Thermoregulatory responses to combined moderate heat stress and hypoxia

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ABSTRACT

Objective: The aim of this study was to examine the cutaneous vascular and sudomotor responses to combined moderate passive heat stress and normobaric hypoxia. **Method:** Thirteen healthy young males, dressed in a water-perfused suit, underwent passive heating (Δcore temperature ~0.7 °C) twice (NORMOXIA; 20.9% O_2 and HYPOXIA; 13% O_2). Chest and forearm skin blood flow (SkBF; laser Doppler flux), local sweat rate (SR; capacitance hygrometry) and core (intestinal pill) and skin temperatures, were recorded. **Results:** HYPOXIA reduced baseline oxygen saturation (98±1 vs. 89±6%, P<0.001) and elevated chest (P=0.03) and forearm SkBF (P=0.03) and HR (64±9 vs. 69±8 beats.min^{-1}, P<0.01). During heating, mean body temperature ($\bar{T}_{BODY}$) thresholds for SkBF (P=0.41) and SR (P=0.28) elevations were not different between trials. The SkBF: $\bar{T}_{BODY}$ linear sensitivity during the initial phase of heating was lower at the Chest (P=0.035) but not different at the forearm (P=0.17) during HYPOXIA. With increasing levels of heating chest SkBF was not different (P=0.55) but forearm SkBF was lower on the forearm (P<0.01) during HYPOXIA. Chest (P=0.85) and forearm (P=0.79) SR:$\bar{T}_{BODY}$ linear sensitivities were not different between trials. **Conclusion:** Whilst sudomotor responses and the initiation of cutaneous blood flow elevations are unaffected, hypoxia differentially effects regional SkBF responses during moderate passive heating.

KEYWORDS: sweating, cutaneous blood flow, hypoxia, hyperthermia

ABBREVIATIONS:

CVC: Cutaneous Vascular Conductance

FIO_2: fractional inspired oxygen

MAP: mean arterial blood pressure

O_2: oxygen

$PETCO_2$: Pressure of end tidal CO_2

SkBF: skin blood flow

SpO_2: peripheral arterial oxygen saturation

SR: sweat rate

$\bar{T}_{BODY}$: mean body temperature

T_{CORE}: core temperature

$\bar{T}_{SK}$:mean skin temperature

INTRODUCTION

The maintenance of internal temperature within narrow limits is critical for optimal health and exercise performance. Appropriate increases in cutaneous blood flow and sweating are critical effector responses for regulating internal temperature during exercise and/or ambient heat stress [15,31]. Skin and core temperatures are key afferent inputs for the reflex neural control of cutaneous blood flow and sweating. In addition, cutaneous blood flow and sweating can be modified by a range of non-thermoregulatory factors, for example, baroreceptors, exercise, disease, sex [2,14,18] and variations in inspired and/or arterial gas pressures, e.g., hypoxia or hypercapnia [22]. Hypoxia can occur in a variety of situations, such as, altitude exposure, deep-sea diving, working in enclosed spaces, surgical procedures and disease [5,16,36]. Furthermore, these situations can be accompanied by heat stress, when appropriate sweat rate and/or cutaneous blood flow responses are vital in order to avoid a thermal related injury. Alterations in cutaneous blood flow and/or sweating induced by hypoxic exposure could increase the risk of a heat related disorder during superimposed ambient heat stress and/or exercise. Previous research has indicated that hypoxia could increase the risk of hypothermic illness during cold stress [16], but the effects of hypoxia on sweating and particularly cutaneous blood flow during heat stress are unclear [22].

In recent studies, acute normobaric hypoxic exposure (10% FIO_2) increased cutaneous blood flow in normothermic conditions [34] and during whole-body cold stress [33]. Furthermore, prolonged normobaric hypoxic exposure (12% FIO_2) increased the cutaneous blood flow response to local skin heating [21]. These findings suggest that hypoxic exposure may promote heat loss via increasing cutaneous perfusion and this may explain an increased risk of hypothermic injuries during combined hypoxia and cold stress exposure, e.g., high altitude ascent, [16]. In contrast, during exercise (50% sea level VO_{2peak}) heat stress (30 °C and 50% relative humidity) during hypoxic exposure (14% FIO_2) Miyagawa and colleagues reported no differences in the

temperature threshold for elevations in forearm blood flow but a reduced forearm vascular conductance:esophageal temperature sensitivity as well as an accentuated esophageal temperature during exercise [23]. These results suggest a reduced cutaneous vasodilation during exercise heat stress under hypoxic conditions, however, venous occlusion plethysmography was used to assess forearm blood flow which provides a discontinuous measure of flow that does not distinguish between different circulatory beds (e.g., skin vs muscle). It is unclear, therefore, if acute normobaric hypoxia affects the cutaneous blood flow responses (e.g., assessed continuously using laser-Doppler flowmetry) to whole-body heat stress, e.g., body temperature thresholds for increases and/or the sensitivity of cutaneous blood flow responses, to whole-body passive heating.

A few conflicting studies exist with regards to the effects of hypoxia on sweating. Increases in forehead sweating sensitivity occurred with acute normobaric hypoxia (13.5% FIO_2) exposure during exercise-heat stress (at the same absolute work rate as the control normoxic trial) [17]. In contrast, Kolka et al., (1987) observed no change in the internal temperature threshold for sweating but reduced local sweat rates for a given increase in internal temperature during hypobaric hypoxic (simulated altitudes of ~2,600 and ~4,600 m, FIO_2 = ~16% and 12%, respectively) exercise-heat stress at similar altitude-specific relative work rates. Similarly, DePasquale and colleagues observed decreased local sweating in response to pilocarpine iontophoresis in normobaric hypoxia (simulated altitude of 3050m; FIO_2 = ~14%) [7]. In the study of Miyagawa and colleagues there was no effect of both normobaric and hypobaric hypoxia on the internal temperature threshold for sweating or the forearm sweat rate:internal temperature sensitivity during exercise-heat stress conducted at the same absolute workload [23]. These findings suggest that hypoxia might modify sweating but given that exercise heat stress of varying intensities or local stimulus models were used in these previous studies and the findings were equivocal it is unclear if acute normobaric hypoxia affects the body temperature thresholds for

increases and/or the sensitivity of sweating responses to whole-body *passive* heating. Furthermore, concurrent and continuous assessment of both cutaneous blood flow and sweat rate responses at various sites, e.g., trunk vs. limbs, have not been examined during a combined hypoxic-heat stress exposure. The aim of this study was to therefore examine the cutaneous vascular and sudomotor responses, including the body temperature thresholds for increases in and the sensitivity (e.g., the slopes) of cutaneous blood flow and sweating elevations, to combined passive heat stress and acute moderate normobaric poikilocapnic hypoxic exposure.

Materials and Methods

Participants

Thirteen recreationally active healthy males (aged, 24 ± 4 y; height, 178 ± 7 cm; mass 79 ± 10 kg) were recruited. Participants had no history of cardiovascular or metabolic disease, were non-smokers and were not on any form of medication. All participants were informed of the methods and study design verbally and in writing before providing written informed consent. The study conformed to the Declaration of Helsinki and was approved by the institutional and local research ethics committees.

Research Design

Participants underwent two separate visits to the laboratory, separated by 3-7 days, and were asked to fast overnight, refrain from alcohol and exercise for 24h and caffeine for 12h before each visit. During each visit participants underwent a passive heat stress to assess thermoregulatory function whilst breathing either normoxic (Normoxia; 20.9% FIO_2) or hypoxic (13% FIO_2 balanced with Nitrogen; Poikilocapnic; Hypoxia) air throughout each trial in a randomised and counterbalanced design. Participants wore a facemask (AD Instruments, Oxford, UK) connected to a two-way non-rebreathing valve in both trials. The inspiratory port was connected via wide-bore tubing to a Douglas bag containing the hypoxic gas (BOC Gases, Surrey, UK) in the Hypoxia trial. The hypoxic gas was humidified by heating water in the bottom of the bag using a ceramic hotplate. Upon arrival to the laboratory, participants were placed in a tube-lined jacket and trousers (Med-Eng., Ottawa, Canada), which covered the entire body except for the head, feet and both forearms. Participants then rested quietly in a semi-recumbent position while 34°C water was perfused through the suit for a 15 min baseline period. Thereafter in the Hypoxia trial, participants breathed the hypoxic gas for, at least, a 15 min baseline period before the heat stress began (and participants continued to breathe the hypoxic gas). Participants were then exposed to a moderate heat stress by perfusing 48°C water through the suit for 60 min or until a rise of

~1°C in core temperature (whichever occurred first; a stipulation of the local ethical committee) and were then immediately cooled. Both visits were completed within 7 days and assessments were conducted in a temperature-controlled laboratory (24 ± 1°C). Testing was performed in the Autumn and Winter months.

Measurements

Heart rate was continuously obtained from a 3 lead electrocardiogram (Powerlab, AD Instruments, Oxford, UK), alongside continuous beat-by-beat arterial blood pressure (BP) from a digit (Finometer PRO, Finapres Medical Systems, Amsterdam, Netherlands). Arterial BP was measured intermittently by brachial auscultation using an autosphygmomanometer (Dinamap V100, GE Healthcare, Buckinghamshire, UK). Mean skin temperature ($\bar{T}_{SK}$) was obtained from the area weighted average of 4 regional temperatures measured from thermocouples (iButtons data logger, Maxim Integrated; San Jose, CA, US) taped to the lateral calf, lateral thigh, upper arm and chest [29]. Local skin temperature was also obtained at the forearm at the sites of sweat rate and cutaneous blood flow measurement (see below). Core body temperature (T_{CORE}) was continuously measured from an ingestible pill telemetry system (CoreTemp, HQInc; Palmetto, FL, US); the pill was ingested with a small amount of tap water (~50 ml) at least 2 h before data collection began and, thereafter, participants did not consume any fluids until after data collection had finished. Mean body temperature ($\bar{T}_{BODY}$) was calculated as $0.9 \bullet T_{CORE} + 0.1 \bullet \bar{T}_{SK}$ [24,40].

Sweat rate was recorded continuously from the dorsal forearm and the mid-sternum (not covered by the water-perfused suit). Dry 100% nitrogen gas was supplied through acrylic capsules (surface area = 2.32 cm^2) attached to the skin's surface at a flow rate of 150 $mL \bullet min^{-1}$, with the relative humidity and temperature of the effluent gas measured by capacitance hygrometry (Vaisala, Helsinki, Finland). Local sweat rate was calculated using the capsule surface area, gas flow rate and the relative humidity and temperature of the effluent gas [20,37]. Local cutaneous

blood flow was also continuously measured at the mid-sternum and dorsal forearm, using laser-Doppler flowmetry (Periflux System 5001, Perimed, Jarfalla, Sweden). Laser-Doppler flow probes were affixed with an adhesive heating ring in close proximity to the sweat rate capsules. Chest and forearm sites were selected to measure cutaneous blood flow and sweating to represent responses on a limb and the trunk. Photographs of the laser-Doppler flow probes and sweat capsules were taken and anatomical landmarks were notated and measured on each participant's first visit to ensure similar probe and capsule placement on the 2nd visit. Cutaneous vascular conductance (CVC) was calculated as the ratio of laser-Doppler flux units to mean arterial blood pressure (MAP) and expressed as both CVC and a percentage of maximum CVC (%CVC_{max}).

Pressure of end tidal CO_2 ($PETCO_2$) was continuously recorded online from the breathing mouthpiece (Breath-by-breath gas analyzer, AD Instruments, Oxford, UK). Respiratory Rate was calculated from the end tidal CO_2 signal. Peripheral arterial oxygen saturation (SpO_2) was monitored via pulse oximetry from a digit (Onyx Vantage 9590, Nonin, Amsterdam, The Netherlands). All baseline and end of heating data were calculated as ~180s averages and all data during heating were sampled as 60s averages every 0.1°C increase in core temperature. All data were sampled at 50Hz with a data acquisition system (PowerLab, ADInstruments, Oxford, UK). Following passive heat stress, local skin heating was performed simultaneously at the chest and forearm laser Doppler flowmetry sites to assess maximal cutaneous blood flow [6].

Statistical analysis

The heat-stress induced thresholds for sweating and cutaneous vasodilation, e.g., elevations in skin blood flow, were determined by the same experienced investigator in a blinded fashion by visually inspecting the sweat rate and skin blood flow data graphed relative to time [3]. Thresholds for sweating and cutaneous vasodilation were defined as abrupt and continued increases in sweat rate and cutaneous blood flow from baseline, respectively, during heat stress [3]. T_{CORE} and $\bar{T}_{SK}$

at the indicated time for the thresholds of sweating and cutaneous vasodilation were then identified and reported as the $\bar{T}_{BODY}$ thresholds for sweating and cutaneous vasodilation. The sensitivity of the sweating and skin blood flow elevations were indexed from the linear sensitivity of the sweat rate/CVC heat stress responses (typically evident during the initial phase of the CVC response) per unit change in $\bar{T}_{BODY}$ beyond the $\bar{T}_{BODY}$ threshold [27,31,41]. Cutaneous and sudomotor responses at each 0.1°C increase in core temperature were also compared between trials.

Analysis was conducted online (IBM SPSS, v 21, New York, US). Paired T-Tests or Wilcoxon rank tests were employed, where appropriate, to compare baseline and end of heating data as well as mean body temperature sweating and cutaneous vasodilation thresholds and sensitivities of sweat rate and cutaneous blood flow responses to heat stress between conditions. A two (condition*core temperature increment) factor linear mixed model was employed to analyse sweat rate and CVC responses during passive heating. Statistically significant interactions were followed up with the least significant difference (LSD) approach to multiple comparisons [28]. Statistical significance was delimited at $P<0.05$. Data are presented as mean (± 1 SD) unless otherwise stated.

Results

Baseline Normothermia: effects of hypoxia

In the Hypoxia trial during normothermic baseline, relative to pre-hypoxia administration, oxygen saturation (P<0.001; see Table 1) and $PETCO_2$ decreased (P=0.01) after hypoxia administration. Heart rate increased (P<0.001) and mean arterial blood pressure did not change with hypoxia (P=0.66). Hypoxia increased chest (P=0.03) and forearm (P=0.03) cutaneous blood flow and $\bar{T}_{SK}$ slightly increased (P<0.001) while T_{CORE} decreased after hypoxia (P=0.04).

Heat Stress: effects of heating

The changes in respiratory, thermoregulatory and hemodynamic data at the end of heating are presented in Table 2. $\bar{T}_{SK}$ and T_{CORE} increased by ~3 and ~0.7 °C during heating (both P<0.001). There was no difference in $\bar{T}_{SK}$ between trials (P=0.10). Oxygen saturation remained lower in Hypoxia throughout heating (P=0.01). Respiratory rate increased and $PETCO_2$ decreased similarly in both conditions (both P>0.05). The heart rate elevation tended to be attenuated during Hypoxia (32±10 vs 26±10 beats·min^{-1}; P=0.08) while blood pressure was maintained in both conditions during heating (P=0.66).

Heat Stress: thermoregulatory function

Cutaneous blood flow

The threshold for cutaneous vasodilation at the chest and forearm occurred in parallel, e.g., at the same $\bar{T}_{BODY}$, in both Normoxia and Hypoxia. Thus, threshold data for both sites were collapsed, e.g., averaged, for analysis. The threshold of cutaneous vasodilation occurred at a $\bar{T}_{BODY}$ of 36.81±0.22 °C in Normoxia and 36.89±0.27°C in Hypoxia, respectively (P=0.41; Figure 1A). When expressed as the increase in $\bar{T}_{BODY}$ from baseline there was also no difference in the

threshold of cutaneous vasodilation between trials (0.27±0.07 and 0.23±0.16°C in Normoxia and Hypoxia, respectively, P=0.32).

During the initial stages of heating chest cutaneous blood flow sensitivity was lower during Hypoxia (3.42±2.34 CVC units·°C^{-1} vs. 5.16±2.26 CVC units·°C^{-1}, P=0.027 Figure 2A) relative to Normoxia. Cutaneous blood flow sensitivity at the forearm was not different between trials however (3.49±1.43 CVC units·°C^{-1} vs. 4.08±1.07 CVC units·°C^{-1}. for Hypoxia and Normoxia , respectively, P=0.124; Figure 2B). When expressed as %CVC$_{max}$ units the chest (P=0.019) and forearm (P=0.325) sensitivity findings were not affected. The chest and forearm cutaneous vascular conductance responses at each 0.1 °C increase in T_{CORE} during heating are presented in Figure 4. Cutaneous vascular conductance increased with increasing levels of heat stress (P<0.01 for both chest and forearm). During heating, there was no difference in chest cutaneous vascular conductance between conditions (P=0.45). Conversely, there was a main effect of condition for forearm cutaneous vascular conductance (P=0.012); at increasing levels of heat stress forearm cutaneous blood flow was lower during Hypoxia.

Sweating

The threshold of sweating at the chest and forearm occurred in parallel, e.g., at the same $\bar{T}_{BODY}$, in both Normoxia and Hypoxia. Thus, threshold data for both sites were collapsed, e.g., averaged, for analysis. The threshold of sweating at the chest and forearm occurred at a $\bar{T}_{BODY}$ of 36.78±0.22 °C in Normoxia and 36.86±0.28°C in Hypoxia (P=0.28; Figure 1B). When expressed as the increase in $\bar{T}_{BODY}$ from baseline there was also no difference in the threshold of sweating between trials (0.24±0.15 and 0.20±0.19°C in Normoxia and Hypoxia, respectively, P=0.39).

Sweating sensitivity at the chest was 0.43±0.23 mg·min^{-1}·cm^{-2}·°C^{-1} during Normoxia and 0.42±0.28 mg·min^{-1}·cm^{-2}·°C^{-1} during Hypoxia (P=0.88, Figure 3A). Similarly, sweating sensitivity

at the forearm was 0.23±0.07 $mg \cdot min^{-1} \cdot cm^{-2} \cdot {}^{o}C^{-1}$ during Normoxia and 0.22±0.06 $mg \cdot min^{-1} \cdot cm^{-2} \cdot {}^{o}C^{-1}$ during Hypoxia (P=0.37, Figure 3B). The chest and forearm sweating responses during passive heating are presented in Figure 5. Sweating increased with increasing levels of heat stress (P<0.001 for both chest and forearm) but there was no main effect of condition at the chest (P=0.47) and forearm (P=0.31).

Discussion

The aim of this study was to examine the thermoregulatory responses to combined acute passive heat stress and moderate normobaric hypoxic exposure. The main findings were that mean body temperature thresholds for cutaneous vasodilation and sweating as well as the sensitivity of sweating responses during passive heating were not affected by Hypoxia. In contrast, there was a regional difference in the sensitivity and cutaneous blood flow responses to heating; a reduced linear sensitivity during the initial phase of heating but unaffected response during prolonged heating occurred at the chest whereas an unaffected linear sensitivity during the initial phase but reduced response during prolonged heating occurred at the forearm during Hypoxia.

Hypoxic exposure results in a range of neural and non-neural, or 'local', adjustments in order to meet the metabolic demand for oxygen, including, an increase in cardiac output with tachycardia, activation of the sympathetic nervous system, increased ventilation and decreased plasma volume [25,30]. Thus, any effects of hypoxia on thermoregulatory function (e.g., baseline cutaneous blood flow, cutaneous vasodilation and sweating thresholds and sensitivities) are possibly mediated via a combination of reflex and/or local effects. In the present study, baseline cutaneous blood flow was slightly elevated with hypoxia in line with previous studies of effects of hypoxia on cutaneous blood flow under normothermic conditions [33,34]. The mechanisms for hypoxia-induced elevations in baseline cutaneous blood flow are not entirely clear but are likely due to local effects of hypoxia, e.g., up-regulation of heat-sensitive transient receptor potential vanilloid 1 channel activation in sensory nerves and/or bioactive nitric oxide production, [21,39] rather than alterations in sympathetic vasoconstrictor nerve activity (e.g., withdrawal of sympathetic cutaneous vasoconstrictor nerve activity) or hyperpnea [33,34]. The slightly larger elevation in baseline cutaneous blood flow at the chest, relative to the forearm, in the present study might be explained by slightly higher local skin temperatures at the chest (34-35 compared

to 31-32 °C) and larger contribution of nitric oxide-dependent mechanisms [4] and/or regional variation in cutaneous vascular responses to hypoxia.

The lack of difference in mean body temperature thresholds for cutaneous vasodilation and for sweating during hypoxia in the present study is in agreement with previous research into the effects of hypoxia on exercise-heat stress thermoregulatory responses [19,23] and is perhaps not surprising given the acute and relatively short exposure to the hypoxic stimulus. Beyond the threshold for cutaneous vasodilation the sympathetic cholinergic system is engaged and is predominantly responsible for the elevations in cutaneous blood flow as a function of body temperature increases [15]. The linear portion of the chest cutaneous blood flow:mean body temperature sensitivity in the initial phase of heating was attenuated during hypoxia in the present study while no significant change was evident at the forearm. The reasons for the regional difference in cutaneous blood flow:mean body temperature sensitivities in the initial phase of heating during hypoxia are not clear. The larger elevation in baseline cutaneous blood flow at the chest with hypoxia might have reduced the 'range' that skin blood flow can increase during heating and thereby the sensitivity of the chest cutaneous blood flow:mean body temperature relation in contrast to a smaller hypoxia-induced elevation in baseline forearm cutaneous blood flow and unaffected forearm cutaneous blood flow:mean body temperature relation. It is unknown if hypoxic exposure modifies regional elevations in skin sympathetic nerve activity during heat stress and caused a reduction in the skin sympathetic nerve activity (sympathetic cholinergic nerves) directed to the chest cutaneous vasculature (see below). Similarly, whether hypoxia affects any of the purported neurotransmitters (e.g., acetylcholine and co-transmitters vasoactive intestinal peptide and pituitary adenylate cyclase-activating peptide) of cutaneous active vasodilation is also unknown [15].

With prolonged heating and further elevations in core temperature chest cutaneous blood flow was not different between trials whereas cutaneous blood flow was lower at the forearm during hypoxia in the present study; the latter of which is in agreement with hypoxia-induced reductions in cutaneous blood flow during exercise-heat stress [23]; although this previous study used venous occlusion plethysmography to index cutaneous blood flow, which provides a discontinuous measure that does not distinguish between different circulatory beds (e.g. skin vs. muscle).The mechanism(s) for restrained forearm cutaneous vasodilation during combined hypoxia and heat stress in the present study may include; hypoxia-induced sympathoexcitation via increased cutaneous vasoconstrictor activity [13] (or reduced active vasodilator activity) that outweighs hypoxia-induced local increases in baseline cutaneous blood flow, and/or increased plasma volume loss and associated decreases in cardiac filling pressure[23]. Whether possible variations in regional cutaneous vascular structure and function contribute to the hypoxia-induced differences in regional cutaneous blood flow responses to heating is unknown as the existence of such local variations in cutaneous vascular function, and especially structure, are unclear. Previous research suggested that cutaneous vasodilation thresholds are lower and skin blood flow is higher on the limbs compared to the trunk [12] but recent research that used similar methods to the present study reported no differences in cutaneous vasodilation thresholds or cutaneous blood flow responses to passive heating between the trunk and limbs [11,35]. That said, the cutaneous blood flow responses to local intradermal acetylcholine application were lower on the back compared to the arm suggesting increased vascular cholinergic sensitivity on the upper limbs relative to the trunk [35]. It is unknown if there is regional variation in the innervation of cutaneous vascular structures and/or density of sympathetic or cholinergic cutaneous nerve receptors [38]. Similarly, whether differences in local skin temperatures and/or surface area (long and thin forearms vs. flat chest) contribute to hypoxia-induced differences in regional cutaneous blood flow responses to heating are uncertain. Finally, whether hypoxia differentially effects

regional alterations in sympathetic and/or cholinergic cutaneous nerve activity or vascular responsiveness during heating is also unknown.

In the poikilocapnic hypoxic condition, a ventilatory-induced hypocapnia occurred relative to the normoxia trial. There has been little research into the interaction between chemoreceptors and thermoreceptors. In resting humans, hypocapnia achieved through voluntary hyperventilation reduces cutaneous blood flow elicited by moderate heat stress in non-glabrous skin [8] and in exercising humans, hypocapnia induced by voluntary hyperventilation attenuates cutaneous vasodilatory responses by increasing the vasodilatory threshold and reducing sensitivity [9]. In contrast, hypercapnia causes modest vasodilation in non-glabrous skin under normothermic conditions [34] whereas superimposed hypercapnia during passive heating does not affect cutaneous blood flow [42]. Overall, these findings suggest that hypocapnia might contribute to the blunted forearm cutaneous blood flow responses to heating during hypoxia but further examination of the cutaneous vascular responses to hypoxia with and without the attendant hypocapnia would be required.

In the present study the mean body temperature thresholds, the sensitivity and local sweating responses during heating were not affected by hypoxia, which are in agreement with previous sweating sensitivity findings with normobaric hypoxia during exercise heat stress [23] but is in contrast to previous studies that reported either an increase in sweating sensitivity (e.g., slopes) with normobaric hypoxia [17] or decreases in sweating sensitivity with hypobaric hypoxia [19] during exercise heat stress and a decreased response to pharmacological post-synaptic sweat gland stimulation [7]. The difference in sensitivity findings between the present and these previous studies could be due to a variety of reasons, including, different sites of local sweat rate assessment (forehead [17] vs. chest and forearm in the present study), differences in sweating stimuli (Iontophoresis via peripheral stimulation in [7]) and the use of hypobaric hypoxic exposure

[19], which, relative to normobaric hypoxic exposure, may input differently to the central and peripheral thermoreceptors, modify local skin influences, change the liquid-vapor interface within the skin itself, induce biochemical changes at the level of the sweat gland [7] and/or cause a greater evaporation of sweat due to an increase in effective mass transfer coefficient [26].

The lack of difference in sweating but altered cutaneous blood flow responses during hypoxia in the present study may seem counterintuitive but other research has shown that variations in regional sweating are not explained by local variations in cutaneous blood flow [12,35]. The slightly reduced core temperature elevation during heating in Hypoxia in the present study despite similar heating protocols (e.g., similar mean skin temperatures and duration of heating) is intriguing and is consistent with previous research that reported lower core temperatures during combined cold and hypoxic stress [32]. Similar local sweat rates and similar or lower local cutaneous blood flow responses would not contribute to a lower core temperature elevation during heating in hypoxia however. The increased chest cutaneous blood flow during the initial phase of heating alongside a likely increased respiratory heat loss via elevated ventilation [1] would potentially be responsible for the attenuated heating-induced core temperature elevation during hypoxia and/or higher local sweat rates/cutaneous blood flow in other regions not assessed in the current study [17].

Limitations

There are a few limitations to the present study that are worthy of consideration. An acute normobaric hypoxic stimulus of approximately 75-90 min was used, which does have relevance to a variety of situations, but hypoxic exposure is often chronic (e.g., altitude ascent, respiratory disease), which can also affect many non-thermal factors, such chemoreceptive, baroreceptive and osmotic stimuli; thus it would have been interesting to assess cutaneous and sudomotor responses after a period of acclimatisation to hypoxia, as well as cutaneous vascular responses to hypobaric hypoxia. A moderate level of hypoxia was used that induced a moderate-large

desaturation, which varied between individuals, and only a moderate alteration in thermoregulatory function was evident. It is thus unknown if a more severe hypoxic exposure would have unmasked greater alterations in thermoregulatory responses to heating with a consideration of the individual variability in ventilatory responses to hypoxia. Similarly, a moderate level of passive heat stress in the supine posture was used in the present study; whether hypoxia would have resulted in more explicit alterations in thermoregulatory function under more severe levels of hyperthermia and increased cardiovascular strain and/or in the upright posture requires further study.

In conclusion, the results of the present study suggest that, whilst sudomotor responses are unaffected, moderate normobaric hypoxia-induced increases in baseline cutaneous blood flow do not affect the initiation of cutaneous vascular responses but differentially affects regional sensitivity and cutaneous blood flow responses during moderate passive heat stress. Despite these hypoxia-induced differences in cutaneous vascular responses to heating the core temperature response to whole-body heating does not appear to be compromised.

Perspective

Acute hypoxic exposure increases cutaneous blood flow under thermoneutral and cold conditions and lowers core temperature during cold stress indicating that hypoxia provokes heat loss. The effect of acute hypoxia on sweating is equivocal and studies have mostly used exercise-heat stress to elevate body temperature and sweating. It is unknown if cutaneous blood flow and sweating responses to passive heating are affected by acute hypoxic exposure. Acute moderate normobaric hypoxia did not affect the body temperature at which cutaneous blood flow and sweating begin to increase but there was regional variation in the cutaneous vascular responses to heating with reduced cutaneous blood flow sensitivity on the trunk during the initial phases of heating and lower cutaneous blood flow at the forearm with more prolonged heating. Sweating

sensitivity was not affected by hypoxia. Despite these hypoxia-induced regional differences in cutaneous vascular responses to heating the core temperature response to whole-body heating was not compromised suggesting that acute moderate hypoxia does not modify the risk of heat illness during moderate heat stress

Conflict of Interest

The authors declare that they have no conflict of interest

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Table 1. Baseline normothermic data (mean ± SD) during the Normoxia trial and before and at least 15 min after Hypoxia administration in the Hypoxia trial.

		Hypoxia	
	Normoxia	**Pre-Hypoxia**	**Post-Hypoxia**
SpO_2 (%)	98 ± 1	98 ± 1	89 ± 6*#
Core Temperature (°C)	36.85 ± 0.20	37.03 ± 0.24	36.97 ± 0.21*
Mean Skin Temperature (°C)	33.80 ± 0.46	33.55 ± 0.77	33.98 ± 0.52*
Heart Rate (beats•min^{-1})	59 ± 8	64 ± 9	69 ± 8*#
Mean Arterial Blood Pressure (mm Hg)[1]	79 ± 6	81 ± 6	80 ± 6
Chest CVC (%CVC_{max})	17 ± 10	17 ± 12	29 ± 26*#
Forearm CVC (%CVC_{max})	11 ± 7	8 ± 4	11 ± 8*
Respiratory Rate (breaths•min^{-1})	15 ± 3	14 ± 2	15 ± 3
Pressure of End Tidal CO_2 (mm Hg)	36 ± 3	37 ± 3	35 ± 4*

*P<0.05 vs. Pre-Hypoxia, #P<0.05 vs. Normoxia. [1]Mean Arterial Blood Pressure data are from intermittent brachial auscultation measurements

Table 2. Changes in hemodynamic and thermoregulatory variables (mean ± SD) during heat stress in Normoxia and Hypoxia conditions.

	Normoxia	**Hypoxia**
SpO_2 (%)	Δ-1 ± 1	Δ0 ± 6
Core Temperature (^oC)	Δ0.79 ± 0.17	Δ0.64 ± 0.19#
Mean Skin Temperature (^oC)	Δ3.30 ± 0.72	Δ2.93 ± 0.75
Heart Rate ($beats \cdot min^{-1}$)	Δ32 ± 10	Δ26 ± 10
Mean Arterial Blood Pressure (mm Hg)[1]	Δ2 ± 3	Δ1 ± 5
Respiratory Rate ($breaths \cdot min^{-1}$)	Δ3 ± 2	Δ2 ± 1
Pressure of End Tidal CO_2 (mm Hg)	Δ-2 ± 3	Δ-3 ± 3

#P<0.05 vs. Normoxia. [1]Mean Arterial Blood Pressure data are from intermittent brachial auscultation blood pressure measurements

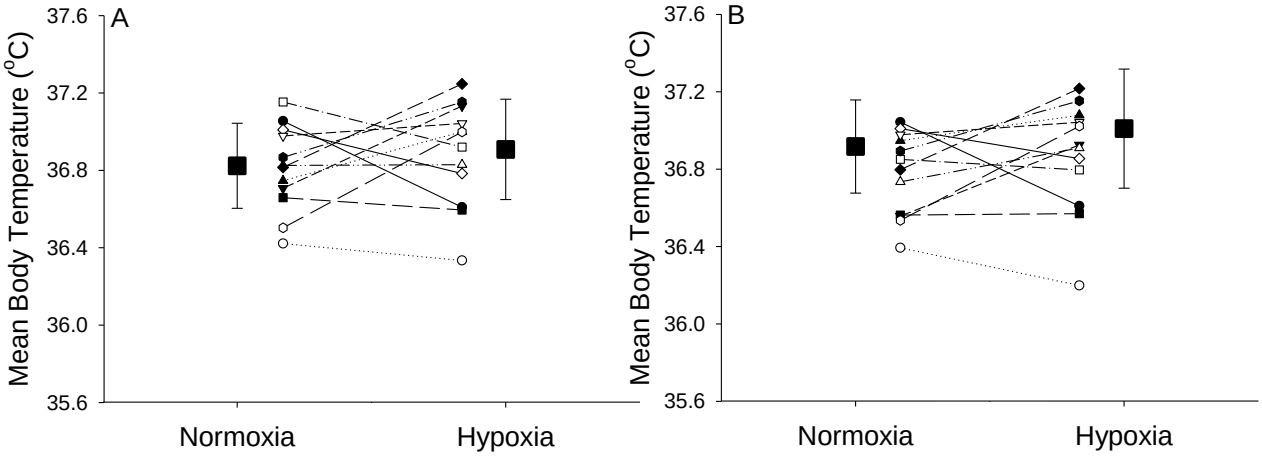

Figure 1. Individual and mean (±SD) mean body temperature thresholds for the threshold of cutaneous vasodilation (A) and sweating (B) during Normoxia and Hypoxia trials.

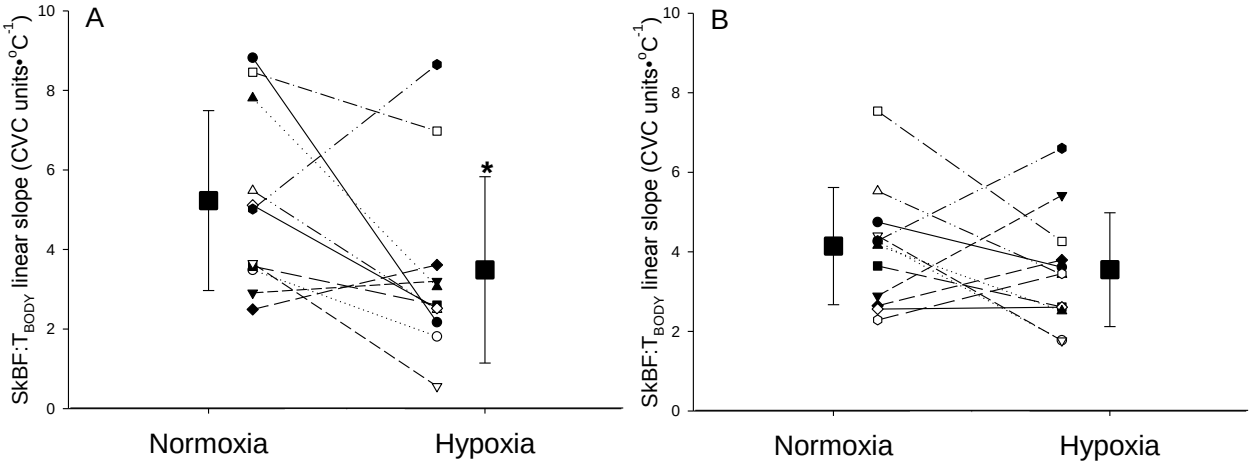

Figure 2. Individual and mean (±SD) cutaneous blood flow sensitivity at the chest (A) and forearm (B) during Normoxia and Hypoxia trials. *P<0.05 vs. Normoxia.

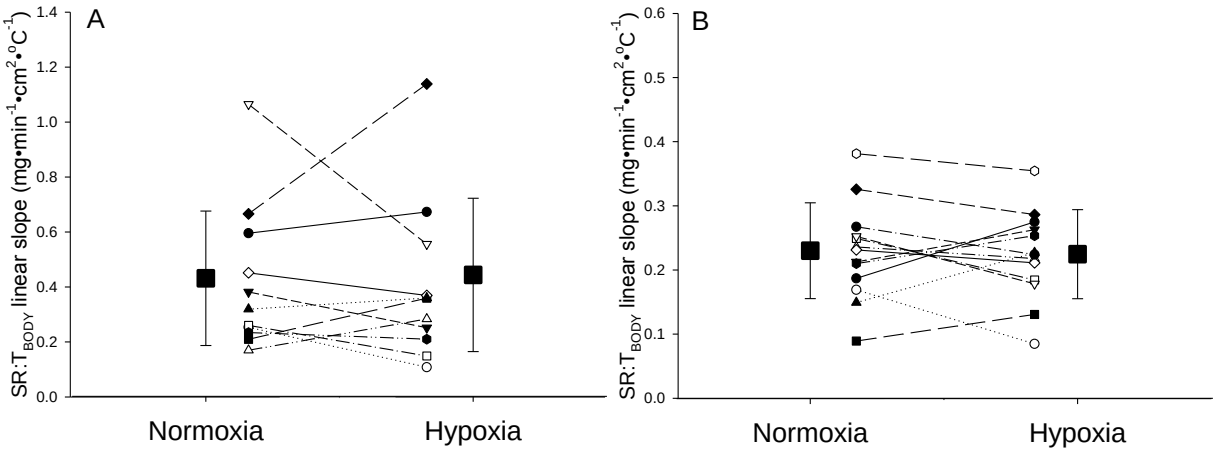

Figure 3. Individual and mean (±SD) local sweating sensitivity at the chest (A) and forearm (B) during Normoxia and Hypoxia trials.

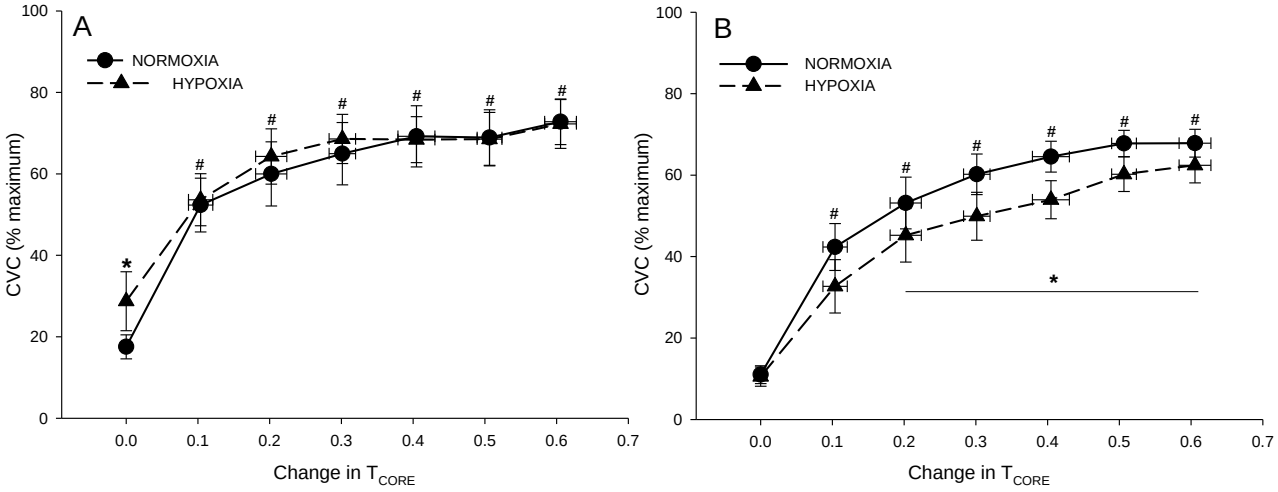

Figure 4. Mean (±SD) local CVC (cutaneous vascular conductance) at the chest (A) and forearm (B) during Normoxia and Hypoxia trials. $^{\#}P<0.05$ vs. baseline, *main effect of condition; $P<0.05$ Hypoxia vs. Normoxia.

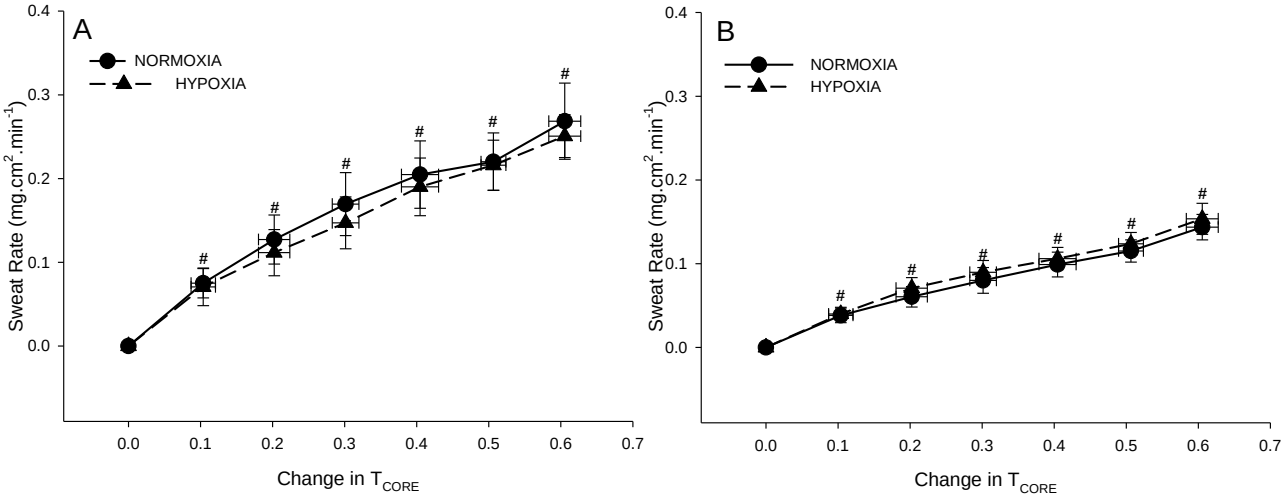

Figure 5. Mean (±SD) local sweating at the chest (A) and forearm (B) during Normoxia and Hypoxia trials. $^{\#}P<0.05$ vs. baseline.