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ORIGINAL RESEARCH

Cutaneous Vascular Responses of the Hands and Feet to Cooling, Rewarming, and Hypoxia in Humans

Heather C. Massey, BSc (Hons), MSc, PhD; James R. House, BSc (Hons), PhD; Michael J. Tipton, BSc (Hons), PhD

From the Extreme Environments Laboratory, Department of Sport and Exercise Science, University of Portsmouth, Portsmouth, UK.

Introduction—This study investigated skin vasomotor responses in the fingers and toes during cooling and rewarming with and without normobaric hypoxia.

Methods—Fourteen volunteers (8 males and 6 females) were exposed to gradual air cooling (mean±SD: $-0.4\pm0.1^{o}C \cdot min^{-1}$) followed by rewarming ($+0.5\pm0.1^{o}C \cdot min^{-1}$) while breathing normoxic air (F_IO_2 0.21 at 761±3 mm Hg) or hypoxic gas (F_IO_2 0.12, at 761±3 mm Hg, equivalent to ~5000 m above sea level). Throughout the gradual cooling and rewarming phases, rectal temperature was measured, and skin temperatures and laser Doppler skin blood flow were measured on the thumb, little finger, and great and little toe pads.

Results—During gradual cooling, skin temperature but not deep body temperature decreased. No differences in cutaneous vascular conductance were found for the toes or thumb ($P=0.169$ great toe; $P=0.289$ little toe; $P=0.422$ thumb). Cutaneous vascular conductance was reduced in the little finger to a greater extent at the same mean skin temperatures (34.5–33.5°C) in the hypoxic compared with normoxic conditions ($P=0.047$). The onset of vasoconstriction and release of vasoconstriction in the thumb and little finger occurred at higher mean skin temperatures in hypoxia compared with normoxia ($P<0.05$). The onset of vasoconstriction and release of vasoconstriction in the toes occurred at similar skin temperatures ($P=0.181$ and $P=0.132$, respectively).

Conclusion—The earlier vasoconstrictor response and later release of vasoconstriction in the finger during hypoxic conditions may result in a greater dose of cold to that digit, taking longer to rewarm following the release of vasoconstriction.

Keywords: vasoconstriction, vasodilatation, nonfreezing cold injury, combined stressors

Introduction

Cold injury is a frequent pathological consequence of exposure to altitude (>2800 m).[1] At altitude, hypoxia coexists with other stressors, in particular cold and dehydration. The central and peripheral responses to local and whole body cooling and, separately, the responses to natural or simulated altitude exposures have been investigated in detail. In contrast, the *combination* of these stressors has had less focus within integrated human research,[2] despite their frequent combined occurrence in the natural world.

Corresponding author: Dr. Heather C. Massey, Extreme Environments Laboratory, Department of Sport and Exercise Science, University of Portsmouth, UK, Spinnaker Building, Cambridge Road, Portsmouth PO1 2ER; e-mail: heather.massey@port.ac.uk.

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Cold exposure results in cutaneous vasoconstriction that lowers skin temperature, particularly in the extremities, and reduces heat transfer from deep body tissues to the environment.[3] Thus, a sustained period of vasoconstriction helps to preserve deep body temperature but increases the risk of frostbite and nonfreezing cold injury (NFCI), such as immersion foot or trench foot.[4] The addition of a hypoxic stimulus (acute or chronic exposure) can prolong cold-induced cutaneous vasoconstriction by slowing rewarming.[5,6] Keramidas et al[6] reported the acute effects of breathing a hypoxic gas mixture (F_IO_2=0.14) on hand skin temperature during rapid cooling in 8°C water. They found no differences in the rate of hand skin cooling between normoxic and hypoxic conditions. This finding may be expected, as immersion in cold water would rapidly lower skin temperature and promote a strong generalized sympathetic response, prompting rapid and maximal vasoconstriction, which would

likely be a stronger stimulus for peripheral vasoconstriction than hypoxia. Cooling of the digits while maintaining the rest of the body in a thermoneutral state may also allow cold-induced vasodilatation, a cyclical increase in local tissue temperature that accompanies a temporary return of blood flow to the digit.[7] No differences in cold-induced vasodilatation response were found between normoxic and hypoxic conditions when the body remained warm and the hand cooled.[6]

Gradual whole body cooling in a cold air environment during exposure may reduce mean body temperature and maintain sympathetic tone; therefore, cold-induced vasodilatation is less likely to occur.[8] In the work of Keramidas et al, during the air rewarming, postimmersion thumb skin temperatures were significantly lower when breathing hypoxic gas compared with normoxic air.[6] They suggest that the lower skin temperatures during rewarming of the hand in hypoxia may be due to a reduced skin blood flow response; however, blood flow was not directly measured in their study.

Any additional reduction in skin blood flow caused by hypoxia in a cold environment increases the "dose of cold" (a stimulus that results in physiological changes due to reductions in the environmental temperature and is applied for a period of time) experienced by the extremities and has the potential to increase both the number and severity of cold injuries. In this way, hypoxia may increase the risk of NFCI for a given air temperature. Although the exact dose required to increase the risk of NFCI is unclear, there are documented cases of NFCI that provide evidence of the conditions and duration of cold air exposure required[9,10]; however, a range of factors may contribute to the mechanism of injury and its severity.[11]

The feet are more exposed to conditions likely to cause NFCI,[12] have a lower blood flow, and can maintain vasoconstrictor tone when deep body temperature is thermoneutral.[13] In addition, behavioral temperature regulation may be slower to respond to cooling of the toes; cortical models indicate that greater discomfort would be felt in the fingers during simultaneous cooling of both fingers and toes. These factors suggest that vasomotor and behavioral responses to changes in temperature in the feet may be different from those of the hands on exposure to cold and hypoxic environments. However, this hypothesis has not been tested in a dynamic air environment, similar to that seen when at altitude, with participants warming and cooling with exercise and rest, shelter and exposure, and the vasomotor response switching from constriction to dilatation. It is the sensitivity of the cutaneous vasomotor response to such changes that determines the "dose" of cold experienced and therefore the risk of cold injury. Thus, it was hypothesized that 1) during a standardized cooling and rewarming profile, vasoconstriction and release of vasoconstriction would occur at higher skin temperatures when breathing a hypoxic gas mixture (F_IO_2=0.12), compared with normoxic air; and 2) vasoconstriction would occur earlier during cooling and be released later upon rewarming in the toes compared with the fingers.

Methods

VOLUNTEERS

Fourteen healthy, nonsmoking volunteers (8 males and 6 females) gave written informed consent to participate in this study ([mean±SD] age 23±2 years, height 1.72±0.11 m, mass 74.7±13.8 kg). Potential volunteers were excluded if they had sojourned at high altitude; flown in the month preceding the experiment; or reported peripheral vascular disease, Raynaud's, or NFCI to any digits. This study was approved by the University of Portsmouth Science Faculty Research Ethics Committee (SFEC 2014-018).

PROCEDURES

Volunteers, wearing shorts and a vest, were instrumented with a rectal thermistor (Grant Instruments [Cambridge] UK, Ltd), which was self-inserted 15 cm past the anal sphincter; skin thermistors (Grant Instruments) were applied to 7 sites (chest, arm, thigh, calf, forearm, and distal pad of the right index finger and right great toe). Multichannel laser Doppler probes (VP1T/7 Moor Instruments, Axminster, UK) were attached to the pads of the right thumb and little finger, great toe, and little toe and remained in position during both normoxic and hypoxic conditions. A pulse oximeter finger sensor (Nonin 7500, Plymouth, MN) was positioned on the middle finger of the right hand, and a 3-lead electrocardiograph was attached for calculation of heart rate (HR). Volunteers also wore a respiratory mask (Hans Rudolf, Shawnee, KS) for the duration of the study for the measurement of end-tidal oxygen and carbon dioxide tensions ($P_{ET}O_2$ and $P_{ET}CO_2$) using a rapid-responding oxygen and carbon dioxide analyzer (Rapidox, St. Ives, UK). Rectal and skin temperatures were recorded at minute intervals on a Squirrel 2020 electronic data logger (Grant Instruments). Laser Doppler (moorVMS-LDF, Moor Instruments), pulse oximeter, and oxygen and carbon dioxide gas analyzers were connected to an analogue to digital recorder (PowerLab, AD Instruments, Australia) and were sampled at 400 Hz, 60 Hz, and 400 Hz, respectively; minute means were calculated.

Participants cycled on a cycle ergometer (Monark, 874E, Vansbro, Sweden) at an external work rate of