Sympathetic neural responses to mental stress during acute simulated microgravity

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Durocher JJ, Schwartz CE, Carter JR. Sympathetic neural responses to mental stress during acute simulated microgravity. J Appl Physiol 107: 518–522, 2009. First published June 18, 2009; doi:10.1152/japplphysiol.00284.2009—Neural and cardiovascular responses to mental stress and acute 6° head-down tilt (HDT) were examined separately and combined. We hypothesized sympathoexcitation during mental stress, sympathoinhibition during HDT, and an additive neural interaction during combined mental stress and HDT. Muscle sympathetic nerve activity (MSNA), mean arterial pressure (MAP), and heart rate (HR) were recorded in 16 healthy subjects (8 men, 8 women) in the supine position during three randomized trials: 1) mental stress (via mental arithmetic), 2) HDT, and 3) combined mental stress and HDT. Mental stress significantly increased MSNA (7 ± 1 to 12 ± 2 bursts/min; P < 0.01), MAP (91 ± 2 to 103 ± 2 mmHg; P < 0.01), and HR (70 ± 3 to 82 ± 3 beats/min; P < 0.01). HDT did not change MSNA or HR, but MAP was reduced (91 ± 2 to 89 ± 3 mmHg; P < 0.05). Combined mental stress and HDT significantly increased MSNA (7 ± 1 to 10 ± 1 bursts/min; P < 0.01), MAP (88 ± 3 to 99 ± 3 mmHg; P < 0.01), and HR (70 ± 3 to 82 ± 3 beats/min; P < 0.01). Increases in MSNA and HR during the combination trial were not different from the sum of the individual trials. However, the increase in MAP during the combination trial was significantly greater than the sum of the individual trials (change of 11 ± 1 vs. 9 ± 1 mmHg; P < 0.05). We conclude that the interaction for MSNA and HR are additive during combined mental stress and HDT but that MAP responses are slightly augmented during the combined trial. These findings demonstrate that sympathetic neural responses to mental stress are unaltered by simulated microgravity.

autonomic regulation; blood pressure; heart rate; muscle sympathetic nerve activity

Mental stress consistently increases heart rate and arterial blood pressure (1–8, 23) and often increases muscle sympathetic nerve activity (MSNA) (1, 2, 6–8). In contrast, acute head-down tilt (HDT), a ground-based analog of microgravity (12, 19, 21, 26, 29), tends to decrease MSNA in response to baroreceptor loading (19, 28). Arterial blood pressure and heart rate are reported to remain unchanged during HDT (9, 24). The neural and cardiovascular interactions between mental stress and acute 6° HDT have not been examined but may have important implications for both the immediate and the long-term health of astronauts. Of interest, both mental stress and HDT have been reported to reduce baroreflex sensitivity (14, 30). Postflight orthostatic intolerance, a major problem for astronauts, has been linked to reductions in baroreflex sensitivity (11, 15, 17, 22).

Investigations examining combined mental stress and baroreceptor loading are limited. Kamiya et al. (21) found that 14 days of 6° HDT bed rest resulted in an augmented MSNA response to mental stress in young males, whereas acute responses to HDT were not examined. Heart rate and blood pressure responses to mental stress were not altered by HDT bed rest (21). Anderson et al. (1) reported that increases in MSNA, heart rate, and blood pressure during mental stress were similar before and after baroreceptor loading. However, loading of the baroreceptors was induced by phenylephrine infusion, a pharmacological technique that does not cause a fluid shift similar to that experienced in microgravity. Thus current findings on neural responses to mental stress during acute baroreceptor loading are limited and do not appear to be directly applicable to astronauts during initial entry into space.

Astronauts frequently experience mental stress during microgravity, which may influence the neural and cardiovascular reflexes important to their safety and health. Many stressors can occur during spaceflight, ranging from headaches and changes in vision (17) to spontaneous events such as oxygen canisters catching on fire (15). Therefore, we seek to determine the neural and cardiovascular responses to mental stress during acute simulated microgravity using the 6° HDT model. We hypothesize sympathoexcitation during mental stress, sympathoinhibition during HDT, and an additive neural interaction during combined mental stress and HDT. We also hypothesize that the cardiovascular responses will be additive during combined mental stress and HDT.

METHODS

Subjects. Sixteen healthy subjects (8 men and 8 women; age 22 ± 0.4 yr, height 175 ± 3 cm, weight 74 ± 4 kg; means ± SE) participated in this study. All subjects were normotensive nonsmokers and abstained from exercise, caffeine, and alcohol for a minimum of 12 h preceding laboratory testing. Female subjects were not taking any form of oral contraceptive. Each subject received an orientation session, which provided an overview to experimental procedures. Testing was approved by the Institutional Review Board at Michigan Technological University, and all subjects provided written, informed consent before participating in the study.

Experimental design. Each subject participated in three randomized trials while lying in a supine position on an electronic tilt table. Each of the three trials included a 3-min baseline, a 3-min intervention, and a 3-min recovery. The three trials included 1) mental stress, 2) 6° HDT, and 3) combined mental stress and 6° HDT. A non-recording rest interval separated each of the three trials. The length of this rest interval varied and was based on the return of hemodynamic measurements to baseline levels (which typically occurred within 5 min).

The 6° HDT position was achieved within 5 s by smoothly tilting the table in conjunction with a voltage regulator until a preset stopper placed at −6° was reached. The 6° HDT was performed to simulate a microgravity condition. The horizontal supine position was also placed at

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achieved within 5 s and verified by a preset stopper. The brief periods (i.e., <5 s) of repositioning were not included as part of recorded data. One investigator directed the mental stress interventions, which required subjects to continuously subtract either the number six or seven from a three-digit number. Subjects were verbally encouraged by a second investigator to work faster, while the first investigator changed the number to subtract from every 5 to 10 s. Upon completion of the three trials, subjects were asked to rate their perceived stress levels according to a standard five-point scale of 0 (not stressful), 1 (somewhat stressful), 2 (stressful), 3 (very stressful), and 4 (very, very stressful) (2).

Measurements. MSNA was measured directly by inserting a tungsten microelectrode (Frederick Haer and Co., Bowdoinham, ME) into the peroneal nerve in the popliteal region behind the right knee. A reference electrode was inserted subcutaneously 2–3 cm from the recording electrode. Both electrodes were connected to a differential preamplifier and an amplifier (total gain of 80,000) to band-pass filter (700–2,000 Hz) to integrate (time constant, 0.1 s) the nerve signal to acquire a mean voltage display of activity. Satisfactory recordings of MSNA were defined by spontaneous, pulse synchronous bursts that increased during end-expiratory apnea but did not change during an auditory stimulation (yell) or while rubbing the skin. Heart rate was measured continuously with a three-lead electrocardiogram. Arterial pressure was measured at rest using an automated sphygmomanometer (Omron HEM-907XL, Omron Health Care, Vernon Hills, IL). Continuous blood pressure was measured via Finometer (Finapres Medical Systems, Amsterdam, The Netherlands). Data sampling occurred at 500 Hz, and data were stored on a computer with specialized software (WINDAQ, Dataq Instruments, Akron, OH). We successfully recorded heart rate and blood pressure in all 16 subjects, whereas MSNA recordings were obtained for 11 subjects (6 men, 5 women) throughout all trials. Blood pressure is reported as mean arterial pressure (MAP) from Finometer measurements.

Data analysis. Data were analyzed using commercial software (WinCPRS, Absolute Aliens, Turku, Finland). All R waves of the electrocardiogram were verified and marked in the time series. MSNA bursts were detected automatically based on amplitude using a signal-to-noise ratio of 3:1 within a 0.5-s window centered on expected 1.3-s bursts. The subsequent bursts were detected automatically based on amplitude using a signal-to-noise ratio of 3:1. Burst peak latency from the preceding R wave. Bursts of MSNA were evaluated as the number of bursts per minute and total activity by one trained investigator. Total activity was determined by calculating the integral of all bursts during the 3-min baseline for each trial and dividing that total by the number of bursts. The subsequent bursts that were equal to the average baseline burst were assigned a value of 100.0. Calculation of total activity was performed by multiplying the total number of bursts by the average normalized burst area.

Statistical analysis. Commercial software (SPSS version 16.0, Chicago, IL) was used to analyze all data. A two-within (condition: HDT, mental stress, combination of HDT and metal stress × time: baseline, intervention, recovery) ANOVA with repeated measures on time was used to compare dependent variables. When a significant condition by time interaction was detected, one-way repeated-measures ANOVAs (time: baseline, intervention, recovery) were performed for each condition, with the least-significant difference pairwise comparison method for post hoc analysis. To probe for sex differences, sex was added as a between factor. The algebraic sum of the changes during the individual mental stress and HDT trials was compared with the combination of the mental stress and HDT trial with paired t-tests. Means were considered significantly different when P < 0.05. All results are presented as means ± SE.

RESULTS

Mean values for MSNA (total activity and burst frequency), MAP, and heart rate during each of the experimental trials are found in Table 1. All variables had similar baseline values across the three trials. A representative neurogram is shown in Fig. 1 for one subject during each of the three baselines and interventions.

Mental stress in the horizontal supine position significantly (P < 0.01) increased MSNA (Δ5 ± 1 bursts/min), MAP (Δ12 ± 1 mmHg), and heart rate (Δ12 ± 2 beats/min). There was a trend for MSNA reduction during HDT, but this did not quite reach statistical significance (P = 0.07). HDT reduced MAP (Δ3 ± 1 mmHg; P < 0.01) but did not change heart rate. Combined mental stress and HDT significantly (P < 0.01) increased MSNA (Δ3 ± 1 bursts/min), MAP (Δ11 ± 1 mmHg), and heart rate (Δ12 ± 2 beats/min).

Increases in MSNA during the combination trial were not different from the sum of the individual trials as shown in Fig. 2. However, Fig. 3 demonstrates that the increase in MAP during the combination trial was significantly greater than the sum of the individual trials (Δ11 ± 1 vs. Δ9 ± 1 mmHg; P < 0.05), whereas increase in heart rate during the combination trial was similar to the individual trials.

Perceived stress during mental stress trial (2.2 ± 0.2 U) and the combined trial (2.6 ± 0.1 U) was significantly (P < 0.01) greater than during HDT alone (0.2 ± 0.1 U). Perceived stress for the sum of the individual trials (2.4 ± 0.2 U) was not different than the combination trial (2.6 ± 0.1 U). MSNA burst frequency (interaction, P = 0.595), total MSNA (interaction, P = 0.803), heart rate (interaction, P = 0.936), and MAP (interaction, P = 0.117) responses were not different between men and women (interaction = condition × time × sex).

DISCUSSION

The present study is the first to examine the acute responses to mental stress during HDT. Our primary finding is that the neural interaction between baroreceptor loading via HDT and mental stress is additive. The increase in heart rate during combined mental stress and HDT was also similar to the sum of the individual mental stress and HDT interventions. In contrast, MAP was slightly augmented during combined mental stress and HDT compared with the sum of the individual trials. Our MSNA and heart rate findings are consistent with our hypotheses and reveal that mental stress is a robust response that is not altered by simulated microgravity.
Mental stress consistently triggers an increase in heart rate and arterial blood pressure, but the neural responses are complex. Increases in blood pressure typically decrease MSNA through baroreceptor feedback, but that does not occur during mental stress (1, 5, 6, 8, 21, 23). Anderson et al. (1) demonstrated that mental stress increases MSNA during phenylephrine infusion, a baroreceptor loading technique. It was suggested that an additive neural interaction may exist, but this was not specifically tested. The results of the present study indicate that increases in MSNA and heart rate are additive during the combination of mental stress and baroreceptor loading induced by HDT. In addition, we found that increases in MAP were slightly augmented during the combination trial vs. the sum of mental stress and HDT alone. These findings, taken in conjunction with the findings of Anderson et al. (1), suggest that mental stress may override or reset the baroreflex.

The HDT model is utilized to induce a redistribution of fluid toward the head, which mimics blood redistribution during initial entry into space. This cephalic fluid shift induces a reduction of MSNA due to loading of the cardiopulmonary baroreceptors (19, 28). This technique can result in a decrease in total peripheral resistance (19, 24, 26) and mean arterial blood pressure (26). The results of the current study indicate that acute HDT decreased MAP and tended to decrease MSNA, whereas heart rate remained unchanged. Typically, HDT does not induce a change in MAP or heart rate (9, 19, 24). However, at least one study reported a decrease in MAP during HDT (26) and noted that the decrease was likely due to a decrease in heart rate. In the present study, the decrease in MAP during HDT was not associated with a decreased heart rate. Therefore, a decrease in peripheral resistance may have contributed to the reduction of MAP during HDT. However, the 2-mmHg drop in MAP during HDT and the potential decrease of peripheral resistance has limited, if any, physiological relevance.

Dysfunction of the baroreflex is thought to be a major contributor to orthostatic intolerance during simulated or actual microgravity (11, 15, 17, 22). Kamiya et al. (22) reported that 14 days of 6° HDT bed rest reduced MSNA responses to 60° head-up tilt. This finding suggests an alteration of the baroreflex, but the authors emphasized it may be difficult to predict orthostatic tolerance based on baroreflex sensitivity (22). It has also been reported that MSNA expressed as burst frequency does not increase during mental stress before 14 days of 6° HDT bed rest but that burst frequency increases during mental stress after the exposure to simulated microgravity (21). This suggests that the baroreflex may inhibit MSNA during mental stress before, but not after, 6° HDT bed rest (21). In contrast, our findings indicate that the baroreflex does not inhibit MSNA responses to mental stress, regardless of whether mental stress was performed alone or in conjunction with simulated microgravity. Thus it appears that acute simulated microgravity does not influence MSNA responses to mental stress.

Spaceflight and simulated microgravity have been linked to rapid reductions in plasma volume that may contribute to orthostatic intolerance (10–12, 16). This rapid reduction in blood volume is attributed to diuresis during acute HDT, whereas urine output is not increased initially during actual spaceflight (10, 13, 18). It is possible that diuresis is prevented during early spaceflight because of a stress-induced sympatho-
excitation (16). We have demonstrated in the present study that MSNA is significantly increased during mental stress in a simulated microgravity condition. Although it was not a specific aim of the present study, it would be of interest to determine whether diuresis is abolished during the combination of HDT and mental stress. It is possible that diuresis is prevented in astronauts during the first day in space because of the stress that they experience. A recent study reported that mental stress reduces renal activity in both the upright and supine posture (23). It is possible that mental stress may be responsible for the divergent response in diuresis when HDT and actual microgravity conditions are compared.

For nearly two decades, the MSNA response to mental stress was thought to be regulated by perceived stress (2), but our laboratory has recently challenged that concept (4). Most recently, it was determined that mental stress elicits comparable increases in heart rate and blood pressure regardless of the MSNA responsiveness (7). However, exaggerated increases of blood pressure occurred during mental stress in men compared with women (7). Because previous mental stress investigations during (1) and following (21) baroreceptor loading tested only male subjects, we sought to determine whether sex differences existed during the combination of mental stress and HDT. The present study did not detect any neural or cardiovascular sex differences during combined mental stress and HDT. Specifically, MAP was similar in men and women during the combination trial.

Our findings indicate that the increase in MAP was slightly augmented during the combination of mental stress and HDT compared with the sum of the individual trials, which may suggest a reduction in peripheral resistance. The classic reduction of forearm vascular resistance (3, 5, 20, 25) during mental stress may have been attenuated during the combination of mental stress and HDT. A previous investigation has suggested that HDT bed rest may reduce both the vasoconstriction and vasodilation capabilities of the forearm (27). Although our study did not particularly address changes in forearm vasoconstriction or vasodilation, this area may deserve further attention to determine whether mental stress alters forearm vascular resistance during acute and prolonged simulated microgravity.

This investigation is the first study to examine the neural and cardiovascular responses to mental stress during acute exposure to simulated microgravity. We conclude that the interaction for MSNA and HR are additive during combined mental stress and HDT but that MAP responses are slightly augmented during the combined trial. The neural responses to mental

Fig. 2. Change (Δ) in MSNA during 6° HDT, MS, the algebraic sum of the individual trials (Sum), and combined HDT and MS (Combo). MSNA was significantly increased from baseline during MS, Sum, and Combo. Changes in MSNA during Combo were not significantly (NS) different from the Sum. *Significant difference vs. baseline (P < 0.01).

Fig. 3. Change in mean arterial pressure (MAP) and heart rate (HR) during HDT, MS, Sum, and Combo trials. MAP was significantly different than baseline during HDT, MS, Sum, and Combo. The increase in MAP was significantly greater during Combo than Sum. Increases in HR during Combo were not significantly (NS) different from the Sum of the individual trials. *Significant difference vs. baseline (P < 0.01). **Significant difference of Combo vs. Sum (P < 0.05).
stress and HDT are independent. This additive neural interaction indicates that, despite a tendency for HDT to reduce MSNA through an increase in central blood volume, mental stress still elicits a significant increase in MSNA. Mental stress experienced during microgravity may contribute to several health-related factors in astronauts that include cardiovascular risk, regulation of arterial blood pressure, and fluid homeostasis.

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