

Normobaric Hypoxia and Submaximal Exercise Effects on Running Memory and Mood State in Women

Yongsuk Seo; Hayden D. Gerhart; Jon Stavres; Curtis Fennell; Shane Draper; Ellen L. Glickman

- BACKGROUND:** An acute bout of exercise can improve cognitive function in normoxic and hypoxic conditions. However, limited research supports the improvement of cognitive function and mood state in women. The purpose of this study was to examine the effects of hypoxia and exercise on working memory and mood state in women.
- METHODS:** There were 15 healthy women (age = 22 ± 2 yr) who completed the Automated Neuropsychological Assessment Metrics-4th Edition (ANAM), including the Running Memory Continuous Performance Task (RMCPT) and Total Mood Disturbance (TMD) in normoxia (21% O₂), at rest in normoxia and hypoxia (12.5% O₂), and during cycling exercise at 60% and 40% $\dot{V}O_{2\max}$ in hypoxia.
- RESULTS:** RMCPT was not significantly impaired at 30 (100.3 ± 17.2) and 60 (96.6 ± 17.3) min rest in hypoxia compared to baseline in normoxia (97.0 ± 17.0). However, RMCPT was significantly improved during exercise (106.7 ± 20.8) at 60% $\dot{V}O_{2\max}$ compared to 60 min rest in hypoxia. Following 30 (-89.4 ± 48.3) and 60 min of exposure to hypoxia (-79.8 ± 55.9) at rest, TMD was impaired compared with baseline (-107.1 ± 46.2). TMD was significantly improved during exercise (-108.5 ± 42.7) at 40% $\dot{V}O_{2\max}$ compared with 30 min rest in hypoxia. Also, RMCPT was significantly improved during exercise (104.0 ± 19.1) at 60% $\dot{V}O_{2\max}$ compared to 60 min rest in hypoxia (96.6 ± 17.3).
- DISCUSSION:** Hypoxia and an acute bout of exercise partially influence RMCPT and TMD. Furthermore, a moderate-intensity bout of exercise (60%) may be a more potent stimulant for improving cognitive function than low-intensity (40%) exercise. The present data should be considered by aeromedical personnel performing cognitive tasks in hypoxia.
- KEYWORDS:** hypoxia, running memory continuous performance task, mood state, women, exercise.

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Hypoxia can be induced by either pathological (chronic obstructive pulmonary disease, sleep apnea) or environmental (changes in altitude or inhaled oxygen concentrations) influences. Previous research with 16 men reported that a 60-min exposure to normobaric hypoxia led to a lower throughput (working memory) score (number of correct responses per minute) on the Running Memory Continuous Performance Test (RMCPT) within the Automated Neuropsychological Assessment Metrics-4th Edition (ANAM⁴), and Total Mood Disturbance (TMD) scores improved with low- to moderate-intensity exercise.^{18,19} A review article indicated that acute aerobic exercise has a positive influence on cognitive function via increased cortical activity, stimulation of the central nervous system, increased neurotransmitters and a change in regional brain blood flow, and increased arousal.²³ A wide range of cognitive dysfunction has been associated with hypoxia, which may be induced from climbing a mountain,

including impairment of short-term memory, verbal fluency, language production, cognitive fluency, meta-memory, and mood state.²³

Although the direct interaction between hypoxia and cognitive dysfunction is not fully understood, it has been suggested that cerebral deoxygenation and altered neurotransmitters are potential bases for negative cognitive effects.¹³ The improvements of cognitive function and mood state have been reported during low- to moderate-intensity exercise at sea level in men.⁵

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However, limited research has examined the effect of hypoxia and exercise on cognitive function and mood state response to hypoxia in healthy women. There are gender-related functional and morphological differences between men and women such as body composition, muscle strength, pulmonary function, cardiovascular function, metabolism, and such brain characteristics as volume, gray matter, white matter, cerebrospinal fluid, and neuronal processes.¹⁷ Gender-related differences in sympathetic nerve activity in response to hypoxia and exercise as indexed by cardiovascular function (tachycardia) have also been reported in human and animal models.⁹

Sympathetic nerve activity is an important role in circulatory adjustment to hypoxia. Indeed, women exhibited lower latency for peak muscle sympathetic nerve activity and faster muscle sympathetic nerve activity recovery to baseline than men in hypoxia.⁹ Vagal tone, indexed by resting heart rate and heart rate recovery following termination of exercise is related to the activity of the prefrontal cortex, which, in turn, relates to executive functions such as working memory, decision making, perception, motor function, and inhibitory response.^{8,21} Thus, the purpose of the current study is to quantify working memory and mood state of women subjected to mild hypoxia and to determine if any declines in working memory and mood state in hypoxia can be restored by an acute bout of exercise. We hypothesized that running memory and mood state would be decreased during rest in hypoxia and running memory and mood state would be restored during low- to moderate-intensity exercise in hypoxia.

METHODS

Subjects

The Institutional Review Board at Kent State University approved this study and all participants gave written informed consent prior to participation. There were 15 young healthy women (22 ± 2 yr of age; height = 165.5 ± 6.5 cm, weight = 62.1 ± 8.8 kg, and body mass index = 22.8 ± 3.3 kg · m⁻²) who volunteered for and participated in the current investigation. Participants were not controlled for any contraceptive drug use because doing so may have led to drug withdrawal side effects (e.g., menstruation timing, bleeding, and menstrual irregularity). However, participants performed the present study when outside of their menstrual cycle (self-report). All participants were physically active and free of pulmonary disease, cardiovascular disease, postural orthostatic tachycardia syndrome, skeletal muscle injury in the lower limbs, and were not exposed to normobaric hypoxia or an altitude above 2500 m (8202 ft) within 2 mo prior to participation in the study.

Equipment

RMCPT and Mood State were assessed through administration of specific subsets of the ANAM⁴, a computerized cognitive performance test battery consisting of a variety of cognitive domains. The ANAM⁴ has been administered to military and sports-related concussion, exposure to radiation, high altitude,

undersea, and toxic conditions.¹³ The ANAM⁴ was designed to minimize the learning effect by randomizing the stimulus (questions in each testing category) and allows researchers to develop specific protocols by selecting from various validated cognitive tests, both of which facilitate repeated-measures testing.⁷

The RMCPT was chosen because running (working) memory is a major component of executive function and plays a role in many daily activities.¹⁸ When a number was displayed, the participants were instructed to click the mouse button as quickly as possible in response to if it matched (left) or did not match (right) the previously displayed number.

The mood state is designed to assess seven specific categories of mood: anger, anxiety, depression, fatigue, happiness, restlessness, and vigor. Specifically, through the use of a laptop, 42 words expressing various emotions were presented to the subject and they were instructed to choose a number between 0 and 6, with 0 being “Not at all” and 6 being “Very Much” for each emotion presented. These emotions are associated with the seven categories of mood state. TMD was calculated as follows: TMD = (negative mood – positive mood), where negative mood is the sum of the anger, anxiety, depression, fatigue, and restlessness scores, and positive mood is the sum of the happiness and vigor scores. Higher TMD scores indicated greater negative mood states.

Procedures

Each participant reported to the laboratory on two separate occasions (familiarization trial/submaximal and maximal $\dot{V}O_2$ assessments and experimental trial). During the familiarization/submaximal and maximal $\dot{V}O_2$ assessments, participants underwent prescreening and were introduced to the simulated altitude chamber. Participants were also familiarized with the protocol and instrumentation, including performing the cognitive function and mood tests a minimum of three times. Participants then performed two exercise protocols on a cycle ergometer (Lode Excalibur Sport, Lode, Groningen, Netherlands) to determine the submaximal exercise intensity that would be used during the subsequent experimental trial. The first protocol required participants to pedal through three 4-min stages at 50, 100, and 150 W to develop the $\dot{V}O_2$ -workrate relationship. Upon completion of the first protocol, participants rested for at least 20 min. The second protocol was a $\dot{V}O_{2max}$ test, which required subjects to pedal on the cycle ergometer through increasing stages of intensity starting at 20 W and increasing by 25 W every minute until volitional fatigue.¹ During both protocols $\dot{V}O_2$ was measured with a TrueOne 2400 metabolic cart (ParvoMedics, Sandy, Utah) and HR was measured with a Polar heart rate monitor (Polar RS800 CX, Polar Electro Oy, Kempele, Finland), respectively. The combination of these two protocols allowed for the determination of $\dot{V}O_{2max}$ as well as the power output required to elicit 60% and 40% $\dot{V}O_{2max}$, which was ultimately reduced by 27% for the experimental trial to adjust for the $\dot{V}O_{2max}$ decrements with altitude.²⁴ The adjusted 60% and 40% exercise intensities were selected as they span the range of exercise intensities previously reported to improve cognitive function at sea level.²²

On the day of the experimental trial, participants reported to the Exercise Physiology Laboratory at Kent State University following a 3-h self-reported fast intended to stabilize substrate utilization¹⁵ and reduce the risk of subjects becoming nauseous during exercise in the hypoxic chamber. Participants were initially equipped with a heart rate (HR) monitor, mouthpiece for the metabolic cart, near-infrared spectroscopy sensors over the frontal lobe (Somanetics, Troy, MI) for regional cerebral oxygen saturation (rSO₂) monitoring and digit pulse-oximeter (Oxi-Go, Roslyn, NY) for peripheral oxygen saturation (S_pO₂) measurement. Participants sat in a chair quietly during 5-min baseline recordings of resting metabolic rate ($\dot{V}O_2$), blood pressure, HR, S_pO₂, and rSO₂. RMCPT and TMD were assessed via the ANAM⁴.

Following baseline measurements during rest in normoxia, participants entered the hypoxia chamber (Colorado Altitude Training, Louisville, CO), where the oxygen concentration was reduced to 12.5% with subsequent increases in %N₂, but no changes in the %CO₂. The 12.5% O₂ is equivalent to the oxygen level present at an altitude of 4300 m (14,110 ft). The room temperature and relative humidity in the hypoxic chamber were consistently 22–24°C and 30–40%, respectively, throughout testing. After resting in a chair for 60 min in the hypoxic chamber, $\dot{V}O_2$, HR, S_pO₂, and rSO₂ were recorded and RMCPT and Mood state were administered at 30 and 60 min.

The 60 min of resting in the hypoxia condition was chosen because, to our knowledge, resting in hypoxia for 60 min is the shortest determined period to result in a decline in cognitive function and mood state in individuals (previously men).^{11,12} Following the completion of 60 min resting in hypoxia, the participants performed 15-min bouts of cycle ergometry at 60% and 40% of adjusted $\dot{V}O_{2\max}$ with a 15-min recovery between bouts. The pedaling rate (rpm) was freely chosen and workload was maintained at the previously tested 60% and 40% of adjusted $\dot{V}O_{2\max}$ in a counterbalanced manner. All aforementioned RMCPT and mood state measurements were performed during the final 5 min of the 15-min exercise stages. Upon completion of the hypoxia trial, participants stepped out of the hypoxia chamber and rested until their S_pO₂ returned to baseline levels.

Statistical Analysis

Using SPSS 19.0, one-way repeated ANOVA was used to examine the effect of hypoxia and exercise on RMCPT, TMD, and physiological measurements. When the ANOVA indicated a significant main effect, post hoc pair-wise comparison with least

significant differences was performed. Statistical significance was set at $P \leq 0.05$ and all data are presented as mean \pm SD.

RESULTS

The average of $\dot{V}O_{2\max}$, adjusted $\dot{V}O_{2\max}$, and maximal HR were 40.8 ± 4.0 , 29.8 ± 2.9 ml \cdot kg⁻¹ \cdot min⁻¹, and 188.3 ± 7.5 bpm, respectively. The corresponding workloads of 60% and 40% were 66 ± 11 and 34 ± 11 W, respectively.

Table I shows physiological responses at rest in normoxia and hypoxia, and exercise in hypoxia. $\dot{V}O_2$, HR, mean arterial pressure (MAP), S_pO₂, and rSO₂ demonstrated a significant main effect for condition [$F(4, 52) = 266.0$, $P \leq 0.001$, $\eta_p^2 = 0.9$; $F(4, 56) = 104.6$, $P \leq 0.001$, $\eta_p^2 = 0.9$; $F(4, 56) = 4.1$, $P = 0.006$, $\eta_p^2 = 0.2$; $F(4, 56) = 72.7$, $P \leq 0.001$, $\eta_p^2 = 0.8$; and $F(4, 56) = 116.7$, $P \leq 0.001$, $\eta_p^2 = 0.9$, respectively]. $\dot{V}O_2$ was significantly increased at 30 min rest in hypoxia ($P = 0.024$) and was not significantly different at 60 min rest in hypoxia compared to baseline. HR was not significantly different at 30 min rest in hypoxia and was significantly increased at 60 min rest ($P = 0.005$) in hypoxia compared to baseline. MAP was not significantly changed at 30 and 60 min rest in hypoxia compared to baseline. S_pO₂ was significantly decreased at 30 and 60 min rest in hypoxia compared to baseline ($P \leq 0.001$). rSO₂ was significantly decreased at 30 and 60 min rest in hypoxia compared to baseline ($P \leq 0.001$, both).

$\dot{V}O_2$ was significantly increased during both 60% ($P \leq 0.001$) and 40% ($P \leq 0.001$) exercises compared to 60 min rest in hypoxia. $\dot{V}O_2$ was significantly higher during 60% exercise compared to 40% exercise ($P \leq 0.001$). HR was significantly increased during both 60% ($P \leq 0.001$) and 40% ($P \leq 0.001$) exercises compared to 60 min rest in hypoxia. HR was also significantly higher during 60% exercise compared to 40% exercise ($P = 0.001$). MAP was significantly increased during both 60% and 40% exercise compared to 60 min rest ($P = 0.011$ and $P = 0.004$, respectively). MAP did not differ between 60% and 40% exercises ($P = 0.4$). S_pO₂ was not significantly changed during both 60% and 40% exercise compared to 60 min rest in hypoxia ($P = 0.1$, $P = 0.2$, respectively). Also, S_pO₂ did not differ between 60% and 40% exercise. rSO₂ was significantly decreased during both 60% and 40% exercise compared to 60 min rest in hypoxia ($P \leq 0.001$, both). However, rSO₂ was not significantly different between 60% and 40% exercise ($P = 0.1$, $\eta_p^2 = 0.5$).

Table I. Oxygen Consumption, Heart Rate, Mean Arterial Pressure, Peripheral Oxygen Saturation, and Regional Cerebral Oxygen Saturation at Baseline, 30 min and 60 min Resting in Hypoxia, and During 60% and 40% Exercise in Hypoxia.

	$\dot{V}O_2$ (ml \cdot kg ⁻¹ \cdot min ⁻¹)	HR (bpm)	MAP (mmHg)	S _p O ₂ (%)	rSO ₂ (%)
Baseline	4.1 \pm 0.5	74.3 \pm 9.1	82.6 \pm 6.2	98.1 \pm 1.0	66.5 \pm 8.8
30 min	4.5 \pm 0.9*	83.5 \pm 13.9	81.3 \pm 7.0	83.3 \pm 5.1*	53.2 \pm 7.6*
60 min	4.4 \pm 0.9	84.8 \pm 11.1*	78.4 \pm 11.3	82.2 \pm 5.1*	52.6 \pm 7.3*
60% Exercise	11.8 \pm 2.8***,†	147.3 \pm 16.3***,†	84.9 \pm 8.1†	80.0 \pm 4.0***	49.1 \pm 6.7***,†
40% Exercise	13.2 \pm 2.5***,†,‡	130.4 \pm 16.8***,†,‡	86.4 \pm 7.8***,†	80.2 \pm 3.5***	49.9 \pm 6.6***,†

Values are mean \pm SD. $\dot{V}O_2$, oxygen consumption; HR, heart rate; MAP, mean arterial pressure. * $P < 0.05$, vs. at Baseline, ** $P < 0.05$ vs. at 30 min in hypoxia, † $P < 0.05$ vs. at 60 min in hypoxia, ‡ $P < 0.05$ vs. at 60% of exercise.

Fig. 1A and 1B illustrates the RMCPT and TMD response to hypoxia and during exercise. RMCPT and TMD demonstrated a significant main effect for time [$F(4, 56) = 2.6, P = 0.047, \eta_p^2 = 0.2$ and $F(4, 56) = 5.4, P = 0.001, \eta_p^2 = 0.3$, respectively]. RMCPT scores were not significantly decreased at 30 or 60 min rest in hypoxia compared to baseline. TMD was significantly worse at 30 min ($P = 0.004$) and at 60 min rest in hypoxia ($P = 0.001$) compared to baseline. However, TMD was not significantly different between 30 and 60 min rest in hypoxia.

During 60% exercise, RMCPT scores significantly improved compared to 60 min rest in hypoxia ($P = 0.013$). However, RMCPT scores were not significantly improved during 40% exercise compared to 60 min rest in hypoxia. TMD was not significantly improved during 60% exercise compared to 60 min rest in hypoxia, but significantly improved during 40% exercise compared to 60 min rest in hypoxia ($P = 0.001$).

DISCUSSION

The present study extends existing knowledge about hypoxia and the effect of exercise on cognitive function and mood state of women. In support of our hypotheses, TMD scores reflected a more disturbed mood state during rest in hypoxia and were improved during exercise at 40% $\dot{V}O_{2\max}$ in hypoxia. Contrary to our hypothesis, RMCPT was unchanged during rest in hypoxia, but improved during 60% $\dot{V}O_{2\max}$.

The present data are consistent with previous studies showing that an acute bout of low- to moderate-intensity exercise in normobaric hypoxia improved working memory and mood state.^{18,19} A previous study reported that the throughput score of RMCPT was improved during 40% and 60% exercise intensity,¹⁸ and past research showed that TMD was significantly improved during 40–60% exercise.¹⁹ However, the results from the current

study contrast with those of previous studies that reported a decline in RMCPT scores after 60 min rest in hypoxia,¹⁸ as these data indicated no significant change in RMCPT following 30 or 60 min in normobaric hypoxia. On the other hand, TMD was significantly more disturbed after exposure to hypoxia at 30 and 60 min. This result is in agreement with a previous study in which TMD was impaired following 60 min of rest in hypoxia.¹⁹ Although RMCPT assesses working memory, which is considered a major component of executive cognitive functioning, it is a simple task, and many studies have reported that more complex tasks are more sensitive to hypoxia than are simple tasks.¹²

In response to hypoxia, S_pO_2 and rSO_2 significantly decreased, which is in agreement with previous studies.²⁰ $\dot{V}O_2$ and HR, however, were significantly increased at 30 and 60 min in hypoxic conditions. These results are also in agreement with previous studies that HR of women significantly increased during 15 and 150 min rest in hypoxic conditions.^{3,9}

It seems paradoxical that RMCPT did not change with hypoxia, despite reductions in rSO_2 and S_pO_2 , as a decrease in rSO_2 due to hypoxia has been considered a major component of cognitive dysfunction. However, more recent investigations reported that executive function measured by RMCPT, Go/No-Go, and mood state were improved during exercise with lower S_pO_2 and rSO_2 .^{18,19} The possible explanation for improvement of RMCPT and TMD can be arousal of the sympathetic nervous system by exercise, as indexed by higher heart rate and oxygen uptake.¹⁰ Indeed, previous researchers demonstrated that improvement of memory load was related to higher heart rate and higher oxygen uptake (faster respiration rate, greater volume of exhaled CO_2).² It can be speculated that the increased $\dot{V}O_2$ and HR may contribute to maintaining RMCPT following 60 min rest in hypoxia, in contrast to men.¹⁸ With respect to TMD, reduced S_pO_2 and rSO_2 during rest in hypoxia might be more sensitive than RMCPT.

The results of RMCPT and TMD during exercise conditions in this study contrast with previous research which reported that RMCPT and TMD improved with both exercise intensities.^{18,19} RMCPT in this study was significantly improved only during 60% exercise intensity. The 40% exercise did not improve RMCPT and the 60% exercise did not improve TMD in the current study.

The present study used the RMCPT and TMD to assess cognitive function and mood state. Additional investigation is warranted to examine possible physiological pathways in different aspects of cognitive function and physiological response between genders in response to hypoxia.

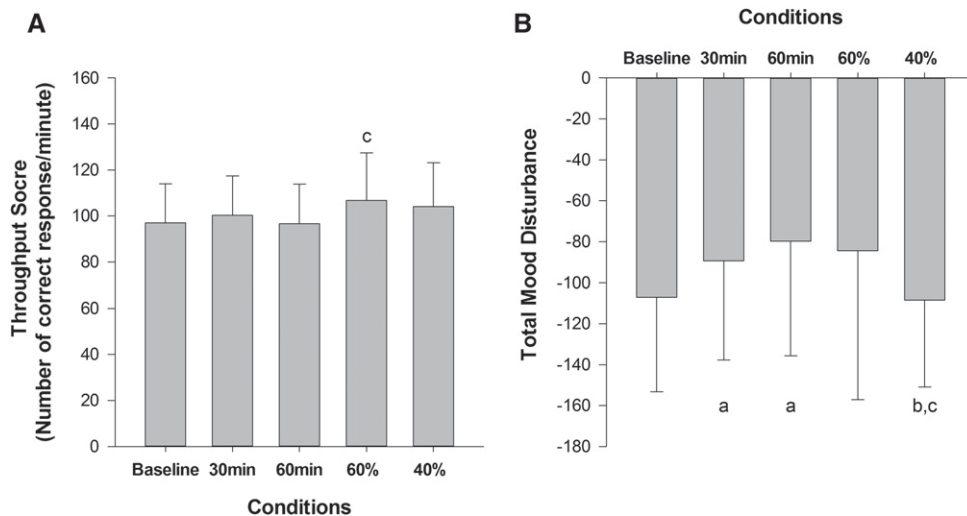


Fig. 1. A) Throughput score and B) Total mood disturbance at baseline following 30 min and 60 min of rest in hypoxia, and during exercise at 60% and 40% $\dot{V}O_{2\max}$ in hypoxia. ^a $P < 0.05$ vs. baseline; ^b $P < 0.05$ vs. 30 min in hypoxia; ^c $P < 0.05$ vs. 60 min in hypoxia; mean \pm SD.

Such physiological measurements include sympathetic nervous activity and bio-markers such as brain-derived neurotrophic factor, dopamine, serotonin, sex-hormones, etc. Moreover, women in this study were not controlled for contraceptive use or female menstrual cycles. Although previous investigations did not control for either contraceptive use or female menstrual cycles,⁶ there can be study variability from varying levels of estrogen and progesterone that play an integral role in metabolic regulation, body fluid, and electrolyte balance,¹⁶ impacting psychological and physiological responses to exercise in hypoxia.⁴ Additionally, although 60% and 40% $\dot{V}O_{2\max}$ exercise intensities were counterbalanced, 15 min of recovery between the two exercises could induce the lack of a significant difference on physiological measurements. This study could have benefited from the utilization of a normoxia control condition rather than a simple baseline measurement, which would allow for comparison between the individual effects of exercise and hypoxia. The findings in the present study should be interpreted with caution since this study recruited only young Caucasian women and used only normobaric hypoxia. Hence, the effect of acute exercise in hypoxia needs to be studied on a more diverse group (e.g., age and ethnicity) and in hypobaric hypoxia because there is a disagreement on physiological differences between hypobaric and normobaric hypoxia.¹⁴ Additional limitations include the lack of counterbalancing of each condition. The exercise conditions were counterbalanced; however, the other conditions, including rest in normoxia and rest in hypoxia, were not. Therefore, the results of this study could be because exercise relieved the participants from boredom after sitting for 60 min. Furthermore, effects of acclimation training and long-term exposure to hypoxia on physiological response and cognitive function need to be evaluated. Future experiments might use pharmacological strategies or nutritional supplementation to assess the interaction between cognitive performance and physiological parameters.

In conclusion, somewhat in contrast to our hypothesis, RMCPT and TMD were partially affected by hypoxia and exercise in hypoxia. Although S_pO_2 and rSO_2 were decreased following exposure to hypoxia and further decreased during exercise, RMCPT and TMD were still improved during exercise at 40–60%. Also, we found that physiological measurements of $\dot{V}O_2$ and HR were significantly higher at 30 and 60 min in hypoxia. Ultimately, this research applies to the aeromedical community because performing low- to moderate-intensity exercise may attenuate detrimental effects on RMCPT and TMD during aeromedical evacuation operations and mountain rescue personnel who need to perform appropriate cognitive tasks.

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