Cerebral Blood Flow Velocity During Combined Lower Body Negative Pressure and Cognitive Stress

John J. Durocher; Jason R. Carter; William H. Cooke; Angelea H. Young; Morton H. Harwood

BACKGROUND: Lower body negative pressure (LBNP) decreases middle cerebral artery blood velocity (MCAv) and can induce hypotension. Mental stress increases MCAv, but the MCAv response to combined LBNP and mental stress (COMBO) is unknown. We hypothesized that performing a stressful cognitive challenge (i.e., mental stress) concurrently with LBNP would prevent LBNP-induced reductions of MCAv.

METHODS: There were 18 subjects (9 men, 9 women; ages 20.1 ± 0.3 yr) who completed 3 randomized 3-min trials: 1) LBNP (−40 mmHg); 2) mental stress (serial subtraction); and 3) COMBO (LBNP + mental stress). All reported values are mean ± SE. Mean arterial pressure (MAP), heart rate (HR), forearm blood flow (FBF), and MCAv were measured continuously. Subjects also reported perceived stress following the mental stress and COMBO trials.

RESULTS: LBNP decreased MAP (Δ−1.4 ± 0.5 mmHg), MCAv (Δ−2.6 ± 1.1 cm · s^{-1}) and FBF (Δ−0.8 ± 0.1 units), and increased HR (Δ2.7 ± 1.2 bpm). Mental stress increased MAP (Δ10.1 ± 1.3 mmHg), HR (Δ17.4 ± 2.2 bpm), and FBF (Δ2.4 ± 0.4 units), while MCAv (Δ2.8 ± 1.3 cm · s^{-1}) tended to increase. COMBO increased MAP (Δ5.3 ± 2.3 mmHg) and HR (Δ21.3 ± 2.6 bpm), and tended to increase FBF (Δ0.5 ± 0.3 units). However, MCAv (Δ-4.6 ± 2.0 cm · s^{-1}) decreased during COMBO. Decreases in MCAv during COMBO were not statistically different from LBNP-induced decreases (Δ−4.6 ± 2.0 vs. Δ−2.6 ± 1.1 cm · s^{-1}). Subjective ratings of perceived stress (standard 0 to 4 scale) tended to be higher during COMBO than mental stress (2.9 ± 0.1 vs. 2.5 ± 0.1 units).

CONCLUSION: Our results suggest that mental stress does not effectively preserve MCAv when combined with central hypovolemia (i.e., LBNP).

KEYWORDS: blood pressure, forearm blood flow, heart rate, LBNP, middle cerebral artery.

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Lower body negative pressure (LBNP) is often used to examine tolerance to progressive hypovolemia in humans.[8] Presyncopal symptoms during LBNP are a result of cerebral hypoperfusion, which is associated with a reduction in middle cerebral artery blood velocity (MCAv), even without concomitant reductions of mean arterial blood pressure (MAP).[2] LBNP consistently decreases mean MCAv,[3,12,26] which contributes to impaired cognitive function.[14]

In contrast to LBNP, mental stress (a stressful cognitive challenge) increases MCAv.[9,16,20] Thus it is plausible that mental stress could preserve mean MCAv during LBNP. A previous study demonstrated that performing a head-down rotation (i.e., a sympathoexcitatory maneuver) during LBNP resulted in preservation of MCAv.[30] Because mental stress is also a sympathoexcitatory maneuver,[10,11] it is possible that mild-to-moderate levels of mental stress might preserve mean MCAv during LBNP and, consequently, help to delay and/or prevent cerebral hypoperfusion.

The purpose of the present study was to determine if mild-to-moderate levels of cognitive challenge during simulated orthostatic stress would preserve mean MCAv. We hypothesized that performing mental stress concurrently with LBNP would prevent LBNP-induced reductions of MCAv.

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METHODS

Subjects

We studied 18 nonobese adults (9 men, 9 women; ages 20.1 ± 0.3 yr; body mass index 23.5 ± 0.7 kg · m^{-2}). Subjects were free of hypertension, indicated by their seated resting systolic blood pressure of 113 ± 3 mmHg and diastolic arterial blood pressure of 69 ± 3 mmHg. All subjects abstained from caffeine, exercise, and alcohol for at least 12 h prior to laboratory testing and had no history of autonomic dysfunction, diabetes, or cardiovascular disease. All women were tested during the early follicular phase (days 2 to 5) of their menstrual cycle to prevent any potential confounding hormonal effect on cerebral blood flow[19] or autonomic responses.[6,7] The Institutional Review Board of Michigan Technological University approved the experimental protocol in advance. Each subject provided written informed consent before the study.

Procedure

Our protocol included three randomized trials: 1) 3 min of LBNP (−40 mmHg); 2) 3 min mental stress (serial subtraction); and 3) 3 min combined LBNP and mental stress (COMBO). All trials were conducted while the subject was lying supine on a flat table. Each intervention was preceded by a 3-min baseline period and 10 min of nonrecording time followed each trial to allow hemodynamic variables to stabilize. LBNP was applied at −40 mmHg while subjects were wearing a neoprene skirt positioned at the level of the iliac crest. Mental stress consisted of serial subtraction, where subjects subtracted 6 or 7 from a 2 or 3 digit number provided randomly every 5 to 10 s. Subtraction was performed as quickly as possible while other investigators provided distractions to make the task stressful. The COMBO trial consisted of simultaneous −40 mmHg LBNP and mental stress. After completion of the mental stress and COMBO trials, perceived stress was rated on a standard 0 to 4 scale of: 0 (not stressful), 1 (somewhat stressful), 2 (stressful), 3 (very stressful), and 4 (very, very stressful).[4] MAP, heart rate (HR), cardiac output, stroke volume, MCAv, expired carbon dioxide (CO_2), and forearm blood flow (FBF) were continuously measured throughout each trial.

Arterial blood pressure was measured while seated at rest and immediately preceding each trial in the supine position using an automated sphygmomanometer (Omron HEM-907XL, Omron Health Care, Vernon Hills, IL). All resting blood pressures were performed in triplicate after at least 5 min of quiet rest. Continuous blood pressure was measured using a Finometer (Finapres Medical Systems, Amsterdam, The Netherlands) and these pressures were normalized to the average of three supine readings from the automated cuff preceding each baseline. HR was recorded using a three-lead electrocardiogram. Finometer data (normalized for sex, age, height, and weight) were also used to derive estimates of cardiac output and stroke volume. Venous occlusion plethysmography (EC6; D. E. Hokanson, Bellevue, WA) was used to measure FBF, which required a cuff on the upper arm (inflated to 60 mmHg) and another on the wrist (inflated to 220 mmHg), along with an insilastic strain gauge on the forearm at the point of greatest circumference. The cuffs were inflated on 15-s cycles (8 s inflation, 7 s deflation) and data were averaged for each minute throughout each 6-min trial. A transcranial Doppler (Care Fusion, Neurocare, Madison, WI) and commercial headgear were used to continuously measure cerebral blood flow velocity by placing a probe at a fixed constant angle over the right temporal window. Cerebral blood flow velocity is reported as mean MCAv in cm · s^{-1}. Data sampling occurred at 500 Hz and data were stored on a computer with specialized software (WINDAQ, Dataq Instruments, Akron, OH). Expired CO_2 was measured from below the nostril during each trial with an infrared analyzer (#17630, Vacumed, Ventura, CA) and recorded as an average every 15 s. We obtained quality expired CO_2 data for 8 men and 8 women; thus, expired CO_2 data is presented for 16 of 18 subjects.

Data were imported and analyzed in the WinCPRS software program (Absolute Aliens, Turku, Finland). R waves from the electrocardiogram were confirmed and marked in the time series. The systolic and diastolic waves were also confirmed and marked from the Finometer. Similarly, transcranial Doppler systolic and diastolic waves were confirmed and marked by a trained investigator. We were unable to obtain clear Doppler waveforms for one woman during the mental stress task, thus MCAv data are presented for 17 of the 18 subjects.

Statistical Analysis

All data were analyzed with commercial software (IBM® SPSS® Statistics Version 20). A two-way repeated measures ANOVA (condition × 3; time × 2) was used for all major dependent variables (MAP, HR, cardiac output, stroke volume, MCAv, CO_2, and FBF). Post hoc paired *t*-tests were used when appropriate (i.e., condition × time, $P < 0.05$) to determine if changes were different across conditions and to compare the baseline versus intervention within each condition. Bonferroni correction was used when comparing across conditions to prevent type I error. Pearson correlation analysis were performed to probe for a potential relationship between changes in perceived stress vs. changes in MCAv, changes in FBF vs. changes in MCAv, changes in CO_2 vs. changes in MCAv, and changes in MAP and changes in MCAv during COMBO. Means were considered significantly different when $P < 0.05$, except when comparing across conditions with Bonferroni correction where $P < 0.0167$ was significant. Results are expressed as mean ± SE.

RESULTS

Baseline MAP, HR, cardiac output, stroke volume, MCAv, expired CO_2, and FBF were similar before each trial as shown in **Table I**. Table I also depicts absolute mean baseline and intervention values for each major dependent variable along with the *P*-value for within each condition. Compared with baseline measurements, LBNP significantly decreased MAP [Δ−1.4 ± 0.5 mmHg; $t(17) = 2.83$, $P = 0.01$], MCAv [Δ−2.6 ± 1.1 cm · s^{-1}; $t(16) = 2.29$, $P = 0.04$], and FBF [Δ−0.8 ± 0.1

Table I. Mean Values for All Baselines and Interventions.

VARIABLE	CONDITION	BASELINE	INTERVENTION	*P*-VALUE
MAP (mmHg)	LBNP	80.7 ± 1.7	79.3 ± 1.9*	= 0.01
	Mental Stress	79.6 ± 1.2	89.7 ± 1.7*	< 0.01
	COMBO	79.7 ± 1.4	85.0 ± 3.0*	= 0.03
HR (bpm)	LBNP	65.3 ± 2.1	67.9 ± 2.3*	= 0.03
	Mental Stress	67.0 ± 2.3	84.4 ± 3.6*	< 0.01
	COMBO	66.6 ± 2.2	88.0 ± 3.8*	< 0.01
CO ($L \cdot min^{-1}$)	LBNP	5.3 ± 0.2	4.5 ± 0.2*	< 0.01
	Mental Stress	5.6 ± 0.2	7.6 ± 0.4*	< 0.01
	COMBO	5.6 ± 0.2	5.4 ± 0.3	= 0.57
SV (ml/beat)	LBNP	82.7 ± 3.4	67.1 ± 3.5*	< 0.01
	Mental Stress	84.3 ± 2.6	90.3 ± 3.5*	< 0.01
	COMBO	84.8 ± 4.3	63.8 ± 4.1*	< 0.01
MCAv ($cm \cdot s^{-1}$)	LBNP	69.8 ± 3.3	67.2 ± 2.9*	= 0.04
	Mental Stress	69.3 ± 3.2	72.0 ± 3.6	= 0.06
	COMBO	68.9 ± 2.9	64.3 ± 2.7*	= 0.03
CO_2 (%)	LBNP	3.8 ± 0.2	3.7 ± 0.2	= 0.10
	Mental Stress	3.7 ± 0.2	1.9 ± 0.2*	< 0.01
	COMBO	3.8 ± 0.2	1.6 ± 0.2*	< 0.01
FBF (units)	LBNP	3.1 ± 0.3	2.3 ± 0.3*	< 0.01
	Mental Stress	3.4 ± 0.3	5.8 ± 0.6*	< 0.01
	COMBO	3.4 ± 0.4	3.9 ± 0.4	= 0.06

Values are mean ± SE.
LBNP, lower body negative pressure; COMBO, simultaneous LBNP and mental stress; MAP, mean arterial blood pressure; HR, heart rate; CO, cardiac output; SV, stroke volume; MCAv, mean middle cerebral artery blood flow velocity; CO_2, expired carbon dioxide; FBF, forearm blood flow.
* Significantly different than baseline ($P < 0.05$).

units; $t(17) = 8.40$, $P < 0.01$], and significantly increased HR [$\Delta 2.7 \pm 1.2$ bpm; $t(17) = -2.30$, $P = 0.03$]. Mental stress increased MAP [10.1 ± 1.3 mmHg; $t(17) = -7.86$, $P < 0.01$], HR [$\Delta 17.4 \pm 2.2$ bpm; $t(17) = -7.91$, $P < 0.01$], and FBF [$\Delta 2.4 \pm 0.4$ units; $t(17) = -2.68$, $P = 0.02$], while MCAv [$\Delta 2.8 \pm 1.3$ cm $\cdot$ s^{-1}; $t(16) = -2.06$, $P = 0.06$] tended to increase. COMBO increased MAP [$\Delta 5.3 \pm 2.3$ mmHg; $t(17) = -2.30$, $P = 0.03$] and HR [$\Delta 21.3 \pm 2.6$ bpm; $t(17) = -8.20$, $P < 0.01$], and tended to increase FBF [$\Delta 0.5 \pm 0.3$ units; $t(17) = -2.00$, $P = 0.06$]. However, MCAv [$\Delta -4.6 \pm 2.0$ cm $\cdot$ s^{-1}; $t(16) = 2.35$, $P = 0.03$] significantly decreased during COMBO. The cardiovascular responses to each intervention are depicted in **Fig. 1**, while cerebral and forearm blood flow changes are shown in **Fig. 2**.

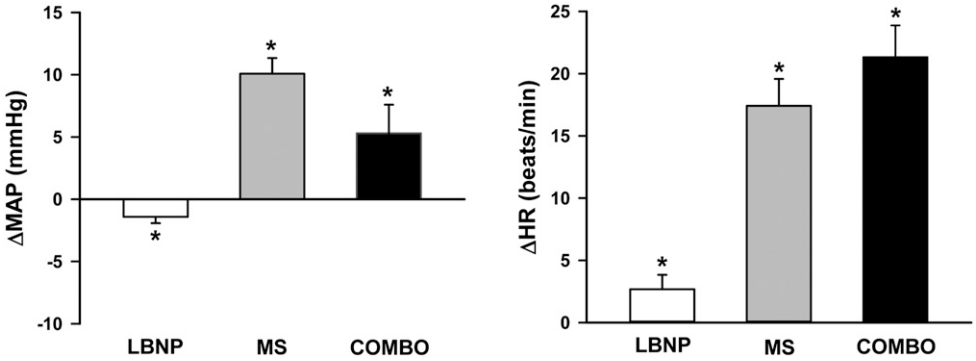

Fig. 1. Mean arterial pressure (MAP; left) and heart rate (HR; right) responses to lower body negative pressure (LBNP), mental stress (MS), and simultaneous LBNP and MS (COMBO). *MAP and HR were significantly different than baseline during LBNP, MS, and COMBO ($P < 0.05$). Results are expressed as mean ± SE.

Changes (Δ) in MAP, HR, and FBF from baseline to intervention were significantly different across conditions (i.e., LBNP, mental stress, and COMBO; $P < 0.02$ for all). Similarly, the change in MCAv from baseline to intervention was significantly different during the LBNP vs. mental stress and the mental stress vs. COMBO trials ($P < 0.01$ for both). However, the decrease in MCAv during COMBO was not statistically different than the decrease in MCAv during LBNP [$\Delta -4.6 \pm 2.0$ vs. $\Delta -2.6 \pm 1.1$ cm $\cdot$ s^{-1}; $t(16) = 0.90$, $P = 0.38$], as depicted on the left panel of Fig. 2. The reduction in expired CO_2 was similar during COMBO and mental stress [$\Delta -2.0 \pm 0.2$ vs. $\Delta -1.7 \pm 0.2$%; $t(15) = 2.06$, $P = 0.06$]. Finally, subjective ratings of perceived stress tended to be higher during COMBO than mental stress [2.9 ± 0.1 vs. 2.5 ± 0.1 units; $t(17) = -2.29$, $P = 0.04$]. Pearson correlation analyses revealed that changes in MCAv during COMBO were not directly related to changes in perceived stress ($P = 0.84$), FBF ($P = 0.71$), CO_2 ($P = 0.44$), or MAP ($P = 0.44$).

DISCUSSION

This study is the first to examine the MCAv responses to combined LBNP and mental stress. We present three new findings. First, in contrast to our primary hypothesis, COMBO elicited a reduction of MCAv, which was observed despite an increase of MCAv during the mental stress trial. Second, our results demonstrate that mental stress appears to induce a robust cardiovascular and emotional response, as MAP and FBF remained significantly elevated during COMBO. Third, combined mental stress and LBNP tended to be more stressful than independent mental stress. Taken together, the decreased MCAv during COMBO might be partially explained by simultaneous increases in limb blood flow, and the increase in perceived stress during COMBO vs. mental stress may in part be a result of decreased MCAv.

LBNP consistently decreases MCAv[12,15,17] by inducing central hypovolemia due to venous pooling in the legs.[1] In contrast, mental stress increases MCAv due to increased cognitive demand[20,21,27] and potentially via increased cardiac output.[22,29] However, our results indicate that MCAv was not preserved by performing mental stress in conjunction with LBNP (i.e., COMBO). The dramatic decrease in MCAv during COMBO in the current study may be partially due to the simultaneous increase in FBF (~21%). While the mental stress component of the COMBO intervention increases FBF,[25,31] the LBNP component of the intervention typically increases calf blood flow.[13] The end result of increased limb blood flow during this combined stressor likely contributed to the significant drop in MCAv

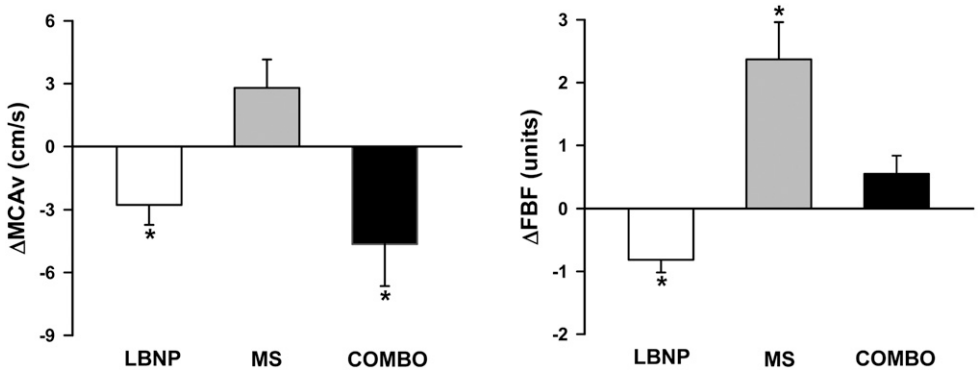

Fig. 2. Middle cerebral artery blood flow velocity (MCAv; left) and forearm blood flow (FBF; right) responses to lower body negative pressure (LBNP), mental stress (MS), and simultaneous LBNP and MS (COMBO). *MCAv was significantly lower than baseline during LBNP and COMBO, while FBF was significantly different than baseline during LBNP and MS ($P < 0.05$). Results are expressed as mean ± SE.

(~6%). Increased blood flow to limbs and compromised venous return is supported by the significant reduction in stroke volume (~21 ml/beat) during COMBO. The reduction in MCAv was not likely a result of compromised cardiac output, as cardiac output was maintained during COMBO (see Table I). We acknowledge that decreases in MCAv during COMBO could also be partially due to decreases in CO_2. However, the reduction of CO_2 and reduction of MCAv during COMBO were not correlated ($r = -0.21$; $P = 0.44$). Thus hypocapnia does not appear to be a primary mechanism for the reduction of MCAv during COMBO. Furthermore, Perry et al.[23] have demonstrated that the relationship between MCAv and CO_2 may be altered during induced changes in MAP.

Despite the reduced MCAv during COMBO, MAP was still modestly increased (~5 mmHg) due to the mental stress portion of the intervention. Perry et al.[24] have shown that changes in MCAv may not be directly associated with increases in MAP during a hypertensive stimulus, but decreases in MCAv appear to be closely associated with decreases in MAP during a hypotensive stimulus. The increase of MAP during COMBO in the present study is not associated with maintenance of MCAv ($r = 0.20$; $P = 0.44$), and thus does not protect against cerebral hypoperfusion. Presyncopal symptoms have been reported during intense LBNP in men and women when MAP was maintained, but MCAv dropped.[2] Although the decrease in MCAv during COMBO was not statistically different than the decrease experienced during LBNP (~6 vs. ~3%), a decrease of approximately double during COMBO could have physiological relevance. Even though presyncopal symptoms may not present until MCAv decreases by about 25 to 35% from baseline,[2,28] MCAv may decrease by as little as 6 or 7% during the progression from an asymptomatic to a symptomatic state.[2] Inducing presyncopal symptoms was not a primary aim of this study, but future studies may examine more extreme levels of mental stress[25] and/or LBNP[8] to determine how the combined stressors might interact and contribute to presyncope.

Perceived stress tended to be higher during COMBO than mental stress alone (2.9 ± 0.1 vs. 2.5 ± 0.1 units). Higher perceived stress during COMBO could result from the additional decrease in MCAv; however, changes in MCAv were not correlated to perceived stress ($r = -0.05$; $P = 0.84$). This correlation analysis is likely limited by the reported perceived stress scores being in a narrow range (1.5 to 4.0 units) and the frequency of the COMBO being rated as very stressful (11 of 17 subjects with quality Doppler waveforms rated COMBO as 3.0 units). Mental stress is employed primarily as a form of cognitive stress[5] and previous studies have indicated that decreases in MCAv can inhibit cognitive performance[14] and lead to cognitive dysfunction.[18] Our COMBO perceived stress results are consistent with Han et al.,[14] in that cognitive performance became more difficult during the reduction in MCAv.

It should be noted that transcranial Doppler ultrasound records blood velocity and not blood flow. Blood flow is reflected faithfully by velocity unless the diameter of the vessel changes. Serrador et al.[26] showed with MRI scans that middle cerebral artery dimensions are not affected by LBNP. We therefore conclude that our cerebral velocity measurements are accurate reflections of cerebral blood flow.

We recognize that recording CO_2 from a nasal cannula could be viewed as a potential limitation. By using this method we detected a significant drop in expired CO_2 during the two interventions where subjects were answering verbal math problems (i.e., mental stress and COMBO). This reduction of CO_2 was likely due to a greater extent of expired air exiting the mouth than the nose while subjects verbally responded. We do not believe this is a major limitation, as expired CO_2 from the nose decreased to a similar extent during the mental stress and COMBO trials as shown in Table I, and the reduction of MCAv during COMBO was not correlated to the reduction of CO_2 as reported above. Thus, it is unlikely that the divergent MCAv responses between mental stress and COMBO were modulated by changes in CO_2. We also acknowledge that cognitive function was not directly evaluated with a performance measurement, such as how many numbers were answered correctly, or the time it took for responses. As mentioned above, the perceived stress rating tended to be higher during COMBO than mental stress, which may indirectly indicate that cognitive function was impaired during COMBO. However, this could be more directly evaluated in future studies using serial subtraction or other forms of cognitive stress, such as the Stroop color conflict, by recording the number of correct vs. incorrect responses and response times. Finally, the men and women in the present study had a mean age of 20 yr, thus some results may not be generalizable to the typical astronaut, or to older adults.

In conclusion, we determined that MCAv is decreased during concurrent mental stress and LBNP, despite an increase of MCAv during the independent mental stress trial. These results indicate that individuals experiencing combined cognitive and orthostatic challenge (e.g., military, astronauts, etc.) may require countermeasures to maintain adequate cerebral blood flow. Decreases in MCAv during COMBO appear to be at least partially due to increased limb blood flow. COMBO tended to be perceived as more stressful than mental stress, which may be an early symptom of decreases in MCAv.

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