Respiratory Muscle Training and Cognitive Function Exercising at Altitude

Joseph Quackenbush; Aubrey Duquin; Samuel Helfer; David R. Pendergast

BACKGROUND: Hiking and trekking often occur at altitudes up to 12,000 ft altitude. The hypoxia-induced hyperventilation at altitude paradoxically reduces arterial CO_2 (P_aCO_2). A reduction in P_aCO_2 results in vasoconstriction of the blood vessels of the brain and thus in local hypoxia. The local hypoxia likely affects cognitive function, which may result in reduced performance and altitude accidents. Recent publications have demonstrated that voluntary isocapnic hyperventilatory training of the respiratory muscles (VIHT) can markedly enhance exercise endurance as it is associated with reduced ventilation and its energy cost. VIHT may be useful in blunting the altitude-induced hyperventilation leading to higher P_aCO_2 and improved cognitive function.

METHODS: This study examined the effects of VIHT, compared to control (C) and placebo (PVIHT) groups, on selected measures of executive functioning, including working memory and processing speed (i.e., Stroop Test, Symbol Digit Modalities Test, and Digit Span Forward) at simulated altitude up to 12,000 ft. Associated physiological parameters were also measured.

RESULTS: The Digit Span Forward Test did not show improvements after VIHT in any group. The VIHT group, but not C or PVIHT groups, improved significantly (17–30%) on the Stroop Test. Similarly the VIHT group, but not the C and PVIHT groups, improved correct responses (26%) and number of attempts (24%) on the Symbol Digit Modalities Test. In addition, reaction time was also improved (16%).

CONCLUSION: VIHT improved processing speed and working memory during exercise at altitude.

KEYWORDS: respiration, altitude, exercise, respiratory muscle training, oxygen consumption, arterial CO_2, brain blood flow.

Quackenbush J, Duquin A, Helfer S, Pendergast DR. *Respiratory muscle training and cognitive function exercising at altitude.* Aerosp Med Human Perform. 2016; 87(1):18–25.

Climbing and trekking at altitudes up to 12,000 ft (3658 m) are common recreational activities. Military operations at this altitude are also common. A decrease in ambient pressure at this altitude affects the cardiorespiratory systems. These changes can impact cognitive function, which in turn may reduce performance and increase risks to the participant. Maintaining cognitive function is important to optimize safety, particularly during ascent and descent. In comparison to sea level, there is a reduced partial pressure of O_2, secondary to reduced barometric pressure. This results in an increase in ventilation ($\dot{V}_E$) for a given $\dot{V}O_2$.[20,24] At sea level, ventilation is driven by arterial CO_2 (P_aCO_2). At altitude the ventilatory drive is mediated via hypoxia. Ventilation is increased primarily by an increase in breathing frequency (fb).[20,23] The hypoxic ventilatory drive increases the work of breathing and the metabolic cost of the respiratory muscles.[24] The relative hyperventilation at altitude paradoxically causes a decrease in arterial CO_2. Moreover, cardiac output is increased at altitude.[8] This leads to reduced transit time and alveolar/end-capillary diffusion equilibration. These changes would exacerbate the reduction in arterial PO_2 from altitude per se. Additionally, oxygen release from the blood to the tissues is impaired by the Haldane effect. This increases oxygen affinity of the blood when the blood pH is rendered more alkaline as during hyperventilation. Individuals exercising ventilation at altitude may become flow limited during higher-intensity exercise. Flow limitation has been shown to increase the work of breathing and contribute to premature

From the Center for Research and Education in Special Environments, Department of Physiology and Biophysics, School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY.

This manuscript was received for review in July 2015. It was accepted for publication in October 2015.

Address correspondence to: David R. Pendergast, Professor, Department of Physiology and Biophysics, 124 Sherman Hall, School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY 14214; dpenderg@buffalo.edu.

DOI: 10.3357/AMHP.4420.2016

fatigue of the respiratory muscles.[12] In fact, maximal aerobic exercise capacity is reduced at altitude.[6,8]

Exercise and hypoxia-induced hyperventilation at altitude may compromise cognitive function. Further hyperventilatory drive caused by respiratory muscle fatigue during sustained exercise has been reported from studies at 1.0 ATM.[5,17] Similar effects have also been reported at depth (during diving).[21] The combined effects of hyperventilation are likely to reduce P_aCO_2. CO_2 is known to be a potent vasodilator. A reduction in P_aCO_2 may induce constriction of the blood vessels of the brain, resulting in local hypoxia. Additionally, blood flow may be diverted to the respiratory muscles from other muscles[10] and perhaps even the brain in spite of the elevated cardiac output reported at altitude.[8] The combination of these effects on brain blood flow may affect cognitive function. Some studies have linked impaired neuropsychological function under hypoxia not only to low oxygen content in the blood,[13,27] but also to a reduced brain blood flow. Oxygen supply to the brain may be reduced by low P_aCO_2 due to the reflex hyperventilation. While the hyperventilation does add oxygen to the blood the simultaneous vasoconstriction due to the lowered CO_2 pressure in arterial blood may actually be more important.[13] Research has shown that subjects exposed to simulated altitude showed improved mental performance when, to induce brain vasodilatation, CO_2 was added to breathing air with reduced O_2 pressure.[13]

Some studies have shown that a short bout of low intensity exercise improves cognitive function.[15] These same studies demonstrated that cognitive function is depressed at higher work rates and at altitude.[15] Many studies at altitude and simulated altitude have shown a significant reduction in cognitive function[3,4,28] and increased reaction time[15] at altitude from 3,900 m to 8,848 m.

Countermeasures to protect cognitive function at altitude like exercise training[28] or treatment with acetazolamide[28] have not been effective. Climbers acclimatized at 7,546 m altitude did not have impaired cognitive function, however acclimatization takes many days. Another possible mechanism to stifle cognitive dysfunction could be to blunt the altitude-induced hyperventilation secondary to respiratory muscle fatigue. This can be achieved by specific training of the respiratory muscles (RMT).[5,17] The predicted benefit of RMT in relation to exercise at altitude would be to mitigate excessive carbon dioxide elimination. Moreover, the training may prevent the shunting of blood from locomotor muscles and the brain by reducing respiratory work at altitude, changes which have previously been shown at increased pressure.[11,21]

A large number of recent publications have demonstrated that RMT can markedly enhance exercise endurance at ground level (+69%)[17] and particularly improves endurance under environmental conditions such as diving (+86%) that a priori challenge lung function.[21] Studies have shown that after RMT the paradoxical hyperventilation due to respiratory muscle fatigue was absent and exercise endurance was extended by 30–86%.[17,21] We propose exercise ventilation at altitude will be reduced after RMT. This may preserve a relatively normal P_aCO_2. Attenuation of this change in P_aCO_2 may promote relaxation of brain blood vessels and improve brain oxygenation and cognitive function.

We hypothesize that specific training of the breathing muscles (RMT) may substantially improve cognitive function during moderate-to-high intensity exercise at altitudes of 10,000 to 12,000 ft (3048 to 3658 m) of simulated altitude. Additionally, we hypothesize that those improvements will be brought about by modifying the hyperventilation that spontaneously occurs with ascent to altitude and is exacerbated by exercise.

METHODS

Subjects

This study was approved by the Institutional Review Board and subjects signed written informed consent prior to study participation. All subjects were given a physical examination and were familiarized with the protocol and procedures, including the altitude chamber. Subjects then performed a short period of specific RMT termed Voluntary Isocapnic Hyperventilation Training (VIHT, described below). Only men were studied due to the requirement of the sponsor. The physical characteristics of the subjects on average were 23.7 ± 2.2 yr of age, 178 ± 2 cm in height, 74.75 ± 3.11 kg in weight, and had $\dot{V}O_{2max}$ on a cycle ergometer in the altitude chamber of $2.95 \pm 0.20\ L \cdot min^{-1}$.

Procedures

This study was a controlled repeated measures design with the subjects acting as their own controls. Two groups of five subjects each performed VIHT for 4 wk after the pre-VIHT testing and then completed the post-VIHT. Another group of five performed a placebo of VIHT (described below). In addition, one group of five subjects served as a control group as they were retested 3 mo after VIHT when their respiratory muscles were de-trained. Due to the complexity and cost of performing these experiments at altitude, the experimental groups were done first to see whether VIHT had a positive effect on cognitive function. Once improvements after VIHT were detected the placebo and control groups were studied. For purposes of improving safety, the first experimental group was studied at an altitude of 10,000 ft (3048 m). Based on the success of these subjects the second five subjects were studied at 12,000 ft (3658 m), as were the placebo and control groups. Subjects were not randomized as they often encountered each other during testing and training and we did not want the control and placebo group to recognize they were doing different things than the experimental group. The VIHT was performed 3 days per week.

Subjects completed a $\dot{V}O_{2max}$ test at sea level inside an altitude chamber on an electrically braked cycle ergometer (Collins Pedal Mate). One week later they completed an exercise endurance test to voluntary exhaustion at altitude in the chamber at nominally 70–75% of their individual maximal $\dot{V}O_{2max}$ previously determined at sea level (pre-VIHT). After the pre-VIHT the subjects completed 4 wk of VIHT consisting of three sessions per week, for 30 min each session (12 sessions). One week after completion of the VIHT, they repeated the pre-VIHT testing using the same equipment and workload (post-VIHT). Subjects in the control group were those that had performed the experimental training protocol previously. A training washout period of 3 mo of no VIHT was implemented. Subsequently the subjects returned to the laboratory and repeated the exercise endurance test to voluntary exhaustion at altitude. The placebo group performed the pre-VIHT, post-VIHT battery of tests. However, instead of doing VIHT subjects performed breath-holds for periods of 10 s with 30 s of rest in between each breath-hold maneuver. They performed 3 sessions per week, for 30 min each session (12 sessions) as were performed for the VIHT. The subjects used the same device as for the VIHT. One training session was comprised of 45 cycles of the breath-hold maneuver. This placebo training was termed (PVIHT).

The subject and two safety monitors participated inside the altitude chamber. There was a technician at a data collection computer and another recording gas volumes and concentrations and keeping time. A third technician operated the chamber and observed the subjects and safety monitors via a porthole in the wall of the altitude chamber and a video monitor. A principal investigator and a medical monitor supervised the experiment and evaluated ECG and arterial O_2 saturation (S_aO_2). Communication from the outside of the chamber to the safety monitors inside was maintained via two-way radio headsets. The subject wore a harness to prevent them from falling from the bike in case of loss of consciousness due to hypoxia. In addition, a safety platform was available inside the chamber to lay the subject supine in the event of loss of consciousness. An aviation-style oxygen mask was available if needed. The altitude tests were performed in a pressure chamber at a pressure equivalent to an altitude of 3000 m (10,000 feet, 0.7 ATA, 70 kPa) or 3658 m (12,000 ft, 0.66 ATA, 67 kPa). The subjects were seated erect in air on a cycle ergometer. Subjects breathed chamber gas during ascent and descent. While exercising, subjects breathed fresh air at chamber pressure from a bag-in-box system via a two-way mouthpiece. The bag-in-box had a linear displacement spirometer connected to the box for setting inspired bag volume and determining tidal volume during the experiment.

Prior to beginning VIHT the subject's maximum oxygen uptake ($\dot{V}O_{2max}$) was determined using a progressive resistance test on an electrically braked (Collins Pedal Mate) cycle ergometer. Subjects pedaled at 60 rpm and the work rate was set initially at 50 W. The workload was increased in 50 W increments until voluntary exhaustion.

One to two weeks after the $\dot{V}O_{2max}$ test the subjects also completed a cycle endurance test to voluntary exhaustion at a workload 70–75% of the predetermined sea level $\dot{V}O_{2max}$. In addition to exercise time, measures of ECG, S_aO_2, $\dot{V}O_{2max}$, $\dot{V}_E$, end-tidal CO_2 ($ETCO_2$), cerebral blood flow velocity (CBFv), and cerebral O_2 saturation were measured throughout the test.

At the surface, S_aO_2, heart rate (HR), mean CBFv (left and right) and cerebral O_2 saturation were measured. After sea level control readings were taken, the chamber was depressurized to 10,000 or 12,000 ft (3048 to 3658 m) simulated altitude. At altitude, control readings were taken at rest. The subject breathed from a mouthpiece with one way inspiratory and expiratory valves mounted inside a facemask. The inspired and expired hoses from the mouthpiece were connected to the respective side (bag) of the bag-in-box. The inspiratory bag had a near constant flow of fresh air so that the subject always had fresh air. The air supplied to the inspiratory bag was compressed air from large storage tanks. Two mass spectrometers were used—one connected to the barrel "dump" line from the expiration bag to determine mixed expired gas concentrations, and the other to the exhalation side of the mouthpiece for determination of $ETCO_2$.

After resting collections the subject began pedaling at 60 rpm with a workload of 70–75% of their individually predetermined $\dot{V}O_{2max}$. Once the subject had pedaled for 2 min, cognitive assessment began. The subject was attached to the expired bag in the bag-in-box system. Gas collections were 1 min and concurrent S_aO_2, HR, and CBFv were recorded. The gas in the expired bag was vented to the outside of the chamber through a dry gas meter for determination of $\dot{V}_E$. After expired gas collection was complete, the subject was connected to the inspired breathing bag containing humidified air. The process of collecting and dumping gas was repeated every 3 min. After the subject reached voluntary exhaustion the chamber was returned to sea level and the subject exited the chamber. The experiments on each subject were done on the same day of the week and at the same time-of-day to minimize the effects of circadian rhythms.

The cognitive tests were given in a specific order following a fixed time schedule. The tests administered were the Stroop Test Primer A, followed by Stroop Test Primer B, and then the actual Stroop Test (Stoelting Co.,Wood Dale, IL). As the Stroop Test Primer A and Stroop Test Primer B were given as practice, only the actual Stroop Test data are reported. The Stroop Test was followed by the Digit Span Forward Test (PsychCorp/Pearson, San Antonio, TX) and Symbol Digit Modalities Test (Western Psychological and Counseling Services, Portland, OR). The time of the testing in relation to exercise time was fixed pre- and post-VIHT. The number of attempts, number of correct responses, as well as the percent correct responses were the dependent variables.

Once the subject had been pedaling for 2 min at altitude, the Digit Span Forward Test commenced and lasted for 2.5 min. A 1-min break followed. The subject then began the Stroop Color Word Test which lasted for 5 min and was again followed by a 1-min break. Next, the Symbol Digit Modalities Test was administered. This test lasted 90 s. After the cognitive tests were completed, the subject continued to exercise. A choice/reaction-time task was performed from completion of the Symbol Digit Modalities Test until exhaustion. For the Digit Span Forward Test and Stroop Color Word Test the subjects' responses were taken and recorded via a microphone inside the facemask.

The Digit Span Forward Test is a widely used test that even had a version incorporated into the first edition of the Wechsler

Intelligence Scale published in 1939.[29] It has remained on subsequent versions of the Wechsler Intelligence Scale and is thus a subtest on the most recent version of the Wechsler Adult Intelligence Scale, 4th edition. The Digit Span test is composed of a Digit Span Forward and Digit Span Backward task and the additive scores of these two subtests yields a Digit Span score. For the purposes of this experiment, only Digit Span Forward was used. The test involves rote learning and memory, simple attention, encoding, and auditory processing.[22] It is also thought to measure the storage and maintenance components of working memory.[31] Digit sequences are presented verbally beginning with two digits and increasing in length by one digit, up to a maximum of nine digits. Two different trials were presented for each string length. The subject was required to repeat the string aloud when the test administrator was done presenting the string.[22] After the experiments, the recorded tapes were played back and the number of attempts and number of correct attempts were determined, and the percent correct responses calculated.

The Stroop Color Word Test assesses the ability of an individual to sort information from his or her environment and selectively react to this information rapidly; it falls under the broad category of executive functioning. For this test the subjects were shown a standard stimulus sheet that had columns of color words (i.e., red, green, blue) printed in different colors of ink. The subject was instructed to say the color of the ink that the word was printed in instead of reading the word itself. The test was comprised of two 45-s trials with 1 min of rest between trials. The number of attempts and number of correct attempts were then determined by listening to the recordings and the percent of correct responses was calculated. This test was born out of the idea by early experimental psychologists that naming colors is slower because it requires conscious effort as opposed to reading names of colors, which was thought to be more automatic. Stroop[25] hypothesized that the difference in color naming and word reading was due to colors being associated with a variety of cognitive functions while words were associated with one behavioral response, namely reading. The challenge in the task stems from interference with consciously naming a color by a more automatic verbal processing response. Volitional control is required on behalf of the subject to suppress the automatic word reading response.

The Symbol Digit Modalities Test was administered last. The Symbol Digit Modalities Test (SDMT) is a well-known neuropsychological test that assesses processing speed and working memory. It involves converting meaningless geometric designs into written and/or oral number responses based on a key that pairs each symbol with a corresponding number, 1-9. In the original version, subjects had to visually scan a key of number/symbol pairings and then verbally tell the examiner the correct number that is associated with randomly presented symbols as fast as possible. In this study, one of the eight strands of symbols of the standard form were randomly selected and shown to the subject, which consisted of (insert number) symbols, and he had to indicate which number was associated with it by pointing to the corresponding number placed in front of them. They were not required to memorize the paired symbol/number associations; the "key" that depicts the paired associations was present for the subject to reference during the task. All data for the SDMT was recorded on a computer located outside of the altitude chamber. A LabVIEW (Austin, TX) program provided a continuous plot of all responses to the SDMT. After completion of the test, the number of attempts and number of correct responses were determined. The outcome measure is the total number of correct responses in 90 s.

A multistimulus choice reaction-time test (devised in-house) was performed after the cognitive tests. A small screen in front of the subject was illuminated with flashes of red, green or blue light initiated in random order by a microcontroller. Before the test began the subject was told which color he should respond to (red, green or blue) by, as quickly as possible, pressing a push button on the handle bar of the ergometer cycle. The microcontroller measured (ms) the time between light illumination and the depression of the pushbutton, after which one of the colored lights would immediately appear to be responded to. If two seconds elapsed without a response the program moved on to the next color illumination. If the push button was depressed when a color other than the one scheduled was flashed, this was recorded and stored on the computer as an attempt, but not a correct attempt. A LabVIEW (Austin, TX) program provided a continuous plot of reaction times. The test continued running until the subject reached exercise exhaustion on the ergometer cycle.

RESULTS

All 10 subjects completed 12 sessions of VIHT and 5 subjects completed 12 sessions of PVIHT. The average (± SD) of the training ventilations for the VIHT group are shown as a function of the number of training sessions in **Fig. 1**. There were significant increases in training ventilations from

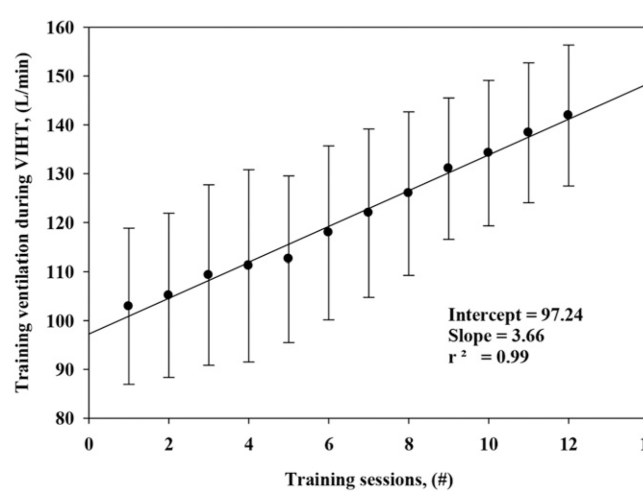

Fig. 1. Ventilation during VIHT training (mean ± SD) is plotted as a function of the number of the training sessions. The solid line is the best linear fit and the characteristics of the fit are shown in the figure. Training ventilation increased significantly as a function of training days.

102.88 ± 15.93 L · min^{-1} to 141.90 ± 14.44 L · min^{-1} [F(1,4) = 41.82, P = 0.003] that amounted to 38% over the 12 wk of training in the VIHT group. The placebo group performed training 5 days a week, however their training was designed not to increase ventilation and the breathing procedure was held constant over the 4 wk of training (12 sessions).

Oxygen saturation at sea level was not different among the three groups and averaged 97 ± 2% saturation. At altitude during both rest and exercise S_aO_2 decreased within the first 2 to 5 min and then did not change significantly throughout the time at each investigated condition. Thus, the steady state values at each condition were compared. At rest at altitude the S_aO_2 decreased from sea level to 90 ± 2% saturation at 10,000 ft and 86 ± 3% saturation at 12,000 ft pre-VIHT [F(1,9) = 230, P = ≤ 0.001] and was not significantly affected by VIHT [F(1,9 = 1.20, P = 0.79]. During exercise S_aO_2 decreased further to 81 ± 3% saturation at 10,000 ft and 84 ± 4% saturation at 12,000 ft pre-VIHT [F(1,9) = 48.71, P = ≤ 0.001], and was not significantly affected by VIHT [F(1,9) = 4.20, P = 0.11]. The data for VIHT and PVIHT groups at 12,000 ft simulated altitude were not different from each other under any of the investigated conditions [F(1,9) = 2.35 to 1.78, P = 0.95 to 0.77]. It is noteworthy that during the tests when the subjects were speaking, their S_aO_2 decreased an average of 5.8 ± 2.5% both on the pre- and post-VIHT and PVIHT tests.

Endurance exercise $\dot{V}O_2$ was 2.18 ± 0.22 L · min^{-1} (70% of 1ATA $\dot{V}O_{2max}$) both pre- and post-VIHT and PVIHT. Endurance exercise time increased significantly in the VIHT groups from 17.27 ± 4.24 to 24.20 ± 2.21 min [F(1,9) = 18.71, P = 0.012], while it did not change in the PVIHT group [17.66 ± 3.11 vs. 16.91 ± 1.8 min, F(1,4) = 0.18, P = 0.69].

There were no significant differences in the pretest data for all cognitive tests taken together between the placebo and control groups and the VIHT group [F(3,19) = 0.63, P = 0.442].

Digit Span Forward Test

For the placebo and control groups there were no significant pre- to post- score differences for either correct responses [12 ± 3 vs. 12 ± 3, F(1,9) = 3.09, P = 0.15] or % correct responses [76 ± 17 vs. 76 ± 17, F = 2.67 (9,1), P = 0.18]. In the VIHT group there was only a 4% (nonsignificant) increase in correct responses [12 ± 3 vs. 12 ± 3, F(1,9) = 3.09, P = 0.15] or % correct responses [F(1,9) = 0.079, P = 0.785]. Thus VIHT did not affect the Digit Span Forward score.

On the Stroop Test the VIHT group improved significantly on correct attempts (17–27%) and their number of attempts (17–30) [F(1,9) = 5.51, P = 0.03 and F(1,9) = 26.96, P = 0.007] (**Fig. 2**) and they maintained their accuracy [% correct = 98 ± 2%, F(1,9) = 0.56, P = 0.475]. The pre- and postvalues for the placebo group for number of attempts [F(1,9) = 0.17, P = 0.70] or correct attempts [F = 0.35 (9,1), P = 0.59] were not significantly different from each other [F(1,9) = 0.35, P = 0.59].

With regard to the Symbol Digit Modalities Test, the VIHT group improved their correct responses (26%) and number of attempts (24%) (Fig. 2), however these differences did not reach statistical significance [F(1,9) = 1.81, P = 0.21 and F(1,9) = 1.97, P = 0.19, respectively]. By contrast, the placebo group did not have any improvements in this test [F(1,9) = 0.06, P = 0.82; F(1,9) = 1.46, P = 0.29] for attempts and % corrects attempts, respectively.

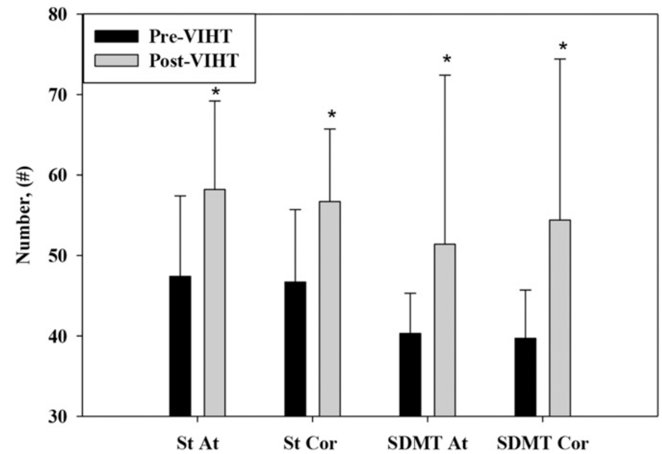

Fig. 2. Number of correct (Cor) and attempted (At) responses for the Stroop Test (St) and Symbol Digits Forward Test pre- and post-VIHT. Values are mean ± SD and the * indicates that the post-VIHT value is significantly different from pre-VIHT (P < 0.05). VIHT significantly increased the number of attempts and correct responses for both the Stroop and SDMT tests.

In addition to the cognitive test improvements, complex reaction time was also improved (**Fig. 3**). In the VIHT group the number answered increased 71% and the correct responses 68%, although not significantly [F(1,9) = 3.348, P = 0.24 and F(1,9) = 0.96, P = 0.38, respectively]. Although the number of answers and correct responses were not significant, the absolute complex reaction time decreased from 373 ± 41 to 335 ± 60 ms [F(1,9) = 4.69, P = 0.05] in the VIHT group, but not in the placebo or control groups [412 ± 194 vs. 411 ± 190 ms, F(1,9) = 0.056, P = 0.82].

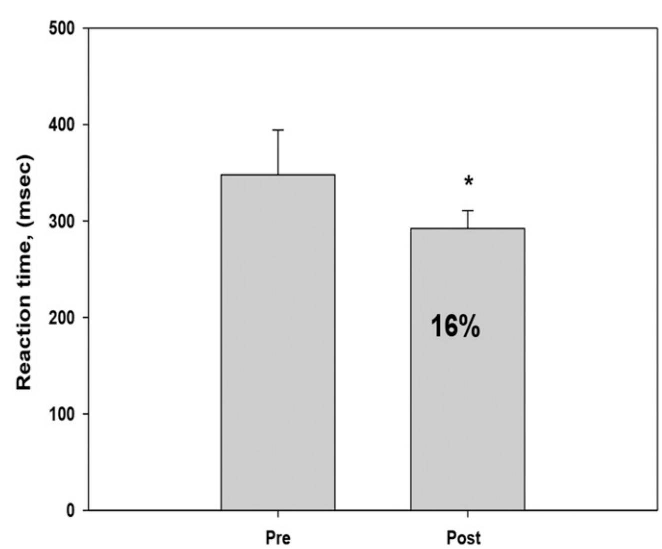

Fig. 3. Reaction times averaged across the exercise time measured during the cognitive protocol pre- and post-VIHT. Values are mean ± SD and the * indicates significant difference from pre-VIHT. Reaction time was 16% faster after VIHT than pre-VIHT.

The physiological data are presented in **Table I** for all groups. The data for the pretest were not different among the groups of tests and thus are shown as the average of all groups. The posttest data for VIHT, Control and Placebo groups, along with statistics are also shown in Table I comparing the individual groups' pre- to posttest values. The $\dot{V}O_2$ on the Pretest averaged 2.41 $L \cdot min^{-1}$ and was not different during the posttests. HR during the exercise averaged 175 bpm and was not different during the posttests for any group. The exercise $\dot{V}_E$ averaged 106.33 $L \cdot min^{-1}$ and was not different during the posttests for any group. Both respiratory rate (53 breaths) and tidal volume (2.06 L) were not different during the posttests for any group. $ETCO_2$ was 4.76% on the pretest and was not different during the posttests for any group. Similarly, CBFv was not different on the posttest compared to the pretest which averaged 38 cm/s. While $\dot{V}_E$ was not affected by VIHT, there was tendency for VT to be higher (13%) and RR lower (8%) after VIHT.

DISCUSSION

To examine the potential benefit of VIHT to maintain cognitive function at altitude this study was conducted while exercising at an altitude common in climbers, trekkers, and military personnel. Collectively, cognitive function was improved by VIHT, but not by PVIHT or in the control group on three of the four cognitive measures. The improvements due to VIHT appear to be executive functioning (Stroop Test), and more specifically processing speed (Symbol Digit Modalities Test and reaction time test) and working memory (Symbol Digit Modalities Test). The hypothesis that VIHT would reduce $\dot{V}O_2$ and $\dot{V}_E$ and thus increase P_aCO_2 and CBFv was not supported by the data from the present study.

Altitude and simulated altitude have been shown to significantly reduce cognitive function.[3,4,28] In addition, intense or fatiguing exercise depresses cognitive function at altitude.[15] Psychosensorimotor, reasoning and mental learning processes of climbers at simulated altitude of 8848 m (29,029 ft) for 31 d deteriorated progressively as they advanced from 5500 to 6500 m (18,045 to 21,225 ft),[1] suggesting that the effects of altitude is a cortico-limbic rather than basal ganglia-sensorimtor system function.[1] Subjects who trekked to 4554 m (14,941 ft) had impaired neurocognitive testing, and it was associated with a marker of loss of integrity of the blood-brain barrier. In addition, decreased brain-derived neurotropic factor and elevated inflammatory factors have been shown at an altitude of 4554 m.[16] Most studies of cognitive function at altitude were conducted at rest. Previous studies during acute exercise[2] and chronic exercise[9] at 1 ATA have demonstrated that the subjects had improved executive function.

Previous studies have looked at the effects of ways to inhibit cognitive dysfunction at altitude. In a cross sectional study it was shown that exercise-trained subjects did not have improved cognitive function at altitude. Specifically, in comparing trained military operators to nontrained subjects tested on the fifth day of ascent to 3900 m (12795 ft), both had decreased accuracy in cognitive tests and took longer to finish. Although trained military operators performed better before ascent, they showed greater declines than nontrained subjects at altitude.[16] A longitudinal study demonstrated that physical fitness enhances cognitive functioning, specifically flexibility and control, but not working memory at altitude.[26] In the present study VIHT resulted in a significant improvement on three of four cognitive tests, thus is a good countermeasure for acute exposure to altitude. The changes in cognitive function with physical fitness have been attributed to dopaminergic modulation based on different Met alleles between runners and an unfit group,[26] although this may or may not be the case after VIHT.

VIHT significantly improved both the number of responses and the number of correct responses on the Stroop task, and thus maintained the accuracy of the increased response rate during exercise at altitude. Improvement in the speed of processing cognitive information was also shown by the significant improvement in choice reaction time by VIHT. The finding that these improvements were during exercise at altitude is important as acute exercise at 40–80% of peak power caused an increase in switching function, and error rates, particularly in

Table I. Physiological Data among the Groups of Subjects for Pre- and Post-VIHT, Post-Control, and Post-PVIHT.

		PRE	VIHT	CONTROL	PLACEBO	F	*P*
$\dot{V}O_2$	$L \cdot min^{-1}$	2.41	2.49	2.15	2.26	3.397	0.207
		0.14	0.13	0.54	0.26		
HR	bpm	175	180	175	167	22.23	0.42
		4	3	2	11		
$\dot{V}_E$	$L \cdot min^{-1}$	106.33	108.98	117.86	95.96	0.986	0.425
		7.48	9.68	10.25	11.4		
RR	breaths	53	49	61	47	0.876	0.448
		3	7	2	8		
TV	L	2.06	2.34	1.93	2.05	3.471	0.203
		0.06	0.29	0.13	0.34		
$ETCO_2$	%	4.76	4.68	4.79	4.72	0.304	0.746
		0.4	0.66	0.52	0.56		
CBFv	$cm \cdot s^{-1}$	38	36	37	35	6.055	0.133
		5	8	7	5		

lower fit persons, on the modified-Stroop task (denomination, inhibition, and switching conditions).[15] The negative effect of exercise is supported by another study that demonstrated that high levels of training that cause a reduction in exercise performance (over training) resulted in lower levels of executive function.[7] These effects appear to have been countered by VIHT in the present study where exercise was carried out at 70–75% of maximal $\dot{V}O_2$ and cognitive function was improved compared to pre-VIHT, but not PVIHT or control.

In the present study, VIHT significantly improved both the number of responses and the number of correct responses on the SDMT, thus maintaining the accuracy of the increased response rate. Although controversies have been longstanding regarding the exact location in the brain in which processing verbal and nonverbal information occurs, it is an accepted notion that the left hemisphere is predominantly responsible for processing language, including speaking, writing, and reading, and to some extent, comprehension of speech. The right hemisphere then has been thought to play a similar predominant role in visual-perceptual, spatial-constructional, and nonverbal reasoning functions. As such, with the SDMT substituting meaningless geometric symbols for numbers involves many functions in both the left and right cerebral hemispheres, in addition to the forebrain commissures that connect the two hemispheres and facilitate integration of verbal and nonverbal cognitive functions involved.

Cognitive deficits at high altitudes (12,000-25,000 ft), Digit Span and Digit Symbol subsets from the Wechsler Adult Intelligence Scale-Revised, the Vandenberg Mental Rotation Test, and the near-contrast sensitivity portion of the Vistech VCTS 6000 Chart showed no effect on a vigilance task, however there were significant deficits in recall for high, but not low memory loads. In the present study VIHT did not significantly improve the scores on the Digit Span Forward test. This suggests that VIHT did not improve recall for high memory loads. However, another explanation is that the Digit Span Forward test has a fixed number of responses, as opposed to the Stroop and SDMT tests where the number of attempts and accuracy were improved, and thus the speed of attempts was not an issue, only the correctness of the responses, which was unaffected by VIHT as the Digit Span Forward is not mediated by a speed of processing component which seems to be the common factor that VIHT affects. At 4500 m it has been reported that there were no deficits in word fluency, word association, or lateralized lexical decision performances indicating frontal lobe function was preserved at altitude[19] and thus the Digit Span Forward test may not have been effected by exercise and altitude in our study pre-VIHT, thus there was no improvement. This point of view is supported by the high percentage of correct response on the pre-VIHT test.

Another index of cognitive function is complex reaction time, which has been shown to be increased at altitude.[15] In addition, reaction time has been shown to increase during moderate exercise (60% $\dot{V}O_{2max}$), however it was not impacted further by hypoxia (15% O_2). Mechanisms of the altitude-induced deficits may be in its effect on slowing action potentials as demonstrated by measures of the auditory event-related potentials.[30] Another study showed changes in latency and amplitude of selected potentials reflecting slowed sensory discrimination and evaluation processes,[14] and this may be responsible for the slow reaction time at altitude. There appear to be wide individual variations in response to altitude, with elite athletes at moderate altitude having no significant effect,[18] while lower fit persons show increased reaction time variability during exercise, increasing with exercise intensity (40–80% of peak power).[15] However, not all studies report such deficits.[19] One study at altitude concluded reduced cognitive function to altered sleep patterns.[4] The subjects' in the present study were not elite athletes and had moderate fitness and thus it would be expected that their reaction times would be slowed at altitude. However, after VIHT their reaction times were significantly improved.

Previous studies have looked at the physiological changes at altitude, however we are unaware of any study that examined these during exercise at altitude while cognitive function was being evaluated. It was interesting that during the speaking part of the cognitive testing the S_aO_2 decreased significantly, presumably due to the reduction of ventilation during talking, although this was not measured. As opposed to our initial hypothesis, there was no reduction in ventilation and consequent increase in $ETCO_2$ at altitude and presumably P_aCO_2 after VIHT. This response is different than previously reported for 1 ATA[5,17] and greater depths.[21] The absence of an effect of VIHT in CBFv during exercise at altitude is consistent with absence of increased $ETCO_2$ at altitude and presumably P_aCO_2. As it was not studied in this or previous studies, we cannot rule out that there may have been redistributions of blood flow within the brain that could benefit cognitive function. The indirect methods of measuring P_aCO_2, cerebral blood flow, as well as cognitive function may have had an impact on the results and conclusions of this study. Thus the improvements in cognitive function seen after VIHT cannot be explained by physiological changes.

In summary, the literature clearly establishes that there are deficits in cognitive function at altitude, particularly during exercise. Exercise training or drug treatment do not appear to be effective countermeasures to inhibit cognitive deficits at altitude. While acclimatization is an effective countermeasure for the altitude-induced cognitive deficits, its use is not applicable to acute hypoxia. The present study demonstrates that training of the respiratory muscles, like whole body aerobic exercise, is an effective countermeasure for altitude-induced cognitive deficits, although the mechanisms of its actions are not clarified.

ACKNOWLEDGMENTS

We acknowledge the subjects for their commitment and effort during the study. We thank Mike Fletcher and Ronald Orpinski for their technical support and James Richburg and Allison Edwards for their assistance in collecting and analyzing the data. The funding for this study was provided by the Department of Defense.

Authors and affiliations: Joseph Quackenbush, M.S., Aubrey Duquin, Ph.D., Samuel Helfer, M.S., and David R. Pendergast, Ed.D., Center for Research and Education in Special Environments, Department of Physiology and Biophysics, School of Medicine an Biomedical Sciences, University at Buffalo, Buffalo, NY.

REFERENCES

1. Abraini JH, Bouquet C, Joulia F, Nicolas M, Kriem B. Cognitive performance during simulated climb of Mount Everest: implications for brain function and central adaptive processes under chronic hypoxia. Pflugers Archiv-Eur J Physiol. 1998; 436(4):553–559.
2. Alves CR, Gualano B, Takao PP, Avakian P, Femandes RM, et al. Effects of acute physical exertion on executive functions: a comparisons between aerobic and strength exercise. J Sport Exerc Psychol. 2012; 34(4):539–549.
3. Asmaro D, Mayall J, Ferguson S. Cognition at altitude: impairment in executive and memory processes under hypoxic conditions. Aviat Space Environ Med. 2013; 84(11):1159–1165.
4. Bahrke MS, Shukitt-Hale B. Effects of altitude on mood, behavior, and cognitive functioning. A review. Sports Med. 1993; 16(2):97–125.
5. Boutellier U, Buchel R, Kundert A, Spengler C. The respiratory system as an exercise limiting factor in normal trained subjects. Eur J Appl Physiol Occup Physiol. 1992; 65(4):347–353.
6. Burtscher M, Faulhaber M, Flatz M, Likar R, Nachbauer W. Effects of short-term acclimatization to altitude (3200 m) on aerobic and anaerobic exercise performance. Int J Sports Med. 2006; 27(8):629–635.
7. Dupuy O, Renaud M, Bherer L, Bosquet L. Effect of functional overreaching on executive functions. Int J Sports Med. 2010; 31(9):617–623.
8. Ferretti G, Boutellier U, Pendergast DR, Moia C, Minetti AE, Howald H, di Prampero PE. Oxygen transport system before and after exposure to chronic hypoxia. Inter J Sports Med. 1990; 11:S15–S20.
9. Guiney H, Machado L. Benefits of regular aerobic exercise for executive functioning in healthy populations. Psychon Bull Rev. 2013; 20(1):73–86.
10. Harms CA, Babcock MA, McCaram SR, Pegeiow DF, Nickele GA, et al. Respiratory muscle work compromises leg blood flow during maximal exercise. J Appl Physiol. 1997; 82(5):1573–1583.
11. Held HE, Pendergast DR. The effects of respiratory muscle training on respiratory mechanics and energy cost. Respir Meurobiol. 2014; 200(1):7–17.
12. Hesser CM, Linnarsson D, Fagraeus L. Pulmonary mechanisms and work of breathing at maximal ventilation and raised air pressure. J Appl Physiol. 1981; 50(4):747–53.
13. Hornbein TF, Townes BD, Schoene RB, Sutton JR, Houston CS. The cost to the central nervous system of climbing to extremely high altitude. N Engl J Med. 1989; 321(25):1714–1719.
14. Kida M, Imai A. Cognitive performance and event-related brain potentials under simulated altitude. J Appl Physiol. 1993; 74(4):1735–1741.
15. Labelle V, Bosquet L, Mekary S, Bherer L. Decline in executive control during acute bouts of exercise as a function of exercise intensity and fitness level. Brain Cogn. 2013; 81(1):10–17.
16. Li P, Zhang G, You HY, Zheng R, Gao YQ. Training-dependent cognitive advantage is suppressed at altitude. Psych Behav. 2012; 106(4):439–445.
17. Leddy JJ, Limprasertkul A, Patel S, Modlich F, Buyea C, et al. Isocapnic hyperpnea training improves performance in competitive male runners. Eur J Appl Physiol. 2007; 99(6):665–676.
18. O'Carroll RE, MacLeod D. Moderate altitude has no effect on choice reaction time in international rugby players. Br J Sports Med. 1997; 31(2):151–152.
19. Pavlicek V, Schirlo C, Nebel A, Regard M, Koller EA, Brugger P. Cognitive and emotional processing at high altitude. Aviat Space Environ Med. 2005; 76(1):28–33.
20. Powell FL. The influence of chronic hypoxia upon chemoreception. Respir Physiol Neurobiol. 2007; 157(1):154–161.
21. Ray AD, Pendergast DR, Lundgren CEG. Respiratory muscle training reduces the work of breathing at depth. Eur J Appl Physiol. 2010; 108(4):811–820.
22. Reynolds CR. Forward and backward memory span should not be combined for clinical analysis. Arch Clin Neuropsychol. 1997; 12(1): 29–40.
23. Robbins PA. Is ventilator acclimatization to hypoxia a phenomenon that arises through mechanisms that have an intrinsic role in the regulation of ventilation at sea level? Adv Exp Med Biol. 2001; 502:339–348.
24. Schoene RB. Limits of human lung function at high altitude. J Exp Biol. 2001; 204(Pt.18):3121–3127.
25. Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol. 1935; 18(6):643–662.
26. Stroth S, Reinhardt RK, Thone J, Hille K, Schneider M, et al. Impact of aerobic exercise training on cognitive functions and effect of associated to the COMT polymorphism in young adults. Heurobio Learn Memory. 2010; 94(3):364–372.
27. Van Dorp E, Los M, Dirven P, Sarton E, Teppema L, et al. Inspired CO_2 during hypoxia: effects on task performance and cerebral O_2 saturation. Aviat Space Environ Med. 2007; 78(7):666–72.
28. Wang J, Ke T, Zhang X, Chen Y, Liu M, et al. Effects of acetazolamide on cognitive performance during high-altitude exposure. Neurotoxicol Teratol. 2013; 35(1):28–33.
29. Wechsler D. Wechsler-Bellevue Intelligence Scale. New York (NY): The Psychological Corporation; 1939.
30. Wesensten NJ, Crowley J, Balkin T, Kamimori G, Iwanyk E, et al. Effects of simulated high altitude exposure on long-latency event-related brain potentials and performance. Aviat Space Environ Med. 1993; 64(1): 30–36.
31. Wilde N, Strauss E. Functional equivalence of WAIS-III/WMS-III digit and spatial span under forward and backward recall conditions. Clin Neuropsychol. 2002; 16(3):322–330.