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Effect of intermittent normobaric hypoxia on aerobic capacity and cognitive function in older people

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ABSTRACT

Objectives: Physical exercise, especially aerobic training, improves physical performance and cognitive function of older people. Furthermore, it has been speculated that age-associated deteriorations in physical performance and cognitive function could be counteracted through exposures to passive intermittent normobaric hypoxia (IH). Thus, the present investigation aimed at investigating the effect of passive IH combined with subsequent aerobic training on hematological parameters and aerobic physical performance ($\dot{V}O_{2\,max}$) as well as peripheral levels of the neurotrophin brain-derived neurotrophic factor (BDNF) and cognitive function.
Design: Randomized controlled trial in a repeated measure design.
Methods: 34 older participants were randomly assigned to an intervention group (IG) or control group (CG). While IG was supplied with passive IH for 90 min, CG breathed ambient air. Subsequently, both groups underwent 30 min of aerobic training three times per week for four consecutive weeks. Aerobic physical performance and cognitive function was tested with spiroergometry and the Stroop test. Blood samples were taken to measure hematological parameters and the peripheral serum BDNF-level.
Results: We found increases in the values of hematological parameters, the time to exhaustion in the load test and an augmented and sustainable improvement in cognitive function within the IG of the older people only. However, in both groups, the $\dot{V}O_{2\,max}$ and serum BDNF-level did not increase.
Conclusions: Based on these results, hypoxic training seems to be beneficial to enhance hematological parameters, physical performance and cognitive function in older people. The current hypoxic-dose was not able to enhance the serum BDNF-level or $\dot{V}O_{2\,max}$.

1. Introduction

The reduced physical performance[1] and cognitive functioning[2] which are associated with old age are generally also accompanied by physiological changes. Deterioration of hematological values and mitochondrial function reduce oxygen-carrying and oxygen-consumption for example. This, in turn, impairs physical performance and makes it harder to perform daily activities. Age-dependent decreases in cognitive function are mostly associated with changes in brain structures[3] and an acceleration in brain atrophy, whereby the severest effect mostly occurs in prefrontal regions.[4] These changes negatively affect the functionality of the brain.[3,5,6]

Many interventions have been shown to induce physiological changes that lead to improved physical performance and cognitive function. We want to highlight the following two: aerobic training and hypoxia.

Aerobic training improve both physical performance[1] and cognitive function[2] and, as a consequence, the quality of life.[7] One key to good physical performance is to increase the maximal oxygen uptake ($\dot{V}O_{2\,max}$), which is determined among others by the red blood cell (RBC) concentration[8] and can be augmented through aerobic exercise.[9] Furthermore, physical exercise increase the expression of the brain-derived neurotrophic factor (BDNF)[10] which is associated with improvements in cognitive functions.[11,12]

Comparable effects can be observed through the application of hypoxia. It has been shown that exercise tolerance,[13] particularly

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the aerobic physical performance through augmented erythropoiesis, angiogenesis and/or mitochondrial capacity[14] come along with increased cognitive function and quality of life.[15] While physiological understanding of hypoxia and its influence on cognitive function is in its infancy, there is first evidence that hypoxia improves BDNF-levels.[16]

The purpose of the present study was to evaluate whether there is a synergy effect of intermittent normobaric hypoxia (IH) and aerobic training on physical performance and cognitive function.

2. Methods

Thirty-six older healthy and physically active adults were recruited who fulfilled the following criteria: age 60–75 years, no stay in an altitude above 1800 m as well as no blood donation in the last two months, no chronic or acute renal, cardiovascular, metabolic, neuronal or orthopedic diseases. The diet of the subjects was not controlled during the study.

The volunteers were randomly (permuted block randomization, proportion 1:1) assigned either to the intervention group (IG: $n = 18$; 9 female, 9 male; age 66.4 ± 3.3 years; weight 78.2 ± 11.8 kg; height 1.70 ± 0.09 m) or to the control group (CG: $n = 18$; 8 female, 10 male; age 67.9 ± 4.4 years; weight 79.0 ± 16.2 kg; height 1.68 ± 0.10 m). Three subjects dropped out because of personal reasons (IG: $n = 17$, CG: $n = 16$). All participants involved signed a written informed consent and passed successfully a medical examination by a medical doctor. The study was approved by the Ethical Committee of the Otto von Guericke University Magdeburg, Germany.

In this single-blind (subjects) simple randomized controlled trial, the participants of the IG and CG performed a four week-lasting intervention, three times per week. The intervention of the IG consisted of an application of passive normobaric hypoxia continuously for 90 min followed by an aerobic training on bicycle ergometers for 30 min under ambient air conditions. Oxygen-reduced air was supplied via facemasks by hypoxia generators (Everest Summit II, Hypoxico®, USA), whereby the fraction of inspired oxygen (FiO_2) was individually adjusted via the oxygen saturation in the blood (SpO_2). In the first week, we adjusted the SpO_2 between 90 and 85% and from the second to the fourth week to 80%. The CG received a placebo-air mixture (ambient air, SpO_2: 95–99%). The following continuous aerobic training was conducted on bicycles. The training load was adjusted in the first week between 65 and 70% and in the second to the fourth week between 70 and 75% of their maximum heart rates. The maximum heart rates were previously determined in a physical load test.[17] The intervention was provided in four groups with maximally nine participants, where two groups trained in the morning and two in the afternoon. To exclude unexpected differences, the participants of CG performed the same intervention in the same location and time together with the participants of IG but without the hypoxic treatment.

Within one week before (pre) and after (post) the intervention, the participants performed the tests of physical performance and cognitive function at the same time of the day. To analyze hematological parameters (red blood cells, RBC: error of measurement: 0.05 Tpt/l; hemoglobin, Hb: error of measurement: 0.1 Tpt/l; hematocrit, Hct: error of measurement: 0.6 Tpt/l) and serum BDNF, blood was drawn immediately prior to the first (pre) and after the last (post) intervention. The amount of serum BDNF-level was determined using the BDNF DuoSet ELISA kit (R&D Systems®, Wiesbaden, Germany). The probes were processed according to the kit instructions. Samples with a coefficient of variation (CV) above 10% were reanalyzed. Changes between the measurements (pre to post and post to follow-up) are represented as ratio of serum BDNF. Blood samples were collected by a medical doctor from a forearm superficial vein under stasis condition for the determination. The participants were instructed to partake of a light meal as well as to drink sufficient water before each intervention starts. Based on the assumption that neuroprogenitor cells reach their full operational capability after three weeks, the performance in the Stroop test was evaluated and serum BDNF was collected three weeks after the intervention time (follow-up: FU).[18]

Physical performance was assessed by a physical load test with incremental protocol (initial load 50 W, 25 W was added every 2 min) on a bicycle (Xrcise Cycle Med, Cardiowise®, Germany) in combination with a spirometry (PowerCube, Ganshorn®, Germany). The test was performed until the subjective physical exhaustion of the participants or the medical assessment of vital parameters by a medical doctor (e.g. heart rate, blood pressure).

The primary outcome of this test was the highest value of oxygen consumption in relation to the bodyweight ($\dot{V}O_{2\,max}$ [ml/min/kg]).

The Stroop test[19] was used to assess the cognitive function, more specifically the executive functions which are primarily located in the frontal lobe of the cortex. This test involves three sheets (word-task, color-task, word-color-task) that measure the information processing speed (all three sheets) and selective attention (last sheet). For all parameters of the Stroop test, the reliability and validity is reported to be high.[20]

The statistical analysis was performed with SPSS 22 (IBM®, Germany). After checking for normal distribution (tested by Kolmogorov–Smirnov-Test), the data were analyzed with a two-way repeated-measures ANOVA with factors time × group (interaction effect, main-time effect, main-group effect). In addition, a one-way repeated-measure ANOVA was used to verify the modification of each group during the intervention period (time effect). For the time effects including data of more than two measurement time points, we use the Bonferroni-correction. Also, effects within the measurements between the groups were tested by a one-way ANOVA (group effect). The effect size was quantified by partial eta-squared (η^2). In case of not normally distributed data, the Mann–Whitney U test for testing differences between the groups and the Wilcoxon test for testing differences from one to another measurement within the groups were used. In all tests, the level of significance was set to $\alpha = 5\%$. Data sets including fewer than thirty-three participants are due to testing errors.

3. Results

The physical load test was performed by the participants until maximal physical exhaustion (respiratory exchange ratio: IG pre: 1.17 ± 0.06, IG post: 1.14 ± 0.07, $p = 0.125$; CG pre: 1.16 ± 0.08, CG post: 1.13 ± 0.07, $p = 0.103$; maximum heart rate: IG pre: 152 ± 17 min^{-1}, IG post: 156 ± 18 min^{-1}, $p = 0.053$; CG pre: 150 ± 18 min^{-1}, CG post: 150 ± 18 min^{-1}, $p = 0.674$). After the intervention, both groups reached a higher peak aerobic power with a significant change only in the CG (IG pre: 149 ± 34 W, IG post: 157 ± 37 W, $p = 0.055$; CG pre: 144 ± 25 W, CG post: 155 ± 32 W, $p = 0.004$). Also, an increase in peak aerobic power goes along with an increase in the time to exhaustion in both groups. However, the enhancement was greater and significant only in the IG (IG pre: 579 ± 166 s, IG post: 625 ± 181 s, $p = 0.018$; CG pre: 566 ± 119 s, CG post: 587 ± 203 s, $p = 0.455$). During a submaximal load (1 W/kg) the heart rate decreases, but not significantly, in the IG, whereas in the CG no change has been found (IG pre: 114 ± 16 min^{-1}, IG post: 112 ± 15 min^{-1}, $p = 0.157$, IG: $n = 17$; CG pre: 112 ± 13 min^{-1}, CG post: 112 ± 13 min^{-1}, $p = 0.882$, CG: $n = 12$; dropouts in CG are caused by measuring error).

The non-normal distributed values (median, interquartile range) of $\dot{V}O_{2\,max}$ did neither significantly increase in both groups

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