV data represent eight subjects.

Study 2. LBF \( (n = 9) \) and leg MSNA \( (n = 5) \) responses were measured in 14 subjects during mental stress in both postures on separate days. A 3-min baseline was recorded in each posture, followed by 5 min of mental stress and a 3-min recovery. Subjects rested in the supine position between all trials, and any subsequent trial did not begin until blood pressure and heart rate returned to baseline.

Mental stress was elicited by mental arithmetic. Subjects repeatedly subtracted the number 6 or 7 from a 2- or 3-digit number. Subjects answered verbally and were encouraged by the investigators to subtract as fast as possible. An investigator provided a new number to subtract from every 5–10 s. The subtraction number, 6 or 7, was randomized. Subject-perceived stress levels during each mental stress trial were recorded at the end of the 5 min using a standard 5-point scale of 0 (not stressful), 1 (somewhat stressful), 2 (stressful), 3 (very stressful), and 4 (very, very stressful) \( (9) \).

Measurements

Duplex ultrasound (HDI 5000, ATL Ultrasound, Bothell, WA) was used to measure RBFV and SMBFV. The renal and superior mesenteric arteries were scanned using the anterior abdominal approach, while the subject was lying supine or during head-up tilt. To scan the aortic and renal arteries were scanned using the anterior abdominal approach, ultrasound was positioned above the heart in the upright and supine postures. The insonation angle for measuring mean blood velocity was 60°. To minimize overestimation of mean blood velocity, the sample volume was maximized. Arterial diameter measurements were taken at the end of diastole (determined by ECG) by measuring the distance between near and far wall intima-media during a longitudinal view. Vessel diameter and blood velocity were averaged from a minimum of 5 heartbeats each minute of the experimental protocol. Arterial blood flow was calculated by multiplying the cross-sectional area \( (\pi r^2) \) of the vessel by the mean blood velocity and by 60. Leg vascular conductance was calculated by dividing LBF by mean arterial blood pressure.

Multifiber recordings of MSNA were measured directly by inserting a tungsten microelectrode into the peroneal nerve posterior to the fibular head. A reference electrode was inserted subcutaneously 2–3 cm from the recording electrode. Both electrodes were connected to a differential preamplifier and then to an amplifier where the nerve signal was band-pass filtered (700–2,000 Hz) and integrated at a time constant of 0.1 s to obtain a mean voltage display of nerve activity. Satisfactory recordings of MSNA were defined by spontaneous, pulse-synchronous bursts that did not change during arousal or stroking of the skin.

Heart rate and blood pressure were continuously recorded during all trials using a Finometer (Finapres Medical Systems, Amsterdam, the Netherlands). During the RBFV and SMBFV trials, when plethysmography cuffs and the Finometer were operating concurrently on separate arms, we recorded ankle blood pressures (Dinamap, General Electric, Waukesha, WI). To compare ankle blood pressures when subjects were supine and upright, we height corrected the upright blood pressures by multiplying the distance between the suprasternal notch and the blood pressure cuff by 0.75 mmHg and then subtracted this number from the upright pressures. During the femoral and MSNA trials, blood pressure was recorded at the brachial artery using the Dinamap.

Data Analysis

Sympathetic bursts were identified from inspection of mean voltage neurograms displayed by a computer program (Chart with Peak Parameter extension; ADInstruments). MSNA was expressed as burst frequency and total activity (the sum of individual burst area expressed in arbitrary units). Resting variables were averaged over time in each posture and were compared using a paired t-test. All data were analyzed using a two-way repeated-measures ANOVA (posture × mental stress). Perceived stress levels were compared using a Wilcoxon rank sign test. Significance was considered at a \( P \) value of <0.05. Results are expressed as means ± SE.

RESULTS

Baseline Heart Rate and Blood Pressure

Baseline measurements during the renal and superior mesenteric trials and the LBF and MSNA are presented in Tables 1 and 2, respectively. The upright posture significantly increased heart rate in all four trials. Blood pressure was the same in each posture, except during the MSNA trials, where it was higher in the upright posture compared with the supine posture. The upright posture reduced vascular conductance in all four vascular beds. The upright posture significantly increased MSNA burst frequency and total activity compared with the supine posture.

Renal Vascular Responses to Mental Stress

Mental stress significantly increased heart rate and mean arterial blood pressure from baseline in both postures; however, no interaction was observed between postures (Fig. 1). RBFV decreased significantly with time in both postures. Renal vascular conductance decreased with time in both postures, and the posture × mental stress time interaction was significant \( (P = 0.05) \); Fig. 2). When changes in RBFV and
renal vascular conductance were expressed as percent change from baseline, there was only a significant mental stress time effect. Perceived stress levels in each posture were not different (upright 3 ± 0.2 units; supine 3 ± 0.2 units).

**Superior Mesenteric Vascular Responses to Mental Stress**

Mean arterial blood pressure and heart rate increased during mental stress, but the increase was not significantly different between postures (Fig. 1). SMBFV and superior mesenteric artery conductance decreased during mental stress in both postures (Fig. 2). The decrease in SMBFV was not significantly different in each posture, but the decrease in superior mesenteric artery conductance was significant (posture × mental stress time). When changes in SMBFV and superior mesenteric artery conductance were expressed as a percent change from baseline, there was no significant interaction. Perceived stress levels in each posture were not different (upright 3 ± 0.2 units; supine 3 ± 0.2 units).

**Forearm Vascular Responses to Mental Stress**

During the renal trials, FBF and forearm vascular conductance increased significantly from baseline during mental stress in each posture (Fig. 3). FBF and forearm vascular conductance increased more in the supine posture compared with the upright posture. However, when changes in FBF and forearm vascular conductance were expressed as percent change from baseline, increases in FBF and forearm vascular conductance did not differ. The response patterns during the superior mesenteric artery trials were the same as during the renal.

**Leg Vascular Responses During Mental Stress in the Upright and Supine Postures**

Mental stress elicited comparable increases in mean arterial blood pressure and heart rate in both postures (Fig. 4). LBF and leg vascular conductance increased during mental stress in both postures. The increase in LBF did not differ between the postures, but the increase in vascular conductance was larger in the supine posture. When changes in LBF and vascular conductance were expressed as a percent change from baseline, the pattern of the leg vascular responses did not differ between the two postures. Perceived stress levels in each posture were not different (upright 3 ± 0.4; supine 3 ± 0.3).

**Hemodynamic Responses During Recovery**

Mean arterial blood pressure and heart rate were not different from their respective baseline in either posture for the RBFV, SMBFV, and MSNA trials. In the LBF trials, mean arterial pressure did not differ from baseline to recovery, but, in the upright trial, heart rate was significantly higher during recovery compared with baseline (upright 87 ± 4 beats/min, supine 60 ± 2 beats/min). Renal, superior mesenteric, and femoral artery blood velocities and their respective conductances returned to baseline in both postures. During the renal trial, FBF was elevated in the supine posture (posture × time, \( P = 0.02 \)), while in the upright posture it returned to baseline. When differences in FBF were expressed as a percent change from baseline, there was no significant posture × mental stress time interaction. Forearm vascular conductance was greater during recovery in the supine (12.1 ± 9.6 units) compared with upright posture (1.8 ± 10.2 units; \( P = 0.013 \)). FBF and vascular conductance did not differ from baseline in the superior mesenteric trials.

**MSNA During Mental Stress in the Upright and Supine Postures**

Increases in mean arterial pressure during mental stress were not significantly different between the upright [change (\( \Delta \))

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### Table 1. Baseline measurements in the supine and upright postures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Renal</th>
<th>Superior Mesenteric</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Upright</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Mean arterial blood pressure, mmHg</td>
<td>88±3</td>
<td>83±6</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>57±2</td>
<td>79±4*</td>
</tr>
<tr>
<td>Forearm blood flow, ml·100 ml⁻¹·min⁻¹</td>
<td>3.2±0.4</td>
<td>1.8±0.2*</td>
</tr>
<tr>
<td>Forearm vascular conductance, units</td>
<td>0.038±0.004</td>
<td>0.017±0.002*</td>
</tr>
<tr>
<td>Visceral blood flow velocity, cm/s</td>
<td>62±4</td>
<td>55±5</td>
</tr>
<tr>
<td>Visceral artery conductance, units</td>
<td>0.75±0.09</td>
<td>0.57±0.08*</td>
</tr>
</tbody>
</table>

Values are means ± SE; \( n \), no. of subjects. *Significantly different from respective supine posture (\( P < 0.05 \)).

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### Table 2. Baseline measurements in the supine and upright postures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Leg Blood Flow</th>
<th>Sympathetic Nerve Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Upright</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Mean arterial blood pressure, mmHg</td>
<td>80±2</td>
<td>88±2*</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>57±2</td>
<td>80±3*</td>
</tr>
<tr>
<td>MSNA burst frequency, bursts/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSNA total activity, arbitrary units</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg blood flow, ml/min</td>
<td>254±41</td>
<td>132±24*</td>
</tr>
<tr>
<td>Leg vascular conductance, units</td>
<td>3.2±0.5</td>
<td>1.5±0.3*</td>
</tr>
</tbody>
</table>

Values are means ± SE; \( n \), no. of subjects. Total activity is equal to sum of bursts area. MSNA, muscle sympathetic nerve activity. *Significantly different from respective supine posture (\( P < 0.05 \)).
Increases in heart rate during mental stress were comparable in the upright (Δ 22 ± 4 beats/min) and supine postures (Δ 20 ± 2 beats/min). Mental stress did not elicit a significant increase in either burst frequency in the upright and supine postures (Δ 1 ± 3 and Δ 3 ± 3 bursts/min, respectively), or percent change in total activity (Δ -4 ± 15 and Δ 46 ± 31%, respectively), and there were no differences between postures. Perceived stress levels in each posture were not different (upright 3 ± 0.2 units; supine 3 ± 0.2 units).

DISCUSSION

This study is the first to examine the influence of posture on neurovascular responses to mental stress. This topic has clinical relevance because both mental stress (11, 17, 27, 37, 38, 44) and changes in posture (16, 18, 19, 27, 31, 37) are associated with an increased risk of cardiovascular dysfunction. Our results provide two new findings. First, posture does not change the response pattern of mean arterial blood pressure and heart rate to mental stress. Second, upright posture attenuates...
uates absolute vascular responses to mental stress, but the pattern of decreases in visceral vascular conductance (renal and superior mesenteric arteries) and increases in peripheral vascular conductance (forearm and leg) during mental stress are similar in both postures. Overall, this comprehensive study demonstrates that mental stress elicits a patterned response of vasoconstriction of the viscera, vasodilation of the limbs, and no change in MSNA in both the supine and upright postures.

Fig. 3. Forearm blood flow (FBF) and vascular conductance (FVC) increased from baseline during mental stress in both postures in the renal trials ($n = 8$). Greater increases in FBF and FVC were observed in the supine compared with the upright postures. Percent changes from baseline in FBF and FVC were not significantly different during mental stress in the supine and upright postures. FBF and FVC responses were similar during the superior mesenteric artery trials.

Fig. 4. Mental stress increased MAP and HR in both postures ($n = 9$). Leg blood flow (LBF) and vascular conductance (LVC) increased from baseline during mental stress in both postures. Greater increases in LVC were observed in the supine compared with the upright postures. Percent changes from baseline in LBF and LVC were not significantly different during mental stress in the supine and upright postures.
An important finding in the present study is the fact that mental stress elicited divergent vascular responses in the viscera and limbs. Other modalities, such as exercise and upright posture, which increase blood pressure and heart rate in humans, have been found to simultaneously constrict the visceral and limb vasculature (26, 33, 34). The results of the present study suggest that the human central nervous system has the ability to elicit patterned vascular responses.

Previous studies investigating the pattern of cardiovascular responses to mental stress have demonstrated that mental stress can modify baroreflex control of heart rate, blood pressure, and MSNA in the supine posture or during baroreceptor loading induced by phenylephrine infusion (1, 2). We found that heart rate and blood pressure increased during mental stress and baroreceptor unloading (i.e., tilting). Collectively, the results of the previous studies and the present study indicate that mental stress is able to modify baroreceptor control of blood pressure.

It has been speculated that there is a link between mental stress-induced forearm vasodilation and lower cerebral perfusion that may contribute to syncope (32). In the present study, we observed that increased blood flow in the periphery was mirrored by decreased blood flow to the visceral organs. The decrease in visceral blood flow may serve as a mechanism to fend off syncope onset caused by increases in blood flow to the limbs. The exact mechanisms responsible for the observed differences in blood flow responses during mental stress between the viscera and skeletal muscle remains unclear. We found MSNA increased in the upright posture, but MSNA responses were not altered during mental stress. This supports our previous finding that the pattern of vascular control during mental stress in the extremities is not associated with sympathetic outflow (8) and is in agreement with a previous study that demonstrated posture did not influence norepinephrine responses to mental stress (41). Furthermore, α-receptor blockade does not alter FBF increases caused by mental stress (13). Blood flow control in the limbs may be controlled by other mechanisms, including nitric oxide and circulating epinephrine (6, 12, 20, 28). Vascular control during mental stress in the viscera may be associated with sympathetic outflow, which directly contrasts with limb blood flow. In the renal artery, Tidgren and Hjemdahl (40) reported that venous overflow of norepinephrine increased by 214% during mental stress and that the increase correlated with renal vasoconstriction. Infusion of epinephrine at rest into the same subjects did not change renal blood flow, which contrasts with the forearms, where β-adrenergic blockade decreases mental stress-induced vasoconstriction (20, 29). Chaudhuri et al. (10) reported that, during mental stress, the percent change in superior mesenteric blood flow in control subjects was greater than that in patients suffering from autonomic failure, suggesting a possible vasoconstriction caused by the sympathetic nervous system. Control of visceral blood flow during mental stress may be similar to the heart, where release of norepinephrine has been found to increase during mental stress disproportionately to norepinephrine from the whole body (14, 15). This suggests that visceral blood flow response patterns during mental stress may be controlled by sympathetic nerve activity. Therefore, measurement of peripheral MSNA during some stressors may not reflect visceral sympathetic control, even though resting MSNA has been found to correlate with renal norepinephrine spillover (43). Another possible reason explaining why the viscera and limb responses to mental stress differ may relate to differences in catecholamine receptor type and density in human vessels (35).

Blair et al. (4) and Barcroft et al. (3) were the first to demonstrate a vasodilation of the forearm during mental stress. This finding has been reproduced by numerous investigators and is a consistent finding (6–8, 12, 20, 36). In contrast, leg vascular responses to mental stress are inconsistent. Some studies report no change in calf vascular conductance during mental stress (8, 23, 36), while others report vasodilation in the calf (4, 24, 25). In a recent study, we comprehensively examined limb vascular responses to mental stress using both venous occlusion plethysmography and Doppler ultrasound and reported vasodilation of the forearm and no change in calf vascular conductance using both techniques (8). The present study demonstrates the classic forearm vasodilation during mental stress, but also reports vasodilation of the leg. The discrepancy between our previous data (8) and the present data is likely due to differences in where the vascular bed was examined. In our first study (8), we used venous occlusion plethysmography and Doppler ultrasound (popliteal artery) to measure calf vascular responses to mental stress, whereas, in the present study, we measured femoral blood flow. Thus differences in the responses to mental stress in the lower limb vasculature may be dependent on the length and size of the vascular bed.

It has been suggested that the forearm vasodilation observed during mental stress may contribute to orthostatic intolerance (7, 32), and the data from the present study raise a new question: does a vasodilation in the leg during mental stress influence orthostatic stability? It is possible that a rapid vasodilation of the peripheral vasculature associated with mental stress could lead to a redistribution of blood and a decrease in cerebral perfusion pressure and thus contribute to orthostatic intolerance. Previously, it could be argued that the vascular bed of the forearm represents a very small portion of the entire vasculature, and vasodilation of the forearm would not have a substantial impact on cerebral perfusion pressure. However, data from the present study indicate that both the forearm and leg vasodilate during mental stress. Studies have not previously assessed the relationship between mental stress-induced vasodilation and orthostatic intolerance, but this study provides new evidence that upright posture does not influence the pattern of peripheral or visceral vascular responses to mental stress. Furthermore, this study is the first to report a simultaneous vasoconstriction of the viscera and a vasodilation of the peripheral vasculature during mental stress, and we suggest that these responses counteract one another to preserve cerebral perfusion.

There are two limitations to the present study. First, we measured changes in renal and superior artery velocities as an index of blood flow. Because of the spatial resolution of our Doppler probe, we were unable to measure diameters of these arteries accurately; therefore, it is unapparent if renal and superior mesenteric artery diameter changed during upright tilt or mental stress. However, paradigms that increase renal vascular resistance (or decrease conductance) do not change the diameter of the conduit artery (30). Second, physiological responses to stress are highly variable and depend on individual responses and laboratory techniques (32). Therefore, repeated trials of mental stress may alter neurovascular function.
differently. Because the present study demonstrated similar stress levels, heart rate increases, and mean arterial blood pressure increases in all mental stress trials, we do not believe that variation in responses to mental stress influenced our results.

In summary, posture does not alter the response pattern of heart rate, blood pressure, or MSNA to mental stress. Mental stress produces divergent vascular responses between the limbs and the viscera. Specifically, mental stress increases both leg and forearm conductance, but it decreases renal and superior mesenteric vascular conductance. Finally, the upright posture reduced conductance in all vascular beds examined, but the pattern of vascular responses during mental stress remains similar between the upright and supine postures.

ACKNOWLEDGMENTS

We thank Damian J. Dycman, Matthew L. Kearney, Erin Muldoon, and Amy E. Fogelman for technical assistance.

GRANTS

This project was supported by grants from the National Institutes of Health (NIH) (HL-77670, and DC-006459). Additional support was provided by NIH-sponsored General Clinical Research Center with National Center for Research Resources Grants M01 RR-10732 and C06 RR-016499.

REFERENCES


