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Forearm neurovascular responses during mental stress and vestibular activation

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[1]*Departments of Medicine and Cellular and Molecular Physiology, Pennsylvania State University College of Medicine, Hershey, Pennsylvania;* [2]*Department of Biological Sciences, Michigan Technological University, Houghton, Michigan; and* [3]*United States Army Institute of Surgical Research, Fort Sam Houston, Texas*

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Carter, Jason R., William H. Cooke, and Chester A. Ray. Forearm neurovascular responses during mental stress and vestibular activation. *Am J Physiol Heart Circ Physiol* 288: H904–H907, 2005. First published October 14, 2004; doi:10.1152/ajpheart.00569.2004.—Autonomic responses may underlie associations among anxiety, vestibular dysfunction, and unexplained syncope. Mental stress (MS), an anxiety-inducing stimulus, causes forearm vasodilation, whereas the vestibulosympathetic reflex (VSR) causes forearm vasoconstriction. The purpose of this study was to examine the combined effects of mental and vestibular stimulation on neurovascular control in the forearm. Heart rate, arterial pressure (Finapres), and forearm blood flow (Doppler) were measured in 10 healthy volunteers in the prone position during *1*) head-down rotation (HDR), *2*) MS (mental arithmetic), and *3*) HDR + MS. Forearm vascular resistance (FVR) increased during HDR (from 232 ± 40 to 319 ± 53 units) and decreased during MS (from 260 ± 57 to 154 ± 22 units). During HDR + MS, FVR did not change [change (Δ) = −31 ± 50 units] and was not significantly different from the algebraic sum of each trial performed alone (Δ = −20 ± 42 units). Arm muscle sympathetic nerve activity (MSNA; microneurography) was measured in seven additional subjects. MSNA increased during HDR (from 13 ± 2 to 17 ± 2 bursts/min) and HDR + MS (from 11 ± 2 to 16 ± 2 bursts/min). Increases in MSNA during HDR + MS (Δ = 5 ± 2 bursts/min) were not different from the algebraic sum of each trial performed alone (Δ = 6 ± 2 bursts/min). We conclude that an additive neurovascular interaction exists between MS and the VSR in the forearm. Activation of the VSR prevented forearm vasodilation during MS, suggesting that activation of the VSR may help protect against stress-induced syncope.

otolith stimulation; vestibulosympathetic reflex; arterial pressure control; mental arithmetic

VESTIBULAR DYSFUNCTION associated with vertigo and syncope may contribute to anxiety disorders (11). Vestibular dysfunction has been shown to alter autonomic activity, which may lead to space and motion discomfort and ensuing panic attacks (11). Although vestibular dysfunction may be a risk factor for anxiety attacks, it is not clear whether an inverse relation exists. In other words, does anxiety contribute to vestibular dysfunction and subsequent syncope?

Mental stress (MS), an anxiety-inducing stimulus, causes forearm vasodilation (5). It has been suggested that MS-induced forearm vasodilation may eventually compromise cerebral perfusion and contribute to syncope (15). In contrast, activation of the vestibulosympathetic reflex (VSR) via head-down rotation (HDR) causes forearm vasoconstriction (14) and may help defend against syncope. Because MS vasodilates the forearm (5) and vestibular activation vasoconstricts the forearm (14), it is possible that the two responses may negate one another or one may override the other when both are performed simultaneously.

The primary purpose of this study was to investigate the forearm vascular interaction between MS and vestibular activation. On the basis of our recent study examining the neural interaction between MS and the VSR in the leg (8), we tested the hypothesis that an additive forearm vascular response exists during MS and otolithic engagement. Additionally, arm muscle sympathetic nerve activity (MSNA) was measured to determine whether the neural responses in the arm are different from the additive interaction previously observed in the leg (8).

METHODS

Subjects. Seventeen volunteers (13 men and 4 women; age 22 ± 1 yr, height 174 ± 2 cm, weight 74 ± 3 kg) participated in the study. All subjects were nonsmokers and in good health as determined by a physical examination. Subjects arrived at the laboratory after abstaining from caffeine and exercise for ≥12 h. The experimental protocol was approved by the Institutional Review Board of Pennsylvania State University College of Medicine, and all subjects gave written informed consent before the study.

Experimental design. In *study 1*, we examined the vascular interaction between MS and vestibular activation. All subjects (n = 10) performed three experimental trials in the prone position. Heart rate, arterial pressure, and forearm blood flow were measured during *1*) HDR to activate the VSR, *2*) mental arithmetic to induce MS, and *3*) simultaneous performance of mental arithmetic and HDR. The duration of each intervention was 5 min, and the order of the three trials was randomized. Each trial began with a 2-min baseline and ended with a 3-min recovery with the head upright, the neck extended, and the forehead supported (15). This position approximates the gravitational orientation of the head for an individual standing upright.

In *study 2*, we examined the neural interaction between MS and the VSR in seven additional subjects. Heart rate, blood pressure, and arm MSNA were measured during the three experimental trials as in *study 1* (i.e., HDR, mental arithmetic, and HDR + mental arithmetic). The experimental procedures were identical to the vascular trials.

Mental arithmetic. During mental arithmetic, subjects continuously subtracted the number 6 or 7 from a two- or three-digit number. The subtraction number (6 or 7) was randomized for the two trials involving mental arithmetic. Subjects answered verbally and were encouraged by an investigator to subtract as quickly as possible. An investigator provided a new number from which to subtract every 5–10 s. Subjects were asked to rate perceived stress using the

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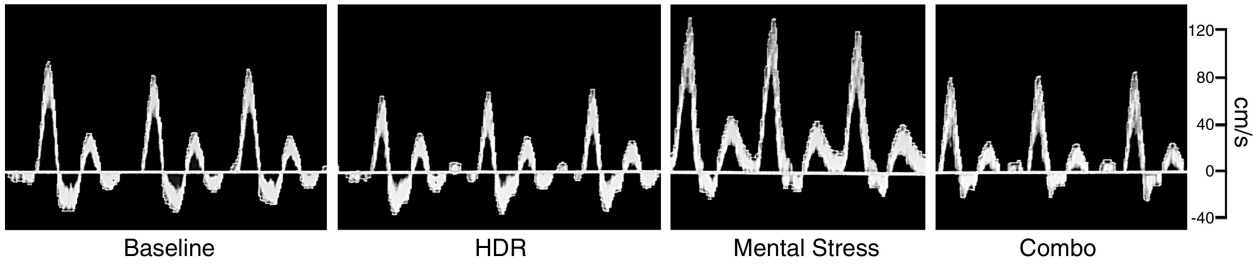

Fig. 1. Ultrasonic-Doppler traces of forearm blood velocity from 1 subject during head-down rotation (HDR), mental stress, and combination trial (Combo). Forearm blood flow, as measured by forearm blood velocity and vessel cross-sectional area, decreased during HDR, increased during mental stress (MS), and did not change during the combination trial.

following standard five-point scale: 0, not stressful; 1, somewhat stressful; 2, stressful; 3, very stressful; and 4, very, very stressful (6). Five-minute rest periods were interspersed between trials to allow heart rate and blood pressure to return to baseline.

Measurements. Continuous heart rate was measured with a three-lead electrocardiogram. Arterial pressure was measured using a Finapres positioned on the middle digit of the subject's left hand positioned at the level of the heart. Duplex ultrasound (model HDI 5000, ATL Ultrasound, Bothell, WA) was used to examine blood velocity and vessel diameter in the arm. Briefly, a linear Array L12 5-MHz Doppler probe with a 6.0-MHz pulsed Doppler frequency was used. The focal zone was at the depth of the brachial artery. Cardiac cycle Doppler signals were analyzed to determine the mean blood flow velocity. Each velocity measurement was normalized with a time constant of 1 s. For each data point, we averaged 15 s of data. Mean blood flow was calculated by multiplying mean blood velocity by the area of the vessel (determined from vessel diameter). Vascular resistance was the ratio of mean arterial pressure to limb blood flow (times 100 and expressed in units), and vascular conductance was the reciprocal.

Multifiber recordings of MSNA were measured directly by insertion of a tungsten microelectrode into the radial nerve of the left arm. 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.

Data analysis. Sympathetic bursts were identified from inspection of mean voltage neurograms displayed by a computer program (Peaks, ADInstruments). MSNA was expressed as burst frequency and total activity (the sum of burst amplitude expressed in arbitrary units). All data were analyzed using repeated-measures ANOVA. When significant condition effects were detected, the source of the significant effect was probed with Duncan's post hoc test. A paired *t*-test was used to compare the algebraic sum of the changes during HDR and mental arithmetic performed separately and the change when HDR and mental arithmetic were performed together. Perceived stress levels were compared using a sign-rank test. Means were considered to be significantly different when $P < 0.05$. Results are expressed as means ± SE.

RESULTS

Forearm vascular responses. Forearm vascular resistance (FVR) significantly increased during HDR [change (Δ) = 87 ± 29 units], significantly decreased during MS ($\Delta = -106 \pm 50$ units), and did not significantly change during HDR + MS ($\Delta = -31 \pm 50$ units; Fig. 1). Changes during HDR + MS were not significantly different from the algebraic sum of HDR and MS performed alone ($\Delta = 20 \pm 42$ units; Fig. 2). Results were comparable when expressed as vascular conductance. Mean values for forearm vascular responses are presented in Table 1.

Arm MSNA responses. Arm MSNA significantly increased during HDR ($\Delta = 4 \pm 1$ bursts/min) and HDR + MS ($\Delta = 5 \pm 2$ bursts/min) but did not change during MS ($\Delta = 2 \pm 1$ bursts/min; Fig. 3). Changes during HDR + MS were not significantly different from the algebraic sum of HDR and MS performed alone ($\Delta = 6 \pm 2$ bursts/min; Fig. 3). Mean values for arm MSNA responses are presented in Table 1.

Cardiovascular responses. Mean arterial pressure and heart rate significantly increased during MS alone and HDR + MS but did not change during HDR. Mean arterial pressure and heart rate changes during HDR + MS ($\Delta = 23 \pm 3$ mmHg and $\Delta = 16 \pm 2$ beats/min) were not significantly different from the algebraic sum of HDR and MS performed alone ($\Delta = 23 \pm 4$ mmHg and $\Delta = 21 \pm 3$ beats/min). Mean values for arterial pressure and heart rate responses are presented in Table 1. The perceived stress levels during MS alone (2.5 ± 0.2 units) and HDR + MS (2.2 ± 0.3 units) were not statistically different.

DISCUSSION

The principal finding of this study is that the forearm vascular interaction between MS and the VSR is additive in humans. MS alone elicits forearm vasodilation and vestibular activation alone elicits forearm vasoconstriction, but these divergent vascular responses appear to offset one another when both stimuli are performed simultaneously. Additionally, the arm neural interaction between MS and the VSR is additive

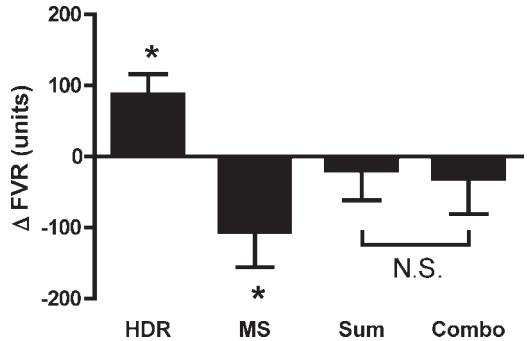

Fig. 2. Change in forearm vascular resistance (FVR) during HDR and MS performed alone, the algebraic sum of changes during HDR and MS performed independently (Sum), and the change when HDR and MS were performed simultaneously (Combo). Comparable results were obtained when expressed as vascular conductance. Values are means ± SE; $n = 10$. *Significantly different from corresponding baseline, $P < 0.05$. NS, not significant.

Table 1. *Cardio- and neurovascular variables recorded during the three experimental trials*

	Baseline	Intervention	Recovery
MAP, mmHg			
HDR	94±2	95±3	95±3
MS	95±2	117±3*	106±3*
Combo	95±4	119±5*	104±3*
HR, beats/min			
HDR	67±2	67±2	68±2
MS	70±2	91±3*	72±2
Combo	70±2	86±3*	70±2
FBF, ml/min			
HDR	52±9	38±7*	51±9
MS	51±9	88±12*	62±11
Combo	57±11	71±16	51±11
FVR, units			
HDR	232±40	319±53*	245±45
MS	260±57	154±22*	233±45
Combo	279±72	248±58	354±90
MSNA, bursts/min			
HDR	13±2	17±2*	12±2
MS	10±3	12±3	16±3*
Combo	11±1	16±2*	18±3*

Values are means ± SE. MAP, mean arterial pressure ($n = 17$); HR, heart rate ($n = 17$); FBF, forearm blood flow ($n = 10$); FVR, forearm vascular resistance ($n = 10$); MSNA, arm muscle sympathetic nerve activity ($n = 7$); HDR, head-down rotation; MS, mental stress; Combo, combination trial (HDR + MS). *Significantly different from corresponding baseline value; $P < 0.05$.

with regard to MSNA. This finding is similar to the neural interaction observed previously in the leg (8), indicating that vestibular- and stress-mediated MSNA responses are independent in humans.

The stress associated with mental arithmetic augments heart rate, arterial pressure, and forearm blood flow in humans. Early studies (3, 5) attributed MS-induced forearm vasodilation to neural and nonneural (humoral) mechanisms. Subsequent studies supported a nonneural mechanism by demonstrating that nitric oxide (7, 9, 10) and circulating epinephrine (13) contribute to the forearm vasodilation during MS, but neural mechanisms remain controversial. In general, studies agree that there is not an active vasodilator response during MS (10, 12) but disagree as to whether a passive vasodilator response exists. Halliwill et al. (10) reported a passive withdrawal of MSNA that was associated with forearm vasodilation during MS. In contrast, Lindqvist et al. (12) reported that axillary blockade did not significantly alter forearm vasodilation. Regardless of the neural contribution, it is clear that MS-induced vasodilation is a complex physiological response.

In contrast to the MS response, the neurovascular responses to vestibular activation are less complex. Vestibular activation via HDR consistently increases MSNA to both limbs (14, 16) and vasoconstricts the arm (14) and leg (16). The vasoconstriction of the forearm appears to be mediated solely by sympathetic activation (14). Because MS and vestibular activation do not induce parallel responses in the forearm, it is possible that one stimulus could override or otherwise affect responses of the other stimulus when both are performed simultaneously. A stress-mediated vasodilation of the forearm, without a concomitant vestibular-mediated vasoconstriction, could contribute to a reduction of arterial pressure and, subsequently, to orthostatic hypotension.

Our data confirm previous studies demonstrating vasodilation of the forearm during MS (5), vasoconstriction of the forearm during HDR (14), and similar levels of perceived stress during MS alone and HDR + MS (8). More importantly, our results demonstrate an additive forearm vascular response between MS and the VSR, suggesting that these two autonomic reflexes do not centrally integrate. Vasoconstriction of the forearm during vestibular activation may play an important role in maintaining arterial pressure in individuals who engage the vestibular system during a stressful situation. For example, the psychological stress associated with a life-threatening situation could vasodilate the forearm and cause syncope (4). Activation of the vestibular system via head movement could potentially defend against syncope by vasoconstricting the forearm to offset the stress-mediated vasodilator response.

Our results also demonstrate that MSNA responses to MS and vestibular stimulation are additive in the arm. This finding, taken together with our previous study revealing an additive leg MSNA response (8), indicates neural independence between these two autonomic reflexes with regard to MSNA output in the upper and lower extremities. However, we did not observe significant increases of arm MSNA during the MS trial as seen previously in the leg (8). This finding is in accord with those of Anderson et al. (1), who reported no change in arm MSNA during MS, but is in conflict with findings of Halliwill et al. (10), who demonstrated a decrease in arm MSNA during MS. The reasons underlying the conflicting neurovascular responses between the present study and the findings of Halliwill et al. are not clear, but sympathetic neural responses to MS have long been recognized as a variable response. More comprehensive studies are warranted to investigate the variable MSNA responses to MS.

In the present study, the anxiety associated with mental arithmetic did not appear to influence the VSR. However, our subjects were not screened for anxiety disorders. Balaban (2) suggests that the parabrachial nucleus serves as a convergence node for vestibular afferents, other visceral afferents, and anxiety signals from the central amygdaloid nucleus. Jacob et al. (11) present data that the autonomic responses related to vestibular dysfunction combine with other visceral input to trigger panic attacks in individuals with a predisposition for panic attacks (i.e., patients with panic disorders), but not in

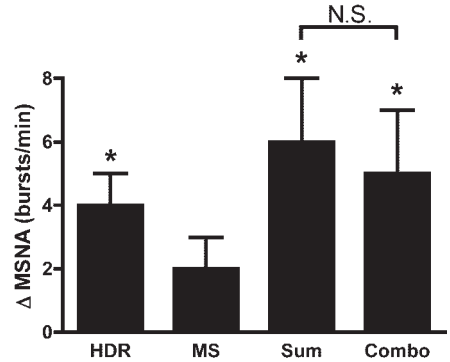

Fig. 3. Change in arm muscle sympathetic nerve activity (MSNA) during HDR and MS performed alone, the algebraic sum of changes during HDR and MS performed independently, and the change when HDR and MS were performed simultaneously. Values are means ± SE; $n = 7$. *Significantly different from corresponding baseline, $P < 0.05$.

those who lack a history of panic disorder. It is possible that subjects with anxiety disorders may exhibit a neurovascular response different from the results in this study. The neurovascular responses to combined mental and vestibular activation have not been investigated in subjects with anxiety disorders. If anxiety-induced stress had an inhibitory effect on the VSR, this could help explain the association between anxiety, vestibular dysfunction, and unexplained syncope.

Anxiety can be defined several ways, but it is often defined as an uncomfortable emotional state associated with *1*) a fear of danger or *2*) a feeling of apprehension and powerlessness. Although our subjects did not experience emotional states associated with perceived danger, it is likely that they experienced feelings of apprehension and powerlessness. It is possible that subjects experiencing danger-related anxiety may exhibit neurovascular responses different from those observed in this study, but this form of anxiety is difficult to induce in a laboratory setting because of ethical issues.

In summary, our results show that MS vasodilates the forearm, HDR vasoconstricts the forearm, and HDR + MS does not change FVR. The forearm vascular response during the combination trial does not differ from the sum of each trial performed individually. These results indicate an additive forearm neurovascular interaction between MS and otolith activation. This finding suggests that the VSR may counteract stress-induced vasodilation in humans.

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