Cerebral Hemodynamics and Executive Function During Exercise and Recovery in Normobaric Hypoxia

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BACKGROUND: Hypoxia and exercise each exhibit opposing effects on executive function, and the mechanisms for this are not entirely clear. This study examined the influence of cerebral oxygenation and perfusion on executive function during exercise and recovery in normobaric hypoxia (NH) and normoxia (N).

METHODS: There were 18 subjects who completed cycling trials in NH (12.5% F_IO_2) and N (20.93% F_IO_2). Right prefrontal cortex (PFC) oxyhemoglobin (O_2Hb) and middle cerebral artery blood velocity (MCAbv) were collected during executive function challenges [mathematical processing and running memory continuous performance task (RMCPT)] at baseline, following 30 min of acclimation, during 20 min of cycling (60% $\dot{V}O_{2max}$), and at 1, 15, 30, and 45 min following exercise.

RESULTS: Results indicated effects of time for Math, RMCPT, and O_2Hb; but not for MCAbv. Results also indicated effects of condition for O_2Hb. Math scores were improved by 8.0% during exercise and remained elevated at 30 min of recovery (12.5%), RMCPT scores significantly improved at all time points (7.5–11.9%), and O_2Hb increased by 662.2% and 440.9% during exercise in N and NH, respectively, and remained elevated through 15 min of recovery in both conditions.

DISCUSSION: These results support the influence of PFC oxygenation and perfusion on executive function during exercise and recovery in N and NH.

KEYWORDS: altitude, oxygen delivery, cognitive function, acute hypoxia.

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Executive function is defined by the ability to control behaviors and work toward the achievement of goals. This domain of cognitive function has been linked primarily (though not exclusively) to prefrontal cortex (PFC) activity through fMRI techniques.[3,22,25] Just as executive functions can be improved through neurological development and cognitive training, they can also be acutely affected by psychological and physiological stimuli. Such impairments in executive functions during acute exposure to hypoxia have been well documented, both in hypobaric (altitude) and normobaric conditions. Previous research has found that at elevations of 3600 m [or its equivalent fraction of inspired oxygen (F_IO_2)] mood state, mathematical performance, working memory, and reaction time are all impaired,[14,15] and in some cases remain impaired up to 24 h.[2] This relationship is suggested to be mediated by a decrease in oxygen delivery to the PFC, evident by a reduction in PFC oxyyhemoglobin (O_2Hb) saturation.[6] There is little evidence to indicate that total cerebral perfusion (i.e., total cerebral blood flow) is affected during asymptomatic hypoxic exposure or during cognitive tasks, suggesting that reduced blood oxygen saturation is primarily responsible for the hypoxia related decrease in PFC O_2Hb saturation.

In contrast to the impairment in executive functions observed during hypoxic exposure, acute exercise has been shown to improve executive functions. This relationship has been linked to increases in serotonin,[30] PFC activity,[21] and down regulation of gamma-aminobutyric acid (GABA).[20] Seo et al.[26] tested the potential mitigating effects of exercise on the normobaric hypoxia-induced decline in executive function, and found that mild to moderate intensity aerobic exercise (40–60% adjusted $\dot{V}O_{2max}$) restored working memory and reaction time during exposure to normobaric hypoxia (12.5%). These results were concomitant with decreases in arterial

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oxygen saturation and O_2Hb saturation of the PFC; an effect also observed in other research.[13,27] This restoration of executive function during periods of decreased PFC O_2Hb contradicts the idea that PFC oxygenation is the primary mediator of executive function. However, there is a lack of research examining the recovery period following exercise in hypoxia and in normoxia. Focusing on the recovery period following a bout of moderate intensity exercise may provide some missing information necessary for understanding the relationships between hypoxia, exercise, and executive function. Therefore, the first aim of this study is to compare cerebral perfusion, PFC O_2Hb and deoxyhemoglobin (DO_2Hb) saturation, executive function, and other physiological variables during exercise and recovery in normobaric hypoxia (NH) compared to a normoxic control (N). We hypothesized that PFC O_2Hb would decrease during exercise in hypoxia, while executive function improved and DO_2Hb increased; and that all of these values would return to baseline during the recovery period. The second aim of this study is to examine the relationships of cerebral perfusion and cerebral oxygenation with executive functions through a correlation analysis. We hypothesized that cerebral oxygenation would have the strongest relationship to executive function in both conditions, but that the relationship would be inverse (negative) in the NH condition. We are hypothesizing this because we anticipate cognitive function to increase during exercise in both conditions while PFC O_2Hb significantly decreases during exercise in the NH condition.

METHODS

Subjects

An a priori power analysis with an estimated effect size of $d = 0.25$ and an assumed power of $1\text{-}\beta = 0.8$ indicated that 17 subjects would need to be recruited to reach statistical significance. An additional subject was recruited to allow for appropriate counterbalancing. Therefore, 18 subjects (9 male and 9 female) participated in this study. Subject characteristics are presented (as Mean ± SD) in **Table I**. All subjects were free of any cardiac, metabolic, or respiratory disease, any musculoskeletal issues prohibiting exercise, or any previous adverse reaction to altitude exposure. Subjects had also not been to altitude (above 2500 m) within 3 mo prior to participating in this study. The protocol for this project was approved by the Kent State University Institutional Review Board and conformed to the standards set by the Declaration of Helsinki. All subjects provided written informed consent prior to participation.

Table I. Subject's Characteristics.

	MEN ($N = 9$)	WOMEN ($N = 9$)
Age	22 ± 3	23 ± 2
Weight (kg)	77.1 ± 9.1	66.9 ± 10.1
$\dot{V}O_{2max}$ (N)	47.7 ± 4.4	34.9 ± 5.3
$\dot{V}O_{2max}$ (NH)	37.8 ± 4.8	31.8 ± 8.0

Values are mean ± SD. $\dot{V}O_{2max}$, Maximal oxygen consumption; N, normoxia (20.9% F_IO_2); NH, Normobaric hypoxia (12.5% F_IO_2).

Equipment

$\dot{V}O_2$ was collected using a ParvoMedics True One 2400 Metabolic Measurement System (Parvo, Sandy, UT). This system collects expired air and analyzes the oxygen and carbon dioxide content of expired air to calculate global oxygen consumption. Data were collected continuously and averaged over 5 min (beginning at the time marker and being average for 5 min beyond that time marker) for each data collection cycle, and are presented in relative $\dot{V}O_2$ ($ml^{-1} \cdot kg^{-1} \cdot min^{-1}$).

Mean arterial pressure (MAP) was collected with a standard aneroid sphygmomanometer and stethoscope at baseline, exercise, and at each recovery time point. The same investigator collected blood pressure throughout data collection for each. MAP was calculated as MAP = (1/3 SBP) + (2/3 DBP).

Peripheral oxygenation (SpO_2) was collected using photoplethysmography (Onyx II 9550, Nonin Medical Inc., Plymouth, MN). A finger pulse-oximeter was placed over the left middle finger and was allowed time to stabilize before recording the value. SpO_2 was also monitored throughout the protocol when data were not being collected for precautionary measures.

Cerebral oxygenation and perfusion of the right prefrontal cortex were assessed via near-infrared spectroscopy (NIRS; Oxymon mk III, Artinis, Elst, Netherlands). This system is commonly used in research to estimate PFC oxyhemoglobin saturation (O_2Hb), deoxyhemoglobin saturation (DO_2Hb), and total hemoglobin saturation (Total Hb).[16,19,24] Total Hb is used here as an indicator of right PFC perfusion, as opposed to total cerebral perfusion, which is indicated by middle cerebral artery blood velocity. Data were continuously sampled at 10 Hz throughout the protocol, and then down-sampled to 1 Hz before being averaged over the last 2 min of each data collection period. Data are presented as an average change from baseline.

MCAbv was assessed unilaterally (right MCA) using Doppler ultrasound (Logic 7 ultrasound system, General Electric Medical Systems, Milwaukee, WI). The M1 section of the MCA was insonated at 2 MHz with a phased array transcranial ultrasound probe (3S phased array probe, General Electric Medical Systems, Milwaukee, WI). The right MCA was selected due to spatial limitations within the normobaric hypoxia chamber. Data were collected over 2 min at the beginning of each cognitive function test, and velocities were averaged over those 2 min.

Mathematical performance (MATH), mood (TMD), and running memory (RMCPT) were collected using a computerized cognitive assessment tool (ANAM,[4] Vista Life Sciences, Parker, CO). This tool allows researchers to create a study-specific testing battery by selecting from a variety of cognitive function tests, and is often used in research to examine cognitive function in different populations and conditions.[7,28,29] MATH and RMCPT were both calculated as throughput scores, which take into account the percent of correct responses and the mean reaction time. These two tasks were collected because of their applicability to real-world situations in which problem solving and working memory can be vital (i.e., emergency situations at altitude). For this same reason reaction time was not

examined independently, and throughput scores were used instead. In order to control for any testing effects, subjects were familiarized with the executive function tests six total times (three times in each of the first two sessions).

Total mood disturbance (TMD) was also collected using the ANAM[4] cognitive assessment tool. TMD was calculated by subtracting the subjects' scores for "vigor" and "happiness" from the sum of their scores for "anger," "restlessness," "anxiety," "depression," and "fatigue." A lower TMD score indicates a more positive mood, and higher score indicates a more negative mood. In order to control for any testing effects, subjects were familiarized with the mood test tests six total times (three times in each of the first two sessions).

Procedure

This study followed a mixed factorial design in which subjects were compared by groups (sex and condition) and across time. Subjects arrived at the lab on four separate occasions, and each session alternated between N (20.9% F_IO_2) and NH (12.5% F_IO_2). The condition of the first session was counterbalanced within each sex (i.e., nine subjects were in N first, and nine subjects were in NH first). A protocol timeline is presented in **Fig. 1**.

The first session began by introducing the study protocol and getting consent from the subjects. Subjects then rested in a seated position for 5 min before resting heart rate, blood pressure, and S_pO_2 were collected. After that each subject was familiarized with the cognitive function tests, followed by assessment of height, weight, and body composition (seven site skin fold). Subjects were then familiarized with the cognitive function tests a second time. After the second familiarization, subjects entered the chamber and acclimated for 10 min before completing a submaximal cycling protocol (Lode Excalibur Sort, Lode, Groningen, Netherlands). This protocol included three 4-min stages of 40, 80, and 120 W. Oxygen consumption ($\dot{V}O_2$) was collected during each stage. Data from this protocol were used to create a regression line between $\dot{V}O_2$ and power output, which was used later to determine the appropriate cycling intensity in Sessions 3 and 4. After recovery from the submaximal exercise test, subjects then performed an incremental maximal cycling protocol. This protocol began at 20 W, and increased by 25 W each minute until volitional fatigue (corroborated by an RER above 1.1, an RPE of > 17, or a plateau in heart rate or $\dot{V}O_2$). Following the max test, subjects were familiarized with the cognitive function tests a third time. Session 2 followed the same format as Session 1, only being performed in the alternate condition as the first and not including assessment of anthropometrics.

Sessions 3 and 4 began by having participants rest quietly for 5 min before resting heart rate, blood pressure, and S_pO_2 were collected. Subjects then entered the chamber and baseline data were collected after a 5-min rest. Next, subjects rested in the chamber for 30 min and data were collected again. After the rest period, subjects cycled at a constant intensity that correlated to 60% of their achieved $\dot{V}O_{2max}$ in the corresponding condition (N or NH). Data were collected during the final 5 min of cycling, and then again at minutes 1, 15, 30, and 45 of recovery.

Statistical Analysis

Data were analyzed using the SPSS Statistics 17 data analysis package (IBM Corporation, Armonk, NY). Anthropometric data, as well as $\dot{V}O_{2max}$, were compared between men and women at baseline by an independent samples *t*-test (Table I). A 2 (condition) $\times$ 7 (time point) repeated measures analysis of variance (ANOVA) was then run for all dependent variables. Any significant main effects were further analyzed with post-hoc analyses. Relationships between cerebral oxygenation, perfusion, and executive function were examined with a Spearman's Rank Correlation Coefficient analysis. Data are expressed as mean $\pm$ SD and level of significant was set a priori at $P \leq 0.05$.

RESULTS

Oxygen consumption indicated a significant main effect of time [$F(6,102) = 352.89$, $P < 0.001$] and a significant time by condition interaction [$F(6,102) = 10.53$, $P < 0.001$]. Post-hoc analyses indicated that $\dot{V}O_2$ significantly increased during exercise in N ($+20.6 \pm 4.76$ ml $\cdot$ kg^{-1} $\cdot$ min^{-1}), and during exercise ($+18.08 \pm 4.30$ ml $\cdot$ kg^{-1} $\cdot$ min^{-1}), R1 ($+1.79 \pm 1.49$ ml $\cdot$ kg^{-1} $\cdot$ min^{-1}), and R2 ($+0.878 \pm 1.33$ ml $\cdot$ kg^{-1} $\cdot$ min^{-1}) in NH (**Fig. 2**).

Peripheral oxygenation indicated main effects of time [$F(6,102) = 12.26$, $P < 0.001$], condition [$F(1,17) = 143.88$, $P < 0.001$], and a significant time by condition interaction

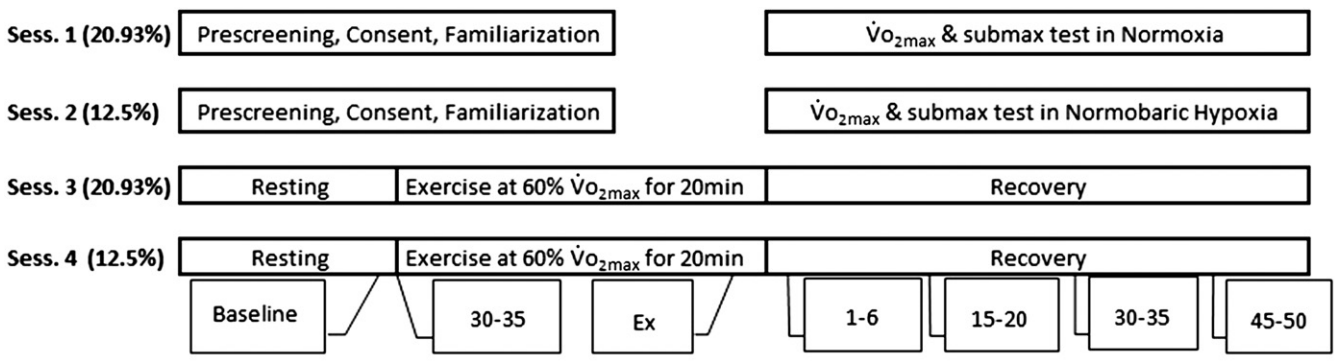

Fig. 1. The experimental procedure and timeline.

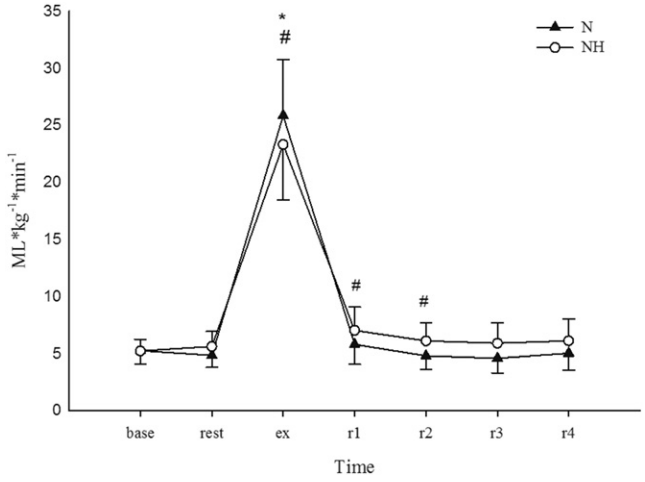

Fig. 2. $\dot{V}_{O_2}$ (ml · kg^{-1} · min^{-1}) compared across time and between N and NH. $\dot{V}_{O_2}$ significantly increased during exercise in both conditions, but remained elevated through recovery in NH. * Indicates effect of time in N, and # indicates main effect of time in NH ($P < 0.05$). $N = 18$. Data are presented as Mean ± SD.

[F(6,102)=8.59, $P < 0.001$] for S_pO_2. Post-hoc analyses revealed that S_pO_2 significantly decreased during exercise in both conditions (-0.72 ± 0.89% and -7.27 ± 6.49% in normoxia and hypoxia, respectively), and remained lower for 30 min after exercise (R1: -0.33 ± 0.59% in N, R2: -1.16 ± 1.09% in N and -2.80 ± 5.56% in NH, R3: -0.77 ± 1.21% in N and -4.80 ± 4.93% in NH; all $P < 0.05$).

Heart rate indicated significant main effects of time [F(6,102) = 173.17, $P < 0.001$], condition [F(1,17) = 8.02, $P = 0.011$], and a significant time by condition interaction [F(6,102) = 2.66, $P = 0.019$] for HR. The time by condition interaction can be explained by a greater increase in heart rate during exercise in N compared to NH (+79.11 ± 16.95 bpm and +65.33 ± 28.95 bpm, respectively; $P = 0.014$).

MAP indicated a significant main effect of time [F(6,102)=4.956, $P < 0.001$] for MAP. When further analyzed, the main effect of time was due to a significant difference between MAP immediately post and 30 min post exercise (94.08 ± 7.38 mmHg and 90.64 ± 6.22 mmHg, respectively; $P = 0.01$).

There was a main effect of time [F(6,102) = 3.67, $P = 0.002$] for math performance. Post-hoc analyses indicated that scores significantly improved during exercise (+2.33 ± 6.31 correct responses × min), and remained elevated immediately post exercise (+2.41 ± 6.73 correct responses × min) and at 30 min post exercise (+3.44 ± 6.69 correct responses × min) (**Fig. 3**).

Running Memory only indicated a significant main effect of time [F(6,102) = 9.64, $P < 0.001$] for RMCPT. Post-hoc analyses indicated that baseline values (105.75 ± 20.22 correct responses × min, all $P < 0.05$) were significantly lower than values at all other time points (Fig. 3). Total Mood Disturbance indicated no significant main effect of time [(F(6,102) = 0.481, $P > 0.050$], environment [F(6,102) = 0.664, $P > 0.050$], nor any interactions for total mood disturbance.

Oxyhemoglobin indicated significant main effect of time [F(6,102) = 37.82, $P < 0.001$], condition [F(1,17) = 10.34,

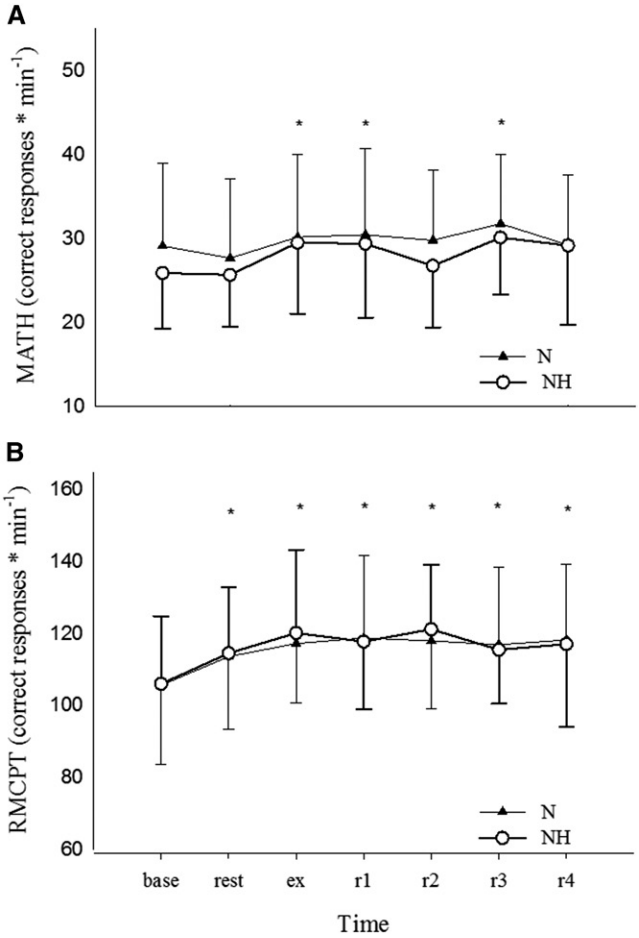

Fig. 3. A) A comparison of mathematical performance (correct responses × minutes) across time and between conditions. Mathematical performance improved during exercise, and was elevated at 1 and 30 min of recovery. B) A comparison of running memory (correct responses × minutes) across time and between conditions. Running memory significantly improved following the 30-min rest period and remained elevated throughout exercise and recovery. * Indicates an effect of time in N ($P < 0.05$). $N = 18$. Data are presented as Mean ± SD.

$P = 0.005$], and a significant time by condition interaction [F(6,102) = 6.43, $P < 0.001$] for O_2Hb. Post-hoc analyses revealed a significant increase in O_2Hb during exercise (+11.06 ± 5.58 AU and +4.26 ± 3.53 AU), immediately post exercise (+12.00 ± 8.08 AU and +8.75 ± 4.26 AU), and 15 min post exercise (+7.30 ± 6.53 AU and +5.16 ± 5.00 AU) in N and NH, respectively; and 30 min post exercise in N (+3.26 ± 5.70 AU; all $P < 0.05$) compared with baseline. The time by condition interaction was explained by significantly greater increases in O_2Hb in normoxia than in hypoxia across all time points except baseline and 45 min post recovery (all $P < 0.05$) (**Fig. 4**).

Deoxyhemoglobin indicated significant main effects of time [F(6,102) = 5.94, $P < 0.001$] and condition [F(1,17) = 6.76, $P = 0.019$], and a significant time by condition interaction [F(6,102) = 5.37, $P < 0.001$] for DO_2Hb. Post-hoc analyses indicated that DO_2Hb saturation increased following adaptation to NH (+0.70 ± 1.02 AU), during exercise in NH (+3.79 ± 3.1 AU), and 15 min after exercise in NH (+1.39 ± 1.91 AU; all

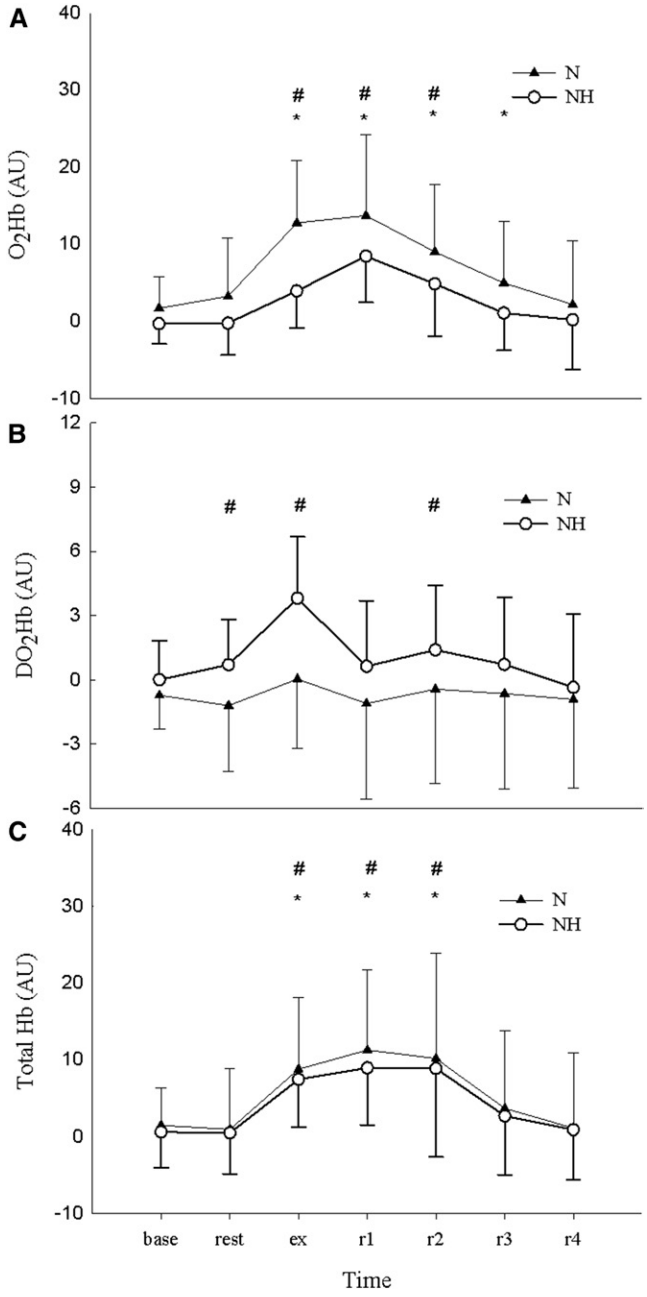

Fig. 4. A) A comparison of O_2Hb [arbitrary units (AU)] across time and between conditions. O_2Hb significantly increased during exercise in N and NH, and remained elevated through 15 min of recovery in NH and 30 min in N. B) A comparison of DO_2Hb (AU) across time and between conditions. DO_2Hb significantly decreased at rest in NH, increased during exercise in N and NH, and was elevated at 15 min of recovery in NH. C) A comparison of total Hb (AU) across time and between conditions. Total Hb significantly increased during exercise in both conditions and remained elevated through 15 min of recovery. * Indicates an effect of time in N, and # indicates an effect of time in NH ($P < 0.05$). $N = 18$. Data are presented as Mean ± SD.

$P < 0.05$). There were no significant changes in DO_2Hb saturation during the normoxic condition (Fig. 4).

Total hemoglobin indicated a significant main effect of time [$F(6,102) = 17.39$, $P < 0.001$] for total Hb saturation. Post-hoc analyses indicated that total Hb significantly increased during exercise (+7.07 ± 7.00 AU) and remained elevated through 15 min of recovery (R1: +8.29 ± 7.1 AU and R2: +7.87 ± 8.67 AU, all $P < 0.05$) (Fig. 4).

Middle cerebral artery blood flow velocity indicated no significant main effects of time [$F(6,102) = 1.86$, $P = 0.093$], condition [$F(1,17)=1.10$, $P = 0.308$; MCAbv = 22.37 ± 0.36 cm · s^{-1} and 24.56 ± 1.11 cm · s^{-1} for N and NH, respectively], nor a significant interaction [$F(6,102) = 1.09$, $P = 0.372$] for MCAbv.

A Shapiro-Wilk test of normality indicated that MATH and RMCPT were both normally distributed in N and NH (all $P > 0.05$); however, the same was not true for O_2Hb, DO_2Hb, and Total Hb (all $P < 0.05$). Therefore, a Spearman's Rank Correlation Coefficient test (a.k.a. Spearman's Rho) was used to analyze the monotonic relationships between O_2Hb, DO_2Hb, Total Hb, MATH, and RMCPT. These data are presented in **Table II**.

DISCUSSION

The purpose of this study was to investigate the influence of cerebral oxygenation, cerebral perfusion, and other physiological variables on executive function by comparing exercise and recovery from exercise in NH to a normoxic control. Mathematical processing and running memory were selected as tests of executive function in this study because of their applicability to free living conditions; for example, the need to calculate daily rations during the ascent of a mountain. Results indicated that neither mathematical processing nor running memory were impaired following 30 min spent in NH; however, both did improve with exercise. This supports previous research observing improvements in cognitive function with exercise.[9,11,21] Furthermore, the improvement in running memory was sustained throughout the entire recovery period. This coincides with the kinetics of O_2Hb in NH and N, and DO_2Hb in NH only. O_2Hb increased during exercise in both conditions, and remained elevated through 30 min of recovery while DO_2Hb increased during rest in NH and remained elevated through 15 min of recovery. As hypothesized, O_2Hb saturation exhibited a significant relationship with mathematical processing in the NH condition; however, this relationship was positive rather than negative. Also, DO_2Hb had a significant negative relationship with mathematical processing in normoxia and when conditions were combined. These data support the idea that mathematical processing is linked to changes in PFC oxygenation. However, it is also important to note that the concomitant increases in O_2Hb and DO_2Hb during exercise and the early stages of recovery are likely influenced by an increase in PFC perfusion.

Although MCAbv did not change during either exercise trial or during recovery, total Hb saturation increased during exercise and remained elevated for 15 min after exercise. This indicates that cerebrovascular perfusion favored the right PFC despite no changes in total brain blood flow. This could potentially be due to vasodilation of the microvasculature perfusing the right PFC in response to metabolic activity. Specifically, increases in glucose metabolism at the PFC could initiate a prostaglandin mediated vasodilatory response. Exercise might

Table II. Spearman's Rank Correlation Coefficient Analysis.

	N			NH			COMBINED		
	O_2Hb	DO_2Hb	TOTAL Hb	O_2Hb	DO_2Hb	TOTAL Hb	O_2Hb	DO_2Hb	TOTAL Hb
Math	0.026 ($P = 0.77$)	−0.279* ($P < 0.01$)	−0.044 ($P = 0.62$)	0.228* ($P = 0.01$)	−0.064 ($P = 0.48$)	0.166 ($P = 0.06$)	0.134* ($P = 0.03$)	−0.206* ($P < 0.01$)	0.067 ($P = 0.28$)
RMCPT	0.107 ($P = 0.23$)	−0.054 ($P = 0.55$)	0.160 ($P = 0.07$)	0.009 ($P = 0.92$)	0.027 ($P = 0.76$)	−0.006 ($P = 0.95$)	0.049 ($P = 0.43$)	−0.027 ($P = 0.66$)	0.066 ($P = 0.29$)

Values are presented as Spearman's Rank Correlation Coefficient. O_2Hb; oxyhemoglobin, DO_2Hb; deoxyhemoglobin, Total Hb; Total hemoglobin.
* $P \leq 0.05$, significant correlations.

augment this effect by increasing overall cerebral glucose metabolism, activating the primary, supplementary, or premotor cortices, or by another mechanism all together. While this is speculative, modifications in cerebrovascular perfusion with exercise have been observed elsewhere.[5,17,18] The increase in DO_2Hb during exercise and at 15 min of recovery also suggests that there is an elevation in cerebral metabolism. This is because the accumulation of DO_2Hb would have to occur due to the consumption of O_2 and (or) an inability for deoxygenated blood to escape the local tissue. The mechanisms for increased PFC oxygenation and perfusion during and following exercise presents a very intriguing line of inquiry. Also of interest is that the increase in O_2Hb during and following exercise was present in both conditions. This suggests a limited ambient supply of oxygen and reduced S_pO_2 do not effect cerebral O_2 delivery. Together, these data support previous research suggesting that the improvements in cognitive function during exercise are related to increased PFC oxygenation and perfusion,[4,8,10] and suggest that these relationships are maintained in normobaric hypoxia.

There are some limitations to the current study. The main limitation to this study is that the duration of hypoxic exposure was not enough to elicit a hypoxia-induced impairment in executive function, as has been observed in previous research.[12,23] Ando et al.[1] demonstrated a similar limitation after introducing their subjects to normobaric hypoxia for 10 min, highlighting the variability in the response to normobaric hypoxia. However, in this protocol S_pO_2 decreased and DO_2Hb increased during exposure to NH, suggesting that the protocol did elicit physiological responses consistent with other research. Also, because the protocol used in this study did not elicit cognitive impairments, we were unable to examine the influence of PFC perfusion and oxygenation specifically on the restoration of cognitive function during exercise in hypoxia. We were only able to test these relationships in N and NH, independent of cognitive impairments. However, the data presented here do provide support for the influence of PFC perfusion and oxygenation on executive function in hypoxia. Future studies should consider using a longer adaptation period in order to elicit hypoxia-related impairments in executive function. We also did not compare male and female data to one another. This is because previous data from our lab and pilot data collected for this study did not indicate a likelihood that changes in executive function would be significantly different between men and women. However, this also limits our ability to make inferences on sex differences in the present study. This may also be an area of future research.

Data from this study suggest that PFC perfusion and oxygenation together influence executive function during exercise and during recovery from exercise in normoxia and NH, and that PFC perfusion and oxyhemoglobin saturation increase during exercise independent of total cerebral blood flow. Future research should compare PFC activity, perfusion, and oxygenation during early hypoxic exposure and throughout a period of cognitive impairment, exercise, and recovery in hypoxia. This will best elucidate the mechanisms responsible for the interactions between hypoxia, exercise, and executive function.

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REFERENCES

1. Ando S, Hatamoto Y, Sudo M, Kiyonaga A, Tanaka H, Higaki Y. The effects of exercise under hypoxia on cognitive function. PLoS One. 2013; 8(5):e63630.
2. de Aquino Lemos V, Antunes HK, dos Santos RV, Lira FS, Tufik S, de Mello MT. High altitude exposure impairs sleep patterns, mood, and cognitive functions. Psychophysiology. 2012; 49(9):1298–1306.
3. Ball G, Stokes PR, Rhodes RA, Bose SK, Rezek I, et al. Executive functions and prefrontal cortex: a matter of persistence? Front Syst Neurosci. 2011; 5:3.
4. Bediz CS, Oniz A, Guducu C, Ural Demirci E, Ogut H, et al. Acute supramaximal exercise increases the brain oxygenation in relation to cognitive workload. Front Hum Neurosci. 2016; 10:174.
5. Delp MD, Armstrong RB, Godfrey DA, Laughlin MH, Ross CD, Wilkerson MK. Exercise increases blood flow to locomotor, vestibular, cardiorespiratory and visual regions of the brain in miniature swine. J Physiol. 2001; 533(Pt 3):849–859.
6. Dobashi S, Horiuchi M, Endo J, Kiuchi M, Koyama K. Cognitive function and cerebral oxygenation during prolonged exercise under hypoxia in healthy young males. High Alt Med Biol. 2016; 17(3):214–221.

7. Dretsch M, Parish R, Kelly M, Coldren R, Russell M. Eight-day temporal stability of the automated neuropsychological assessment metric (anam) in a deployment environment. Appl Neuropsychol Adult. 2015; 22(4): 304–810.
8. Eggenberger P, Wolf M, Schumann M, de Bruin ED. Exergame and balance training modulate prefrontal brain activity during walking and enhance executive function in older adults. Front Aging Neurosci. 2016; 8:66.
9. Faulkner J, Lambrick D, Kaufmann S, Stoner L. Effects of upright and recumbent cycling on executive function and prefrontal cortex oxygenation in young healthy men. J Phys Act Health. 2016; 13(8):882–887.
10. Giles GE, Brunye TT, Eddy MD, Mahoney CR, Gagnon SA, et al. Acute exercise increases oxygenated and deoxygenated hemoglobin in the prefrontal cortex. Neuroreport. 2014; 25(16):1320–1325.
11. Hwang J, Brothers RM, Castelli DM, Glowacki EM, Chen YT, et al. Acute high-intensity exercise-induced cognitive enhancement and brain-derived neurotrophic factor in young, healthy adults. Neurosci Lett. 2016; 630:247–253.
12. Kim CH, Ryan EJ, Seo Y, Peacock C, Gunstad J, et al. Low intensity exercise does not impact cognitive function during exposure to normobaric hypoxia. Physiol Behav. 2015; 151:24–28.
13. Lefferts WK, Babcock MC, Tiss MJ, Ives SJ, White CN, et al. Effect of hypoxia on cerebrovascular and cognitive function during moderate intensity exercise. Physiol Behav. 2016; 165:108–118.
14. Li XY, Wu XY, Fu C, Shen XF, Wu YH, Wang T. Effects of acute mild and moderate hypoxia on human mood state. Space Med Med Eng (Beijing). 2000; 13(1):1–5.
15. Li XY, Wu XY, Fu C, Shen XF, Yang CB, Wu YH. Effects of acute exposure to mild or moderate hypoxia on human psychomotor performance and visual-reaction time. Space Med Med Eng (Beijing). 2000; 13(4): 235–239.
16. Liu X, Sun G, Zhang X, Xu B, Shen C, et al. Relationship between the prefrontal function and the severity of the emotional symptoms during a verbal fluency task in patients with major depressive disorder: a multi-channel NIRS study. Prog Neuropsychopharmacol Biol Psychiatry. 2014; 54:114–121.
17. Lucas SJ, Ainslie PN, Murrell CJ, Thomas KN, Franz EA, Cotter JD. Effect of age on exercise-induced alterations in cognitive executive function: relationship to cerebral perfusion. Exp Gerontol. 2012; 47(8): 541–551.
18. MacIntosh BJ, Crane DE, Sage MD, Rajab AS, Donahue MJ, et al. Impact of a single bout of aerobic exercise on regional brain perfusion and activation responses in healthy young adults. PLoS One. 2014; 9(1):e85163.
19. Maggioni E, Molteni E, Zucca C, Reni G, Cerutti S, et al. Investigation of negative bold responses in human brain through NIRS technique. A visual stimulation study. Neuroimage. 2015; 108:410–422.
20. Mooney RA, Coxon JP, Cirillo J, Glenny H, Gant N, Byblow WD. Acute aerobic exercise modulates primary motor cortex inhibition. Exp Brain Res. 2016; 234(12):3669–3676.
21. Moriya M, Aoki C, Sakatani K. Effects of physical exercise on working memory and prefrontal cortex function in post-stroke patients. Adv Exp Med Biol. 2016; 923:203–208.
22. Ongür D, Price JL. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb Cortex. 2000; 10(3):206–219.
23. Pilmanis AA, Balldin UI, Fischer JR. Cognition effects of low-grade hypoxia. Aerosp Med Hum Perform. 2016; 87(7):596–603.
24. Saito H, Wakai J, Sekiguchi M, Kikuchi S, Konno S. The effect of selective serotonin reuptake inhibitor (SSRI) on pain-related behavior in a rat model of neuropathic pain. Eur Spine J. 2014; 23(11):2401–2409.
25. Selemon LD, Goldman-Rakic PS. Common cortical and subcortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: evidence for a distributed neural network subserving spatially guided behavior. J Neurosci. 1988; 8(11):4049–4068.
26. Seo Y, Burns K, Fennell C, Kim JH, Gunstad J, et al. The influence of exercise on cognitive performance in normobaric hypoxia. High Alt Med Biol. 2015; 16(4):298–305.
27. Subudhi AW, Dimmen AC, Roach RC. Effects of acute hypoxia on cerebral and muscle oxygenation during incremental exercise. J Appl Physiol. 2007; 103(1):177–183.
28. Woodhouse J, Heyanka DJ, Scott J, Vincent A, Roebuck-Spencer T, et al. Efficacy of the ANAM general neuropsychological screening battery (ANAM GNS) for detecting neurocognitive impairment in a mixed clinical sample. Clin Neuropsychol. 2013; 27(3):376–385.
29. Xie SS, Goldstein CM, Gathright EC, Gunstad J, Dolansky MA, et al. Performance of the automated neuropsychological assessment metrics (ANAM) in detecting cognitive impairment in heart failure patients. Heart Lung. 2015; 44:387–394.
30. Zimmer P, Stritt C, Bloch W, Schmidt FP, Hubner ST, et al. The effects of different aerobic exercise intensities on serum serotonin concentrations and their association with Stroop task performance: a randomized controlled trial. Eur J Appl Physiol. 2016; 116(10):2025–2034.