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ORIGINAL ARTICLE

Cold-induced vasodilation responses before and after exercise in normobaric normoxia and hypoxia

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Abstract

Purpose Cold-induced vasodilation (CIVD) is known to protect humans against local cold injuries and improve manual dexterity. The current study examined the effects of metabolic heat production on cold-induced vasodilation responses in normobaric hypoxia and normoxia.

Methods Ten participants immersed their non-dominant hand into 5 °C water for 15 min. Minimum finger temperature (T_{min}), maximum finger temperature (T_{max}), onset time, amplitude, and peak time were measured before and after exercise under normoxia (21% O_2) and two levels of normobaric hypoxia (17% O_2 and 13% O_2).

Results Neither T_{min} nor amplitude was affected by hypoxia. However, T_{max} was significantly decreased by hypoxia while reduction in onset time and peak time trended towards significance. T_{min}, $T_{max,}$ and amplitude were significantly higher during post-exercise CIVD than pre-exercise CIVD.

Conclusion The CIVD response may be negatively affected by the introduction of hypoxia whereas metabolic heat production via exercise may counteract adverse effects of hypoxia and improve CIVD responses.

Keywords Cold-induced vasodilation · Normobaric hypoxia · Exercise · Body temperature

Abbreviations

BP	Blood pressure
CIVD	Cold-induced vasodilation
HR	Heart rate
MHP	Metabolic heat production
NH13	13% O_2
NH17	17% O_2
NN21	21% O_2
SpO_2	Peripheral oxygen saturation
T_b	Mean body temperature
T_{max}	Maximum finger temperature
T_{min}	Minimum finger temperature
T_{re}	Rectal temperature
T_{sk}	Skin temperature
VO_2	Oxygen uptake
VO_{2max}	Maximal oxygen uptake

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Introduction

According to a previous study, approximately 35 million people travel annually to altitudes above 3000 m for occupational and recreational purposes (Dumont et al. 2005). The characteristics of high-altitude environments include low oxygen concentration, cold, and wind that enhance heat loss (O'Brien et al. 2015). These environments are

associated with a higher incidence of local cold injury due to environmental (cold and hypoxia) and behavioral factors (reduced physical activity and energy intake) (Keramidas et al. 2014; Gorjanc et al. 2018).

Acute cold exposure causes vasoconstriction which results in reduced blood flow to the extremities and a decrease in skin temperature, consequently conserving heat (Kim et al. 2013). Interestingly, approximately 5–10 min after cold exposure, a temporary vasodilation occurs which increases peripheral blood flow and peripheral skin temperature, termed cold-induced vasodilation (CIVD) (Daanen 2003). In addition to typical CIVD responses, the extremities (hands, feet, cheeks, nose, and ears) can respond in many ways and in potential forms as outlined in previous studies including (1) continuous vasoconstriction (no CIVD), (2) proportional control form, and (3) slow and steady rewarming (O'Brien 2005; Cheung 2015). CIVD is thought to protect humans against local freezing and non-freezing cold injuries and improve manual dexterity by dilating the blood vessels, decreasing vascular resistance, and increasing the delivery of oxygen to the exposed extremities in a cyclic fluctuation pattern (Daanen 2003; Ducharme et al. 1991; Muller et al. 2010).

In addition to thermal balance, hypoxia and/or high-altitude exposure is another influential factor to CIVD responses. Hypoxia, reduced level of tissue oxygenation, can result from external (carbon monoxide and low partial pressure of oxygen in ambient air) and internal factors (diffusion limitation in the lungs and perfusion limitation into tissue, etc.) (Sarkar et al. 2017). A previous field study at 5100 m of altitude observed an attenuated CIVD response compared to sea level (Daanen and Van Ruiten 2000). However, evidence has indicated that CIVD responses are mediated by thermal balance and originates from core temperature to maintain body temperature homeostasis (Flouris and Cheung 2009; Flouris et al. 2008), which can be positively influenced by acute exercise (Dobnikar et al. 2009). Previous studies observed that CIVD responses were enhanced with elevated core temperature (Dobnikar et al. 2009; Flouris et al. 2008; Daanen et al. 1997), indicated by a short CIVD onset with high core and skin temperatures, whereas the delayed CIVD onset was associated with low core and skin temperatures (Daanen et al. 1997). A better understanding of the interaction between CIVD responses and body temperature at various hypoxia levels could promote the health and performance of those who participate in occupational and recreational activities. Therefore, the purpose of the present study was to investigate the effects of systemic hypoxia on the CIVD response before and after submaximal exercise. We hypothesized that CIVD responses would be impaired with low oxygen and would be improved after submaximal exercise.

Methods

The Institutional Review Board at Kent State University approved this study and all participants signed an informed consent form prior to participation. The current study was carried out in a repeated measures, within-participant design. The study included three experimental trials: normobaric normoxia (21%O_2: NN21) and two levels of normobaric hypoxia (17% O_2: NH17 and 13% O_2: NH13). Experimental trials were counterbalanced and separated by at least 48 h to ensure full recovery.

Participants

Ten healthy nonsmoking men (mean ± SD; age 23 ± 3 years; height 179.5 ± 5.2 cm; weight 83.3 ± 9.1 kg; % body fat 10.7 ± 6.0) volunteered for this study. This sample size was determined based on a power analysis with an assumed power of 0.8 that ten participants would need to be recruited to reach statistical significance between pre- and post-exercise in both NN21 and NH13.

All participants were recreationally active and were screened via medical history questionnaire. Participants were excluded if they reported the presence or history of cardiovascular, pulmonary, metabolic disease, cold injury, Raynaud's disease, sickle cell anemia, or any other condition or medication that affected circulation or other cardiovascular variables. Furthermore, participants were excluded if they were recently exposed to normobaric hypoxia or an altitude above 2500 m within 2 months prior to participation. Women were not included in this study due to established gender differences in thermoregulation (Wagner and Horvath 1985) and recognized rhythmic changes in core temperature during menstrual cycles (Nagashima 2015).

Experimental procedure

Prior to the experimental trial, participants reported to the laboratory on a separate day to complete informed consent, introduction, and measurement of maximal oxygen uptake (VO_{2max}). Participants underwent pre-screening with a medical history questionnaire to ensure they were free of all exclusion criteria and fully aware of the outlined protocol for the subsequent experimental sessions. Participants were introduced to the normobaric hypoxic chamber and to the study protocol to be carried out over the course of the subsequent sessions. Participants were also instructed to abstain from strenuous exercise, caffeine, and alcohol for at least 24 h prior to each experimental trial. After pre-screening, participants performed a maximal cycling exercise test to determine VO_{2max} on an automatically

braked cycle ergometer (Lode Excalibur Sport, Lode, Groningen, Netherlands). The protocol for VO_{2max} is outlined by Amann et al. (2004). Participants began the test at an intensity of 20 W, with intensity increasing by 25 W every minute until volitional fatigue. Participants were required to maintain a cadence between 60 and 80 rpm throughout the maximal protocol. Oxygen uptake (VO_2) was measured with a TrueOne 2400 metabolic cart (Parvo Medics, Sandy, Utah), while heart rate (HR) was constantly recorded with a Polar heart rate monitor (Polar RS800 CS, Polar Electro Oy, Kempele, Finland). When the pedaling cadence was no longer maintained, or the subject stopped cycling, the test was ended, and VO_{2max} was recorded along with maximum heart rate and final power output in Watts.

The VO_{2max} test was utilized to calculate a relative intensity for each subject to produce a desired level of 400 W metabolic heat. This intensity was kept constant between the three experimental trials (NN21, NH17, and NH13). The equation for metabolic heat production is as follows:

$$\frac{VO_2 \times \left(\left(\frac{\text{RER}-0.7}{0.3}\right) \times e_c\right) + \left(\left(\frac{1-\text{RER}}{0.3}\right) \times e_f\right)}{60},$$

where "RER" is respiratory exchange ratio, "e_c" is the caloric equivalent of a liter of oxygen when carbohydrates are oxidized (21.1 kJ) and "e_f" is the caloric equivalent of a liter of oxygen when fat is oxidized (19.6 kJ) (Cena and Clark 1981).

On each day of the experimental trial, participants reported to the laboratory at the same time of day, following a 3-h self-reported fast intended to stabilize substrate utilization and reduce the risk of nausea during testing. Upon arrival at the laboratory, participants changed into athletic shorts, t-shirt, and shoes and self-inserted a rectal thermistor (ITP010-11, Nikkiso—Therm Co., Ltd., Japan) 13 cm past the anal sphincter to measure rectal temperature (T_{re}). Then participants sat on a chair quietly for approximately 30 min in a thermoneutral condition [25 °C, 40% relative humidity (RH)]. Participants wore a HR monitor and four skin thermistors (ITP082-25, Nikkiso—Therm Co., Ltd., Japan) were affixed with a transparent dressing film (Tegaderm, 3 M, St. Paul, MS) onto the chest (0.3), triceps (0.3), thigh (0.2), and calf (0.2) for the calculation of weighted mean skin temperature (T_{sk}) (Ramanathan 1964).

Thermocouples for T_{re} and T_{sk} were continuously monitored using a data logger throughout the trials (Model N543, Nikkiso—Therm Co., Ltd., Japan). Subsequently, the mean body temperature (T_b) was calculated as 0.8 (T_{re}) + 0.2 (T_{sk}) (Hardy and Du Bois 1938). Finger temperature was also recorded on the proximal nail fold of the middle finger of the non-dominant hand (T_f) for CIVD parameters using the same skin temperature thermistor as previously described. In this study, five CIVD response parameters were described as illustrated in Fig. 1: (1) minimum finger temperature (T_{min}), (2) maximum finger temperature (T_{max}), (3) onset time (time from cold water immersion to minimum finger temperature), (4) amplitude (temperature difference between T_{min} and T_{max}), and (5) peak time (time from T_{min} to T_{max}).

Blood pressure (BP) was obtained by automated BP analysis (Cardio dynamics, San Diego, CA). SpO_2 was assessed through the use of a manual pulse oximeter (Oxy-Go, Roslyn, NY) placed onto the dominant hand ring finger. Following a baseline measurement outside the hypoxic chamber, participants moved into the hypoxic chamber (Colorado Altitude Training, Louisville, CO) for a 60-min resting period in a thermoneutral condition [25 °C, 40% relative humidity (RH)] as a control period to allow body temperature and oxygen saturation to stabilize. Following this resting period, participants immersed the non-dominant hand up to the ulnar styloid in a 6-L, 5 °C water bath for 15 min (Model: Isotemp 4100, Fisher Scientific, Pittsburgh, PA). After 15 min of cold water immersion, participants cycled on a cycle ergometer for 30 min at a fixed rate of 400 W of metabolic heat production. Throughout the 30 min of cycling, participants were required to maintain a cadence between 60 and 80 rpm. Immediately following the submaximal bout of exercise, participants sat on a chair and immersed their non-dominant hand back into 5 °C water for another 15 min. All participants were instructed to sit

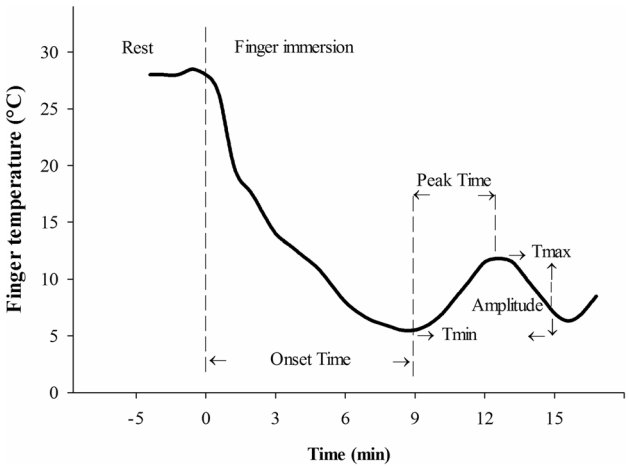

Fig. 1 Typical CIVD response and measure parameters of finger skin temperature and time during immersion in 5 °C cold water. T_{min} minimum finger temperature, T_{max} maximum finger temperature; *amplitude* temperature difference between T_{min} and T_{max}, *onset time* time from cold water immersion to minimum finger temperature, *peak time* time from T_{min} to T_{max}

upright on a chair quietly and maintain the same posture during the baseline and two immersion phases. Temperature variables were measured continuously while VO_2, HR, SpO_2 and BP were obtained during the final 5 min of each time point and averaged at 1-min intervals.

Data analysis

Using SPSS 19.0, two-way (three hypoxia levels by five time points) repeated measure analyses of variance (ANOVA) was utilized for T_{re}, T_{sk}, T_b, VO_2, SpO_2, and HR. Another two-way repeated measure ANOVA [three hypoxia levels by two time points (pre- and post-exercise)] was employed for CIVD parameters. When a significant F ratio for main effect and interaction was detected, post hoc pairwise comparison with least significant differences (LSD) was conducted to determine specific differences. An additional one-way ANOVA was conducted to examine the differences in CIVD parameters between hypoxia levels (NN21, NH17, and NH13) at pre- and post-exercise CIVD. Statistical significance was set at $p < 0.05$ and all data are presented as mean ± standard deviation (SD).

Results

The rate of metabolic heat production was maintained at 400 W across hypoxia levels, which corresponded to an exercise intensity of 123 ± 30 W across all participants. Net metabolic rate and exercise efficiency were 524.8 ± 36.8 W and 21.7 ± 3.6%, respectively. Baseline measurements of T_{re}, T_{sk}, T_b, VO_2, HR, and SpO_2 showed no difference between normoxia and both levels of normobaric hypoxia (NN21, NH17, and NH13).

Measurements of T_{re}, T_{sk}, and T_b across hypoxia levels and time are presented in Fig. 2. No significant effect of hypoxia levels on T_{re} was found ($F(2,18) = 2.728$, $p = 0.092$, $\eta_p^2 = 0.233$). A significant main effect of time on T_{re} was found ($F(4,36) = 9.291$, $p \leq 0.001$, $\eta_p^2 = 0.508$) with pairwise comparisons showing increased T_{re} during exercise and post-exercise compared to rest and pre-exercise. T_{sk} did not show a significant effect of hypoxia levels ($F(2,18) = 0.997$, $p = 0.388$, $\eta_p^2 = 0.1$). T_{sk}, however, did increase over time ($F(4,36) = 22.464$, $p \leq 0.001$, $\eta_p^2 = 0.714$) with pairwise comparisons revealing that exercise and post-exercise T_{sk} were higher than baseline, rest, and pre-exercise. T_b showed a similar pattern to T_{sk} with no difference between hypoxia levels ($F(2,18) = 1.753$, $p = 0.202$, $\eta_p^2 = 0.163$) but a significant effect of time ($F(4,36) = 39.117$, $p \leq 0.001$, $\eta_p^2 = 0.813$). No interactions were found for T_{re} ($F(8,72) = 0.901$, $p = 0.520$, $\eta_p^2 = 0.091$), T_{sk} ($F(8,72) = 0.692$, $p = 0.697$, $\eta_p^2 = 0.071$), or T_b ($F(8,72) = 1.997$, $p \leq 0.0.59$, $\eta_p^2 = 0.182$) (Fig. 2).

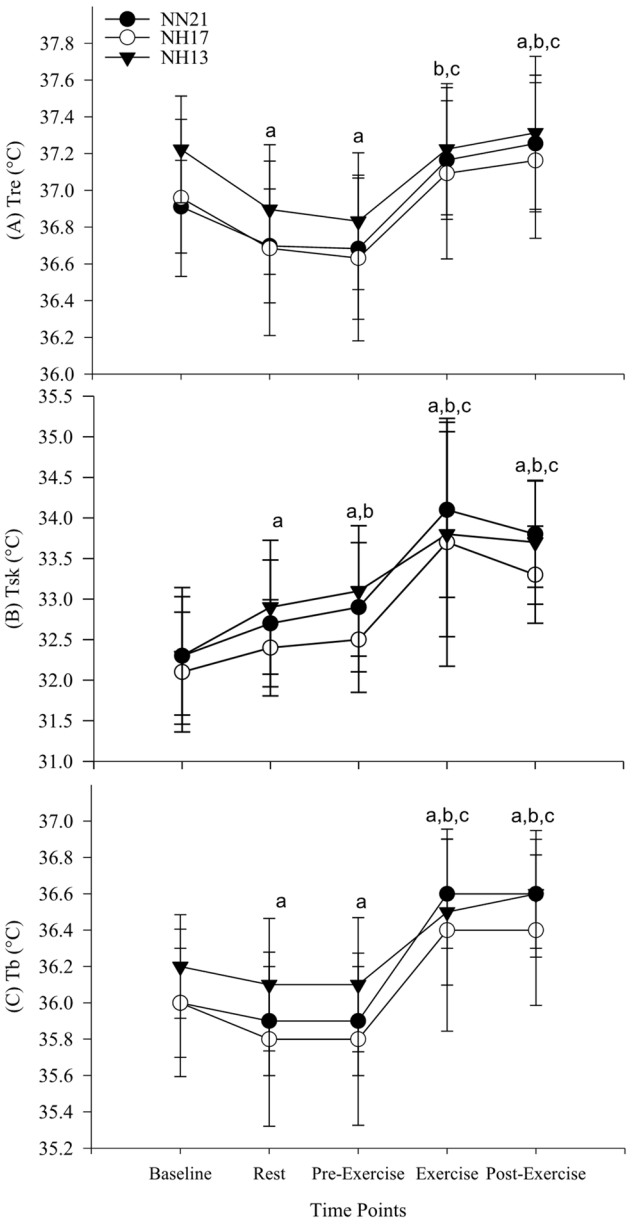

Fig. 2 **A** Rectal temperature, **B** mean skin temperature, and **C** mean body temperature response in NN21, NH17, and NH13. Values are mean ± standard deviation ($n = 10$). *NN21* 21 O_2, *NH17* 17% O_2, *NH13* 13% O_2; [a]$p \leq 0.05$ versus baseline; [b]$p \leq 0.05$ versus resting; [c]$p \leq 0.05$ versus pre-exercise, [d]$p \leq 0.05$ versus exercise

Measurements of VO_2, SpO_2, and HR across hypoxia levels and time are presented in Fig. 3. A two-way repeated measure ANOVA indicated that there were significant main effects for hypoxia levels on VO_2 ($F(2,18) = 3.959$, $p = 0.038$, $\eta_p^2 = 0.306$) with pairwise comparisons revealing that VO_2 in NN21 during exercise was significantly higher than NH17

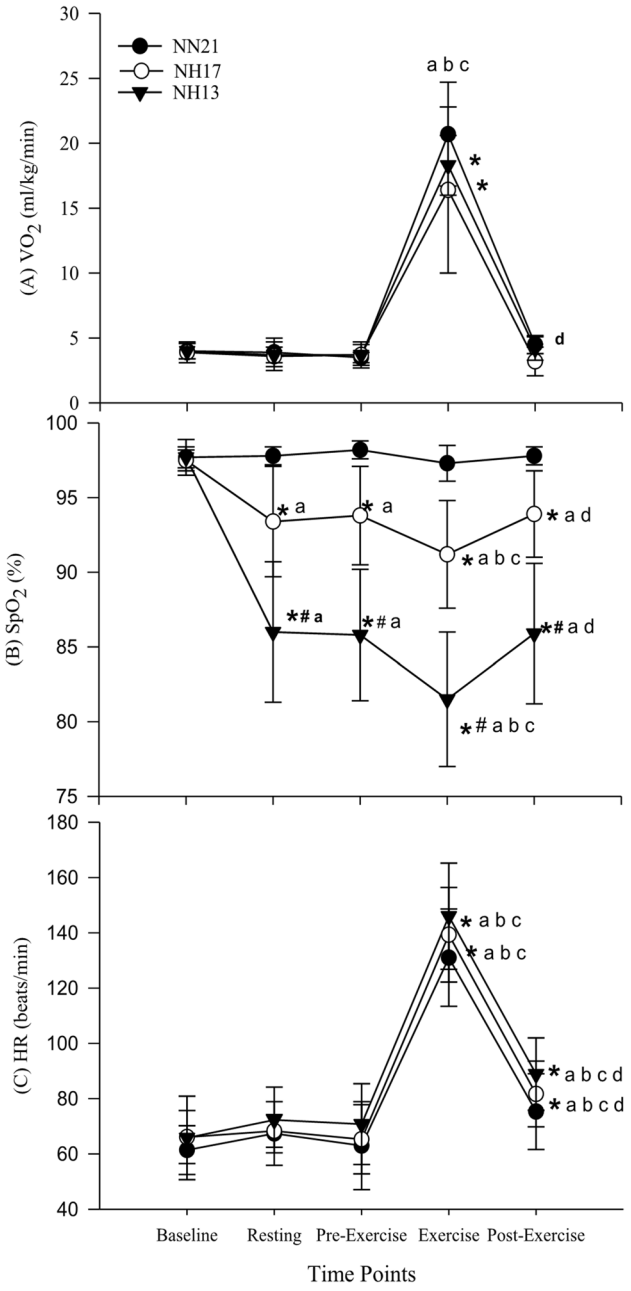

Fig. 3 **A** Oxygen uptake, **B** peripheral oxygen saturation, and **C** heart rate response in NN21, NH17, and NH13. Values are mean ± standard deviation ($n = 10$). *NN21* 21% O_2, *NH17* 17% O_2, *NH13* 13% O_2. [a]$p \leq 0.05$ versus baseline; [b]$p \leq 0.05$ versus resting; [c]$p \leq 0.05$ versus pre-exercise; [d]$p \leq 0.05$ versus exercise; *$p \leq 0.05$ versus NN21; [#]$p \leq 0.05$ versus NH17

and NH13. A significant effect of time was seen for VO_2 ($F(4,36) = 172.533$, $p \leq 0.001$, $\eta_p^2 = 0.950$). VO_2 also showed a significant interaction ($F(8,72) = 4.376$, $p \leq 0.001$, $\eta_p^2 = 0.327$) between time and hypoxia levels. SpO_2 showed a significant main effect of hypoxia levels ($F(2,18) = 60.9$, $p \leq 0.001$, $\eta_p^2 = 0.871$) with pairwise comparisons revealing

Table 1 Cold-induced vasodilation (CIVD) parameters at pre- and post-exercise between conditions (NN21, NH17, and NH13)

	Pre-exercise	Post-exercise
T_{min} (°C)		
NN21	10.0 ± 0.4	10.4 ± 0.5[#]
NH17	10.0 ± 0.4	10.4 ± 0.6[#]
NH13	10.0 ± 0.2	10.3 ± 0.5[#]
T_{max} (°C)		
NN21	10.5 ± 1.0	12.0 ± 1.9[#]
NH17	10.3 ± 0.8	11.2 ± 1.6*,[#]
NH13	10.1 ± 0.4	11.1 ± 1.1*,[#]
Amplitude (°C)		
NN21	0.3 ± 0.7	1.4 ± 1.6[#]
NH17	0.3 ± 0.7	0.7 ± 1.2
NH13	0.1 ± 0.3	0.7 ± 0.7[#]
Onset time (s)		
NN21	541.3 ± 187.1	520.8 ± 211.7
NH17	663.8 ± 193.5	575.2 ± 254.8
NH13	686.0 ± 220.8*	602.2 ± 221.3
Peak time (s)		
NN21	237.5 ± 182.9	254.8 ± 142.8
NH17	205.3 ± 189.3	203.0 ± 159.6
NH13	183.6 ± 192.0	124.1 ± 98.0

Values are mean ± SD

T_{min} minimum finger temperature, T_{max} maximum finger temperature, *amplitude* temperature difference between T_{min} and T_{max}, *onset time* time from cold water immersion to minimum finger temperature, *peak time* time from T_{min} to T_{max}

*Significant difference compared to NN21 condition ($p \leq 0.05$)

[#]Significant difference compared to pre-CIVD ($p \leq 0.05$)

that SpO_2 was lower in NH13 and NH17 at all time points except for baseline compared to NN21. Furthermore, SpO_2 at rest, pre-exercise, exercise, and post-exercise was lower in NH13 compared to NH17. SpO_2 showed a significant effect of time ($F(4,36) = 234.000$, $p \leq 0.001$, $\eta_p^2 = 0.792$) with NH17, with NH17 decreasing after baseline and staying decreased throughout the experimental protocol. A significant interaction between time and hypoxia levels was found for SpO_2 ($F(8,72) = 19.576$, $p \leq 0.001$, $\eta_p^2 = 0.685$) where decrements in SpO_2 over time were stronger in hypoxia. HR had a significant effect between hypoxia levels ($F(2,16) = 6.705$, $p = 0.008$, $\eta_p^2 = 0.456$) with HR being higher in NH13 compared to NN21 during exercise and post-exercise. HR also showed a significant main effect of time ($F(4,32) = 146.803$, $p \leq 0.001$, $\eta_p^2 = 0.948$) with HR significantly elevated during exercise. No time by hypoxia level interaction was found for HR ($F(8,64) = 1.681$, $p = 0.120$, $\eta_p^2 = 0.174$) (Fig. 3).

Table 1 presents CIVD parameters at pre- and post-exercise between the three hypoxia levels. T_{min} did not

show a significant effect of hypoxia levels ($F(2,18) = 0.087$, $p = 0.917$, $\eta_p^2 = 0.010$); however, a significant effect of time (pre- versus post-exercise) was found ($F(1,9) = 18.323$, $p = 0.002$, $\eta_p^2 = 0.671$). Post-exercise T_{min} was increased as compared to pre-exercise. No time by hypoxia level interaction was found for T_{min} ($F(2,18) = 0.017$, $p = 0.983$, $\eta_p^2 = 0.002$). T_{max} showed a significant difference between hypoxia levels ($F(2,18) = 3.764$, $p = 0.043$, $\eta_p^2 = 0.295$) with NH17 and NH13 being significantly lower than NN21. Furthermore, T_{max} had a significant effect of time ($F(1,9) = 17.442$, $p = 0.004$, $\eta_p^2 = 0.615$) with post-exercise values being higher than pre-exercise. A significant time by hypoxia level interaction for T_{max} was found ($F(2,18) = 5.060$, $p = 0.018$, $\eta_p^2 = 0.360$) with the effect of exercise appearing stronger in NN21 compared to NH17 and NH13. Amplitude had no effect of hypoxia level ($F(2,18) = 1.867$, $p = 0.183$, $\eta_p^2 = 0.172$) but a significant effect of time ($F(1,9) = 9.252$, $p = 0.014$, $\eta_p^2 = 0.507$) with post-exercise values being higher than pre-exercise in NN21 and NH13. No interaction was found for amplitude ($F(2,18) = 3.162$, $p = 0.067$, $\eta_p^2 = 0.260$). Onset time did not show a significant effect of hypoxia level ($F(2,18) = 3.027$, $p = 0.074$, $\eta_p^2 = 0.252$), time ($F(1,9) = 1.025$, $p = 0.338$, $\eta_p^2 = 0.102$), or significant interaction ($F(2,18) = 0.373$, $p = 0.694$, $\eta_p^2 = 0.040$). Similarly, amplitude did not show a significant hypoxia level effect ($F(2,18) = 2.916$, $p = 0.080$, $\eta_p^2 = 0.245$), time effect ($F(1,9) = 0.125$, $p = 0.732$, $\eta_p^2 = 0.014$), or interaction ($F(2,18) = 3.162$, $p = 0.067$, $\eta_p^2 = 0.260$) (Table 1).

A one-way ANOVA was conducted to determine the effect of metabolic heat on CIVD response between hypoxia levels. Pre-exercise CIVD response parameters indicated no significant main effect for hypoxia level on T_{min} ($F = 0.104$, $p = 0.902$), T_{max} ($F = 1.436$, $p = 0.264$), amplitude ($F = 0.545$, $p = 0.589$), and peak time ($F = 0.484$, $p = 0.624$) (Table 1). However, in pre-exercise there was a significant main effect of hypoxia level on onset time ($F = 4.339$, $p = 0.029$) (Table 1). Onset time during pre-exercise was significantly delayed in NH13 (686.0 ± 220.8 s) compared to NN21 (541.3 ± 187.1 s) ($p = 0.043$), whereas onset time was not significantly delayed in NH17 (663.8 ± 61.2 s) compared to NN21, but trended towards being delayed ($p = 0.063$) (Table 1). Post-exercise CIVD response parameters indicated a significant main effect for hypoxia level on T_{max} ($F = 5.065$, $p = 0.018$) (Table 1). T_{max} was significantly lower in NH17 ($p = 0.017$) and NH13 ($p = 0.031$) compared to NN21 (Table 1). There were no significant main effects for hypoxia level on T_{min} ($F = 0.058$, $p = 0.944$), amplitude ($F = 2.921$, $p = 0.080$), onset time ($F = 0.599$, $p = 0.560$), and peak time ($F = 3.356$, $p = 0.058$) (Table 1 and Fig. 4).

Discussion

The main findings of the present study are that (1) onset time of CIVD response parameters was significantly delayed by more than 2 min in NH13 compared to NN21. (2) A fixed rate of MHP enhanced T_{min}, T_{max}, and amplitude in post-exercise CIVD response parameters compared to pre-exercise CIVD. With respect to onset time, exercise was found to be less effective at improving the CIVD response.

Several studies have investigated the effect of hypoxic exposure on the CIVD response (Daanen and Van Ruiten 2000; Geurts et al. 2006; Dobnikar et al. 2009; Keramidas et al. 2015; Fukuda-Matsuda et al. 2007). A previous field study measured the CIVD response in acclimatized and non-acclimatized participants to an altitude of 5100 m compared to sea level. The study found a significant decrease in T_{max}, amplitude, and peak time, but no difference in T_{min} or onset time with altitude exposure in the non-acclimatized participants (Daanen and Van Ruiten 2000). Furthermore, Keramidas et al. (2014) reported that acute normobaric hypoxia (14% O_2) reduced T_{max} of the finger compared to normoxia and delayed the rewarming responses in both the glabrous and nonglabrous regions of the hand. The same study, however, reported no difference in T_{min} following acute exposure to normobaric hypoxia. The current study is in conflict with these results, as the current data find no difference in T_{max} at pre-exercise CIVD between normoxia and hypoxia. However, as seen in Table 1, we observed a decrease in T_{max} with lower oxygen content at pre-exercise, although non-significant. Furthermore, the current study shows a significant increase in onset time with decreasing oxygen content at pre-exercise, whereas onset time was shown previously to decrease at 3000 m compared to sea level (O'Brien et al. 2015). The previous study, which challenges the results of the current data, provides a limitation in that core body temperature was not measured to control for the possible effect of increased core body temperature on onset time outcomes. The authors describe this as a possible explanation for the result of decreased onset time, instead of the expected increased onset time with hypoxia. The present study provides an accurate measurement of core temperature and can confirm, as shown in Fig. 2a, that there was no main effect of hypoxia levels on T_{re}; thus, the hypoxia levels effect on onset time at pre-exercise cannot be attributed to differences in body temperature as was hypothesized in the previous study (O'Brien et al. 2015). This discrepancy may result from physiological differences between normobaric and hypobaric hypoxia. Indeed, a previous study reported that hypobaric hypoxia exhibits greater hypoxemia, hypocapnia, blood alkalosis, and a lower arterial oxygen saturation for the same ambient oxygen partial

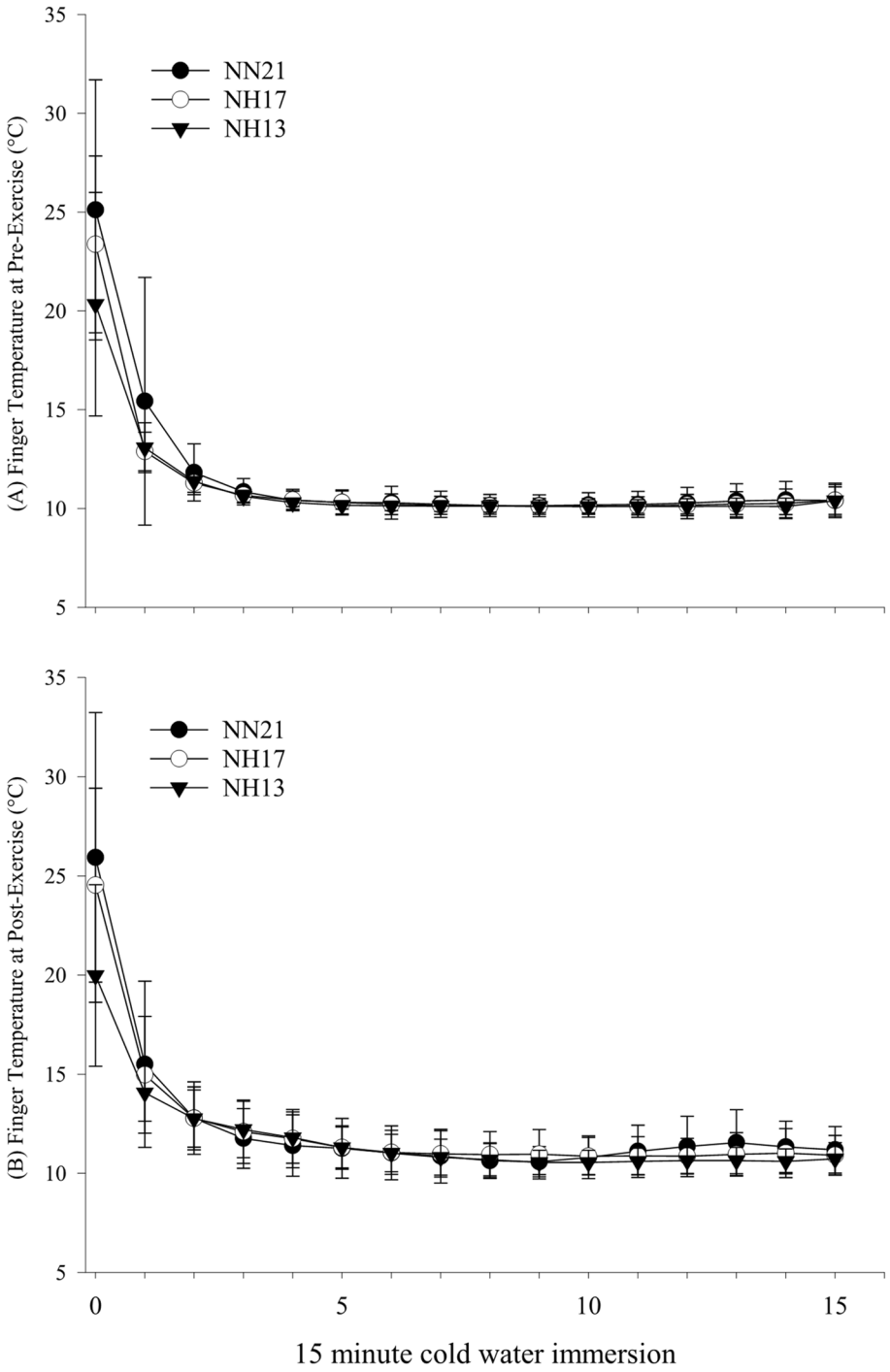

Fig. 4 Average nail fold temperature of middle finger during cold water hand immersion (**a**) before and (**b**) after the exercise in NN21, NH17, and NH13. Values are mean ± standard deviation ($n = 10$). Data are averaged at 1-min intervals. *NN21* 21 O_2, *NH17* 17% O_2, *NH13* 13% O_2

pressure due to greater breathing frequency, a lower tidal volume and minute ventilation in hypobaric hypoxia compared to normobaric hypoxia (Savourey et al. 2003).

Peak time in the current study showed no effect of differing hypoxia levels in either pre- or post-exercise CIVD responses. Additionally, no change in peak time was displayed from pre- to post-exercise CIVD measurements. This result is not in agreement with the previous findings of Daanen and Van Ruiten (2000) who show decreased peak time with decreasing oxygen content. However, it can be seen in Table 1 that a similar trend exists ($p = 0.080$) in the current data for both pre- and post-exercise CIVD measurements. Furthermore, the effect of metabolic heat production seemed to have no effect on T_{peak} in the current study. While T_b has been shown to affect CIVD responses onset time, T_{max}, and T_{min} (Daanen 2003; Daanen and Ducharme 1999; Daanen et al. 1997), it seems that peak time may remain unaffected by core and skin temperature changes.

CIVD response parameters of T_{min}, T_{max}, and amplitude were higher after submaximal exercise (post-exercise) compared to pre-exercise. These results are in agreement with previous studies, indicating that slightly higher core body temperature and T_{sk} increases T_{min}, T_{max}, and amplitude (Daanen et al. 1997; Kim et al. 2013). Interestingly, onset time was significantly influenced by oxygen availability during pre-exercise, showing a delayed onset time with decreasing oxygen availability (Table 1). Metabolic heat production via exercise mitigated the hypoxic effect on onset time although it was non-significantly shorter in post-exercise across hypoxia levels compared to pre-exercise (Table 1). This result is in agreement with a previous study, indicating that the shortest onset time was observed with the highest T_{sk} (Daanen et al. 1997). Another study concluded that the CIVD response is related to core body temperature and T_{sk} (Daanen and Ducharme 1999). This study supports the notion that increased body temperature, resulting from exercise, may lead to a decrease in onset time. The current study adds to this idea in that it supports the same relationship even at various levels of hypoxia.

These data, taken together, support a conclusion that the effect of systemic hypoxia on reducing the CIVD response may be counteracted by the influence of increased T_b. This conclusion has been suggested previously using field data (Daanen 2003; Daanen and Van Ruiten 2000); however, the addition of this study in a more controlled setting helps affirm this to a greater degree. Additionally, the current study adds precision to the conclusion by measuring T_{re}, T_{sk}, and mean T_b rather than relying on oral temperature alone.

After consideration of the current data, practical implications of the results must be addressed. These data suggest that the CIVD response may be decreased by the introduction of hypoxia while the addition of metabolic heat production via exercise may counteract these effects and improve CIVD responses. These results are important in that CIVD has been found to possibly improve manual dexterity (Heus et al. 1995; Geurts et al. 2006) and lessen pain sensation (Adams and Smith 1962; Kreh et al. 1984). For individuals who work or recreate in hypoxia, increased manual dexterity and decreased pain sensation may improve work or physical performance. Those in such hypoxic situations may be able to introduce moderate-intensity exercise to increase body temperature and restore function of CIVD responses, thus increasing functional outcomes as mentioned previously.

Limitations

Several limitations to this study exist and should be considered for generalization and interpretation. First, this study was limited by a duration of the immersion time to elicit a cyclic temperature fluctuation although a fixed rate of 400 W MHP improved T_{min}, T_{max}, and amplitude during 15 min of immersion. Second, the study design employed only males as participants in the study, which limits the external validity of the results to coed military, athletic, and workforce populations. Lastly, only one finger temperature was recorded for CIVD response in the current study because of laboratory equipment availability. The measurement of additional finger temperature would provide a better understanding of CIVD responses since there are well-known variabilities in finger temperature (Montgomery and Williams 1976; Ceron et al. 1995; Duckro et al. 1986). In addition, it is necessary to consider that placement of finger skin thermistor where the arteriovenous anastomoses (AVAs) are abundant (nail bed or pad of finger) may have elicited stronger CIVD responses because the AVAs are thought to play a significant role in CIVD responses (Daanen 2003). Therefore, future studies are needed to investigate CIVD responses in larger samples, longer durations of immersion and more diverse populations to evaluate the cyclic CIVD responses. Further, the current study did not measure skin blood flow, which limited its ability to detect actual hemodynamic changes of CIVD in the hand and finger.

Several strengths of this study are worth noting. First, this study design allowed for the comparison of CIVD responses to both exercise and hypoxia exposure independently and concurrently. Second, the design allowed for comparison of CIVD response variables in two different levels of normobaric hypoxia as well as a normoxia. This allowed for the formation of basic understanding surrounding a possible stepwise relationship of CIVD responses and hypoxia or altitude level.

Future examination of this topic would benefit from focusing on the effect of CIVD on local and central nervous responses. Additional investigation into CIVD should include possible effects on chronic disease patients (diabetes, hypertension) or peripheral neuropathies (impaired circulation). Future research would also benefit from a design which allows determination of the optimal exercise or heat production dose to encourage increased CIVD response in normobaric hypoxia. Furthermore, examination of the effect of exercise on CIVD responses following long-term resting to hypoxia would benefit the current body of literature.

Conclusion

The current study sought to examine the effect of metabolic heat production on CIVD responses at two levels of normobaric hypoxia. The results of the study showed an increased CIVD response in T_{min}, T_{max}, and amplitude as well as a trend towards decreased onset time in normobaric hypoxia. These data suggest that decreases in CIVD response

variables seen with exposure to normobaric hypoxia may be able to be counteracted by metabolic heat production via exercise. Individuals who work or participate in recreational activities in hypoxia may be able to use moderate-intensity exercise to improve the CIVD response, thereby enhancing manual dexterity or decreasing pain.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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