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A 10-day confinement to normobaric hypoxia impairs toe, but not finger temperature response during local cold stress

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ABSTRACT

The study examined the effects of a 10-day normobaric hypoxic confinement on the finger and toe temperature responses to local cooling. Eight male lowlanders underwent a normoxic (NC) and, in a separate occasion, a normobaric hypoxic confinement (HC; FO_2: 0.154; simulated altitude ~3400 m). Before and after each confinement, subjects immersed for 30 min their right hand and, in a different session, their right foot in 8 °C water, while breathing either room air (AIR) or a hypoxic gas mixture (HYPO). Throughout the cold-water immersion tests, thermal responses were monitored with thermocouples on fingers and toes. Neither confinement influenced thermal responses in the fingers during the AIR or HYPO test. In the foot, by contrast, HC, but not NC, reduced the average toe temperature by ~1.5 °C (p=0.03), both during the AIR and HYPO test. We therefore conclude that a 10-day confinement to normobaric hypoxia *per se* augments cold-induced vasoconstriction in the toes, but not in the fingers. The mechanism underlying this dissimilarity remains to be established.

1. Introduction

Results regarding the effect of prolonged hypoxic exposure on peripheral responses to cold are equivocal; a few studies have observed an enhancement of local cold tolerance (Amon et al., 2012; Felicijan et al., 2008; Mathew et al., 1977; Keramidas et al., 2015a), while others have reported either an impairment (Savourey et al., 1997; Castellani et al., 2002), or no change (Daanen and van Ruiten, 2000; Keramidas et al., 2015a). The discrepancies between findings in previous studies might be explained by whether the hypoxia was combined with exposure to cold and exercise, components that can also affect, in an independent manner, the responses to local cold stimulus (Keramidas et al., 2010; Livingston et al., 1976; Purkayastha et al., 1992). It has recently been shown that a 10-day exposure to hypoxia *per se* (simulated altitude of ~4100 m) does not alter the hand-temperature responses during immersion in cold water, while breathing normoxic or hypoxic air (Keramidas et al., 2015a).

Local cold tolerance as implied by the cold-induced vasodilation response (CIVD) is not a generalizable response across hand and foot (Cheung and Mekjavic, 2007). Specifically, CIVD is of less magnitude (van der Struijs et al., 2008) and appearance rate (Cheung and Mekjavic, 2007; Reynolds et al., 2007) in toes than fingers. Despite these differences between hand and foot, only two studies (Amon, 2009; Felicijan et al., 2008) examined the CIVD in both body parts before and following altitude acclimatization; the first study (Amon, 2009) before and after a four-week sleep-high train-low regimen and the second (Felicijan et al., 2008) before and following a three-week high-altitude mountaineering expedition. Interestingly, both interventions increased the digit skin-temperature responses, and more so in the toes than in the fingers. In both studies, the authors stated that it was impossible to distinguish whether these adaptive effects were induced by hypoxia, cold, or exercise. Consequently, the effect of prolonged hypoxia exposure *per se* on finger vs. toe responses to a cold stimulus needs to be elucidated.

The purpose of the present study was to examine the effects of a 10-day confinement to normobaric hypoxia on the finger- and toe-temperature response to local cold stress, while breathing either a normoxic (ambient air at 940 m above sea level) or a hypoxic gas mixture. Based on our previous work (Amon, 2009; Amon et al., 2012; Keramidas et al., 2015a), we hypothesized that the hypoxia stimulus would not influence finger temperature, but would attenuate the cold-induced reduction in toe temperatures in response to local cooling. Our hypotheses were tested in a cross-over designed study, with subjects participating in 10-day confinements both in hypoxia (HC) and

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normoxia (NC) separated by a 22-day washout period.

2. Materials and methods

The study was conducted at the hypoxic facility of the Olympic Sports Center Planica (Ratece, Slovenia) situated at an altitude of 940 m. The study was part of a larger project investigating the effects of a 10-day hypoxic confinement on several functions of cardiovascular, respiratory, thermoregulatory and metabolic systems. Results from the other investigations have been (Kounalakis et al., 2013; Mekjavic et al., 2016), or will be reported elsewhere.

2.1. Subjects

Eight healthy males with a mean ± SD age of 20 ± 5 years, stature of 181 ± 5 cm and weight of 72.4 ± 4.4 kg participated in the study. All participants were near-sea level residents, and had not been exposed to altitude > 500 m during the month preceding the experiments. They were nonsmokers, and had no history of any cardiovascular, pulmonary or metabolic disease. All of them were physically active on a recreational basis and had no, or very limited, previous experience with cold exposure experiments. The subjects were informed in detail about the experimental procedures, and gave their written consent to participate in the study. The protocol was approved by the National Committee for Medical Ethics at the Ministry of Health of the Republic of Slovenia and conformed to the Declaration of Helsinki.

2.2. Study outline

The overall experimental protocol is depicted in Fig. 1. All subjects underwent two 10-day confinement periods on two separate occasions, and in a counterbalanced fashion, separated by a 22-day wash-out period. During the first 10-day period, one group (n=4) was confined to a normoxic area of the facility (NC), and the other group (n=4) to the hypoxic area (HC) of the facility. During the HC, subjects lived continuously (24 h per day) at a simulated altitude of approximately 3400 m, which was achieved by maintaining the fraction of oxygen (FO_2) at 0.154.

Before and after each confinement period, all subjects conducted a blood examination and an incremental exercise test to exhaustion. On a separate day, they performed four cold-water immersion tests: i) a normoxic (AIR) cold-water hand and ii) foot immersion test, and iii) a hypoxic (HYPO) cold-water hand and iv) foot immersion test. During the HYPO tests, subjects breathed through a low-resistance two-way respiratory valve (Model 2, 700 T-Shape, Hans Rudolph, Inc. Shawnee, USA). The inspiratory side of the valve was connected via a respiratory corrugated tubing to a 200-L Douglas bag filled with the premixed humidified breathing mixture (FO_2: 0.154). The tests were conducted in a counterbalanced order, and separated by at least a 60-min interval. The sequence of the tests was the same for each subject during both testing periods. Subjects immersed their right limb. All tests were performed at the same time of the day (afternoon) to ensure that the effect of diurnal variations was similar.

2.3. Normoxic and hypoxic confinement

The two confinement periods commenced at 09:00 h and finished 10 days later at 09:00 h. During each period, subjects were confined to a total area of ~110 m^2, which included three double-sleeping rooms and a living room. Throughout the confinement, subjects were requested not to engage in any strenuous activity, and to limit their physical activity to slow walks in the living area. Subjects consumed the same standardized diet on each day, and were allowed to drink water and tea *ad libitum* (for more details about the subjects' nutrition see Mekjavic et al., 2016). Heart rate (HR) and capillary oxyhemoglobin saturation (SpO_2) were monitored with finger pulse oximeters (Wriston 3100, Nonin, Plymouth, Massachusetts, USA) during the night.

During the hypoxic confinement, hypoxia in the living area was achieved using an O_2 dilution system (b-Cat, Tiel, the Netherlands), based on the vacuum pressure swing adsorption principle. The O_2 level was monitored and recorded continuously with O_2 sensors (PGM-1100, Rae Systems, San Jose, California, USA). The environmental conditions were kept similar during the entire confinement; the temperature was 21.4 ± 1.5 °C and the relative humidity 47 ± 3%.

2.4. Testing sessions

2.4.1. Hematological tests

After an overnight fast, venous blood samples (2 mL) were drawn from an antecubital vein of the subjects to determine hemoglobin concentration ([Hb]), erythrocyte volume fraction (EVF) and the concentration of red blood cells (RBCs). The samples were analyzed by a hematology laboratory (Adria laboratories d.o.o., Ljubljana, Slovenia) using the cytochemical impedance method (ABX Pentra 120, Horiba Medical, Montpellier, France).

2.4.2. Exercise testing

Subjects performed an incremental exercise test to exhaustion on an electrically braked cycle ergometer (Daum Electronic, Furth, Germany) to determine their peak oxygen uptake (VO_2peak) and peak power output (PPO). A metabolic cart (Quark CPET, Cosmed, Rome, Italy) was used to acquire the breath-by-breath respiratory responses during the test. The exercise load was increased by 25 W min^{-1} until exhaustion. Attainment of VO_2peak was confirmed according to the following criteria, listed in priority order: i) severe fatigue or exhaustion resulting in an inability to maintain exercise at a given workload (cycling cadence < 60 rpm), ii) a plateau in VO_2, and iii) a subjective rating of perception of effort at, or near maximal.

2.4.3. Cold-water immersion tests

Prior to the beginning of the test, subjects were accustomed to the laboratory conditions for ~20 min. They were dressed in a T-shirt, short trousers and socks, and were sitting on a chair. The mean temperature, relative humidity and barometric pressure in the labora-

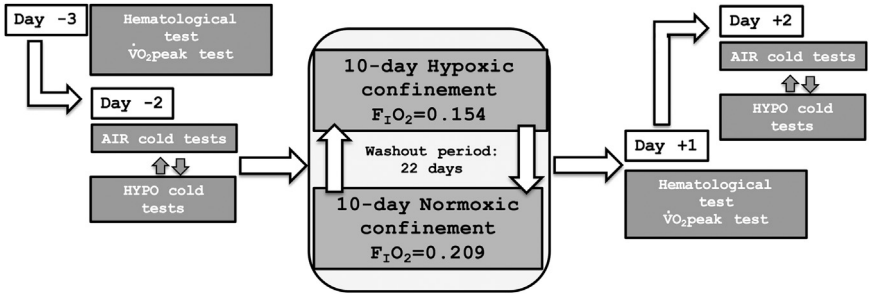

Fig. 1. Schematic representation of the experimental protocol. The project was conducted at 940 m above sea level at the hypoxic facility of the Olympic Sports Center in Planica (Slovenia). VO_{2peak}: Peak oxygen uptake, AIR: normoxic cold-water immersion test; HYPO: hypoxic (FO_2: 0.154; simulated altitude ~3400 m) cold-water immersion test.