Hypoxia-induced manipulations of relative exercise intensity do not alter steady-state thermoregulatory responses or maximal heat loss capacity during exercise

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THESIS ABSTRACT

This study sought to determine the independent influence of hypoxia on thermoregulatory responses to exercise in compensable and uncompensable hot conditions. Eight participants completed three experimental trials of cycling in either normoxia (21% O_2) or hypoxia (13% O_2) in order to manipulate relative exercise intensity (%VO_{2peak}), since VO_{2peak} was reduced by ~30% in hypoxia. When trials were matched for %VO_{2peak}, changes in core temperature and local sweat rates (LSR) were significantly lower in the hypoxic trial as a result of a lower rate of metabolic heat production (H_{prod}) in order to maintain a similar %VO_{2peak} compared to normoxia. However, when H_{prod} was fixed between normoxic and hypoxic trials the systematic differences in core temperature and LSR were eliminated. Conversely, at a fixed H_{prod} skin blood flow (SkBF) was greater in hypoxia compared to normoxia by ~40%. Despite improvements in SkBF, the potential for maximum heat loss was unaffected during an incremental humidity ramp protocol, resulting in no difference between normoxia and hypoxia in the critical ambient vapour pressures at which core temperature inflected upwards. These data further demonstrate, using a within-subjects design, that metabolic heat production, irrespective of large differences in %VO_{2peak}, determines thermoregulatory responses during exercise. Furthermore, this study suggests that the influence of large differences in skin blood flow on heat dissipation may be lesser than previously thought.

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PREFACE

The work presented in this thesis is my own and I take full responsibility for its content. The thesis article in section 3.1 was co-authored by Matthew Cramer, Nicholas Ravanelli, Dr. Pascal Imbeault, and Dr. Ollie Jay. The certificates of ethical approval for this study from the University of Ottawa Health Sciences and Sciences Research Ethics Board are included in the appendix. This study was funded in part by a Gatorade Sports Science Institute student research grant awarded to Geoff Coombs.

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CHAPTER 1: INTRODUCTION

Hypoxia is defined by lower than normal levels of arterial oxygen which can lead to insufficient availability of oxygen in certain tissues, commonly referred to as hypoxemia when oxygen-hemoglobin saturation levels are <88% (13, 63). These conditions are most often found at high altitudes (i.e., >2500 m above sea level), at which more than 140 million of the world's population live (56). Certain respiratory conditions, such as chronic obstructive pulmonary disorder (COPD) and emphysema, can also cause hypoxemia at sea-level by limiting gas exchange (i.e., diffusion of oxygen) in the lungs (63). Hypobaric hypoxia occurs at higher altitudes due to a lower barometric pressure, resulting in a reduced partial pressure yet constant concentration of oxygen; whereas normobaric hypoxia occurs when the barometric pressure remains similar to that of sea level, but the concentration of oxygen is reduced from its atmospheric norm of approximately 21%. In general, physiological responses to both types of hypoxia are similar, but this distinction can have subtle yet important influences (6), which will be discussed later.

High altitude expeditions and research date back centuries; however, the latter decades of the 20th century saw greater interest in mountaineering, as well as athletic events and active tourism at high altitudes. Although the medical and athletic implications of hypoxia are well documented (28, 78), little research has examined thermoregulatory function in individuals experiencing hypoxemia and previous studies on this topic have reported inconsistent findings from various experimental protocols (e.g., rest, exercise, hypobaric, normobaric, cold, and hot conditions). Although scarce information on whole-body thermoregulatory responses to hypoxia exists, some research has examined local responses of sweating and skin blood flow. Reductions

of local sweat rates at various levels of hypoxia have been reported during exercise at altitude-specific percentages of maximal aerobic capacity and by pharmacological induction (17, 44), while exercise at fixed workloads have found no effect of hypoxia (54) and greater increases in forehead sweating in hypoxia (35). Mechanistically, hypoxia may cause greater cutaneous vasodilation (72) which is supported by measures of cutaneous perfusion (2, 70); however, other studies have reported conflicting evidence (54, 69). Therefore, it is unclear from the current literature whether conditions of low oxygen availability (hypoxia) alter thermoregulatory function.

One of the main challenges of exercise in a hypoxic environment is the limitation to the body's peak volume of oxygen consumption (VO_{2peak}) (46, 49). Thus, for a given amount of work, an individual will be working at a greater percentage of their VO_{2max} in a hypoxic environment. Traditionally, relative exercise intensity (i.e., $\%VO_{2peak}$) has been thought to determine thermoregulatory responses during exercise in compensable conditions (71). However, recent work from our laboratory has demonstrated that despite large differences in VO_{2peak} (33), changes in core temperature are primarily determined by the rate of metabolic heat production per unit of body mass (W/kg) with relative exercise intensity only marginally explaining additional variance in steady-state local sweat rates (9). Given the large reductions in VO_{2peak} in hypoxic conditions, these previous studies may be further substantiated using a within-subjects design by implementing hypoxia as a model to manipulate relative exercise intensity for a given rate of metabolic heat production.

1.1 Rationale

The current literature presents inconsistent findings regarding local thermoeffector responses and whole-body heat balance during exercise in hypoxic conditions. This topic

warrants further investigation to determine if thermoregulatory responses are altered in hypoxic conditions, potentially placing individuals at greater risk of thermal and cardiovascular injury. Additionally, hypoxia may serve as a within-subject model to substantiate recent work from our laboratory concluding that heat production, not relative exercise intensity, determines changes in core temperature during exercise.

1.2 Objectives

The objectives of the current thesis were to determine 1) if an acute exposure to hypoxia independently influences steady-state heat loss responses and changes in core temperature during exercise in compensable conditions; 2) if hypoxia-induced manipulations of relative exercise intensity influence changes in core temperature and sweating independently of metabolic heat production; and 3) if hypoxia alters the maximum potential for heat dissipation during exercise (i.e., the limits of physiological compensation) in uncompensable hot-humid conditions.

1.3 Hypotheses

It was hypothesized that 1) hypoxia does not independently influence changes in core temperature or sweating responses, but skin blood flow is elevated compared to normoxia; and 2) despite large differences in VO_{2peak}, changes in core temperature during exercise in compensable conditions do not differ between normoxia and hypoxia for a given rate of metabolic heat production; however, when exercise intensity is normalized for $\%VO_{2peak}$ the change in core temperature is lower in hypoxia secondary to a lower rate of metabolic heat production; and 3) hypoxia-induced vasodilation elevates skin blood flow and consequently improves maximal potential for heat dissipation.

1.4 Relevance

Hypoxia may serve as an effective mechanism for manipulating skin blood flow, which would allow investigations of the importance of skin blood flow for heat loss. For example, it has been reported that skin blood flow is attenuated in older populations during heat stress, perhaps placing them at greater thermal risk due to cardiovascular complications of dealing with hyperthermia (75). Using a within-subject design, we also hope to substantiate recent work from our laboratory identifying the largest determinants of changes in core temperature during exercise that may have important implications for the design of thermoregulatory studies.

The results of this study may also be of importance to health and safety guidelines for individuals working, exercising, or living at high altitude. New findings may be applied to occupational and recreational fluid replacement standards or to determine the limits for consecutive time spent working outdoors in hot conditions. The results may also benefit hypoxemic populations, such as those suffering from respiratory diseases such as COPD or emphysema, that live in hot climates. Knowledge gained about the thermoregulatory capacity of these populations may influence revisions in public policy regarding weather warning criteria that could lead to a decrease in heat related illnesses and complications in at-risk populations.

1.5 Delimitations and Limitations

The participants recruited for the study were young and healthy individuals. Therefore, the results cannot be directly applied to other populations, such as children, the elderly, or those with chronic health conditions. However, the results may provide an indication of expected results in the non-recruited populations, as well as validating methods that could be used to test other populations in the future. The study was performed in a normobaric hypoxia chamber;

therefore the results may not apply directly to hypobaric hypoxic environment, which is ideal for examining the physical properties of altitude related to heat loss (i.e., the latent heat of evaporation, convective heat transfer coefficient), whereas the normoxic hypoxia chamber allows the physiological responses to hypoxia to be isolated. Conversely, the results will be of great value for individuals who experience hypoxemia at lower altitudes, where ambient conditions are generally much hotter in any instance.

CHAPTER 2: REVIEW OF THE LITERATURE

Human Heat Balance

The primary risk associated with hyperthermia is the rise in core body temperature resulting from heat stored within the body. At rest, the human body regulates its core temperature around 37°C and deviations from this by ±3°C can be potentially fatal. During exercise, or in hot and humid conditions, heat will be stored in the body until heat loss mechanisms are able to match the rate of heat production. That is to say that the core temperature will rise and subsequently plateau at a new steady-state value once heat loss equals heat production, or in other words, heat balance is achieved. These principles comprise the bases of the conceptual heat balance equation (42, 62, 64), written as:

$$S = M - W - C - R - K - (C_{res} + E_{res}) - E_{sk} \qquad \text{(Eq. 1)}$$

The left portion of the equation (S) represents heat storage in the body and the remaining variables on the right side of the equation represent all of the different avenues for the body to gain or lose heat. When S = 0, heat production and heat loss are equal and heat balance is achieved, therefore core temperature is in steady-state. If S > 0, then greater heat gain compared to loss will result in heat imbalance and consequently a continuous rise in core temperature as heat is stored. If S < 0, then heat lost to the environment is greater than heat gain and this imbalance will result in a continuous reduction of core temperature. Conditions that allow for S = 0 are considered compensable, and conditions that do not allow for heat balance to be restored (e.g., S < 0 or S > 0) are considered uncompensable. M, W, C, R, K, C_{res}, R_{res}, and E_{sk} are defined in greater detail below.

Metabolic Heat Production (M-W)

Metabolic energy expenditure (M) is comprised of the free energy released during the transfer of stored chemical potential energy—in the form of carbohydrates, lipids, and amino acids—to adenosine triphosphate (ATP). Energy used by cells to maintain basal metabolic rate and to produce muscular contractions is supplied by ATP. During exercise the rate of muscular contractions increases substantially, which creates a greater demand for ATP and metabolic energy expenditure can therefore increase more than tenfold during moderate intensity exercise. However, the biochemical processes that convert ATP to kinetic energy are not 100% efficient. In cycling, mechanical efficiency can reach maximum values up to about 25%, which means that this fraction of total metabolic energy expenditure was used to directly perform mechanical work, while the remaining 75% of free energy is accounted for by heat released during substrate oxidation (20, 22, 77). Therefore, the rate of metabolic heat production in the body is calculated as the rate of metabolic energy expenditure (M) minus the rate of external work (W). Metabolic energy expenditure can be estimated from indirect calorimetry, using measurements of inspired and expired oxygen (O_2) and carbon dioxide (CO_2), as demonstrated below:

$$M = VO_2 \frac{\left(\frac{RER - 0.7}{0.3} e_c\right) + \left(\frac{1 - RER}{0.3} e_f\right)}{60 \times BSA} \times 1000 \ [\mathrm{W \cdot m^{-2}}] \qquad \text{(Eq. 2)}$$

Where VO_2 is the rate of oxygen consumption ($L \cdot min^{-1}$), e_c and e_f are the caloric equivalents per litre of oxygen for the oxidation of carbohydrates (21.13 kJ) and fat (19.62 kJ), respectively (57), and RER is calculated as the ratio between the rate of carbon dioxide production (VCO_2) and VO_2 ($RER = VCO_2/VO_2$). Body surface area (BSA) is calculated using the equation from Dubois & Dubois (18), expressed in metres squared.

Dry Heat Exchange

Dry heat exchange with the environment occurs through convection (C), radiation (R), and conduction (K). As previously mentioned, dry heat exchange can occur as heat loss or gain from the body depending on the temperature gradient. Conduction (K) is the transfer of heat along a temperature gradient between two objects that are in direct contact with each other. In most instances, conduction is considered to be negligible due to low amounts of contact with the ground when standing and the insulating properties of shoes. For the purpose of this thesis, conduction between the bike and the subject's back, legs, and feet was also considered negligible. Therefore, there is little opportunity for heat to be transferred on a whole-body level and K can be assumed to be zero.

Convective heat transfer (C) is heat flux between an object and a fluid medium through movement (i.e., air or liquid). The rate and direction of convective heat transfer is proportional to the velocity of movement between the object and the medium, and the temperature gradient between the two surfaces in contact. It can be calculated using the following equations:

$$C = h_c\left(T_{sk} - T_a\right) \text{ [W·m}^{-2}\text{]} \qquad \text{(Eq. 3)}$$

$$h_c = 8.3v^{0.6} \text{ [W·m}^{-2}\text{·K}^{-1}\text{]} \qquad \text{(Eq. 4)}$$

Where h_c refers to the convective heat transfer coefficient ($W \cdot m^{-2} \cdot K^{-1}$) and is practical for a seated subject facing an air velocity of 0.2-4.0 $m \cdot s^{-1}$ (55), T_{sk} is the mean temperature of the skin (°C), T_a is the temperature of the ambient air in the environment (°C), and v is the air velocity ($m \cdot s^{-1}$).

Thermal radiation (R) is the transfer of heat by means of electromagnetic waves between two objects along a temperature gradient. Heat exchange through radiation depends on the person's physical orientation relative to other surrounding radiating bodies/objects and the temperature gradient between the skin and the environment. It can be calculated from the previous equation with h_r substituted for h_c as follows:

$$R = h_r \left(T_{sk} - T_a\right) \text{ [W·m}^{-2}\text{]} \qquad \text{(Eq. 5)}$$

$$h_r = 4\varepsilon\sigma \cdot \frac{BSA_r}{BSA} \cdot \left[\frac{T_{sk}+T_r}{2} + 273.15\right]^3 \text{ [W·m}^{-2}\text{·K}^{-1}\text{]} \qquad \text{(Eq. 6)}$$

Where h_r refers to the radiative heat transfer coefficient (W·m^{-2}·K^{-1}) and T_r refers to the mean radiant temperature of the environment (°C), which is assumed to be equivalent to T_a in the laboratory, ε is the weighted area emissivity of the clothing body surface area (assumed to be 0.95 – ND), σ is the Stefan-Boltzmann constant (5.67x10^{-8} W·m^{-2}·K^{-1}), and BSA_r/BSA is the effective radiative area of the body (ND), dependent on the physical posture of the individual (i.e., sitting, standing), which was assumed to be 0.70 for seated subjects in this experiment (64).

Ambient air and radiant temperatures that are greater than mean skin temperature will result in radiative heat gain, respectively, considering that the temperature gradient in these instances favours heat flow towards the body. Convective heat losses increase proportionally (to a point) with increased movement of the medium (e.g., air velocity) given that the layer of air (or liquid) nearest to the skin will equilibrate with skin temperature.

Evaporative Heat Loss

Sweat evaporation (E) is by far the most potent mechanism of heat loss in the human body under hot conditions due to the body's ability to secrete sweat at a high rate, and the high

latent heat of vaporization of sweat (2,426 J/g) (76). The rate of evaporation of sweat from the skin depends on the convective flow of air and the water vapour pressure gradient between the skin and the surrounding air. It can be calculated from the following equation:

$$E_{sk} = h_e\left(P_{sk} - P_a\right) \text{ [W·m}^{-2}\text{]} \qquad \text{(Eq. 7)}$$

$$h_e = 16.5 \cdot h_c \text{ [W·m}^{-2}\text{·K}^{-1}\text{]} \qquad \text{(Eq. 8)}$$

Where h_e refers to the evaporative heat transfer coefficient (W·m^{-2}·kPa^{-1}), 16.5 is the Lewis relation (K/kPa), $P_{sk,s}$ refers to the water vapour pressure of the skin (kPa) (usually saturated), and P_a refers to the water vapour pressure of the ambient air (kPa) which can be calculated using equation 10. Both saturated water vapour pressure and $P_{sk,s}$ can be calculated from Antoine`s equation (Eq. 9):

$$P_{s,a} = \exp\left(18.956 - \frac{4030.18}{T_a + 235}\right) \text{ [kPa]} \qquad \text{(Eq. 9)}$$

$$\phi = \frac{P_a}{P_{sa}} \qquad \text{(Eq. 10)}$$

Where $P_{s,a}$ refers to saturated water vapour pressure, ϕ refers to relative humidity (%), and T_a refers to the ambient air temperature (°C).

The required amount of evaporative heat loss to maintain heat balance (E_{req}) can be calculated as metabolic heat production minus dry heat loss and respiratory heat loss:

$$E_{req} = M - W - (C + R + K + C_{res} + E_{res}) \text{ [W·m}^{-2}\text{]} \qquad \text{(Eq. 11)}$$

Respiratory Heat Loss

When inhaled, air is warmed from body heat in the lungs and upper respiratory tract. Heat is subsequently lost through convection (C_{res}) when the air is exhaled to the cooler environment. To facilitate diffusion of the oxygen into the alveoli, inhaled air is also becomes saturated with moisture from the respiratory tract and lungs. Therefore, heat is also lost through evaporation when the saturated air from the lungs is exhaled back into the environment where water vapour pressure is much lower (E_{res}). Thus, respiratory heat loss depends on the temperature and vapour pressure of inspired air and the environment, as well as the ventilatory rate of the individual (53). Total respiratory heat loss can be calculated with the following equation:

$$C_{res} + E_{res} = [0.0014(M - W)(34 - T_a) + 0.0173(M - W)(5.87 - P_a)\ [\mathrm{W \cdot m^{-2}}] \quad \text{(Eq. 12)}$$

Where M-W refers to metabolic heat production ($W \cdot m^{-2}$), T_a refers to the temperature of the ambient air (°C), and P_a refers to ambient vapour pressure (kPa).

2.1 Thermoregulatory Responses

Sweating

While radiation and convection contribute largely to heat loss in cold or thermoneutral conditions, the evaporation of sweat is the most important avenue of heat loss during passive heat stress or during exercise in hot conditions. Droplets of sweat, in the form of a hypotonic solution, are expelled from millions of sweat glands in the dermis onto the skin surface where tremendous amounts of heat (2430 J/g/°C) are required for the vaporisation of the liquid. Changes in central (core) and peripheral (skin) temperatures initiate sweating via sympathetically mediated cholinergic stimulation from the anterior-optic hypothalamus (29). Sweating is

primarily a central response since it responds in proportion to changes in core temperature and interventions or physiological conditions such as training/acclimation and dehydration can have major effects on sweating by altering the onset threshold of the response (26, 58, 61). However, sweating can be initiated peripherally by deviations in local temperature even in the absence of central drive and the sensitivity of centrally driven sweat rates can be modified peripherally by local heating or cooling of skin (59, 60). Thus, sweating is an integrated response from central and peripheral signals with a ratio of approximately 10:1 for the central component. The absolute quantity of sweat produce—whole-body sweat loss—is determined by the evaporative requirement to maintain heat balance (E_{req}), which is the difference between metabolic heat production and the sum of all avenues of dry heat loss (24). E_{req} can be calculated using Equation 11 and is mainly driven by absolute metabolic heat production.

Skin blood flow

Cutaneous vasodilation is typically considered a thermoregulatory response and it plays an important role by facilitating the transfer of heat and fluid from the body core to the periphery, although actual heat exchange is dependent on temperature and vapour pressure gradients between the environment and skin surface. Elevations of skin blood flow are controlled under two branches of sympathetic control. First, there is a withdrawal of adrenergic vasoconstrictor tone and therefore reduction in total peripheral resistance, followed by active vasodilation mediated by cholinergic nerve stimuli (51) which can lead to skin blood flow values up to 8 L/min during sever heat stress (68). The primary determinant of rises in skin blood flow is thought to be changes in core temperature but it is also very sensitive to changes in skin temperature, and the onset threshold and sensitivity of the response can be affected by central or peripheral modifiers in the same way as sweating (51).

2.2 Hypoxia and Thermoregulation

Few studies have measured the core temperature response and thermoregulation during exercise from a whole-body heat balance perspective in hypoxic environments. One of the first to do so was Asmussen and Nielsen (1) who reported similar rises in rectal temperature at low and high altitude (4000 m) during low intensity exercise in thermoneutral conditions; however, thermoeffector responses were not measured in this study. Later, Greenleaf et al. (27) tested only three subjects in a hypobaric chamber at three different altitudes. In this study, changes in rectal and esophageal temperature were not different between two levels of high altitude compared to sea level, despite higher evaporative heat losses which were mainly due to respiratory heat losses given an increased ventilatory rate in hypoxic conditions and slight increases in evaporative efficiency from the skin given the lower vapour pressure at altitude. The authors also noted that tissue conductance was reduced by similar proportions to the increase in evaporation, potentially as a compensatory effect through assumed decreases in peripheral circulation. However, their measure of tissue conductance was likely confounded by the greater core to skin temperature gradient caused by reductions in skin temperature secondary to greater evaporative efficiency. Although their measure of tissue conductance and assumed decreases in peripheral circulation may have been obscured, it is possible that heat was stored more centrally due to lower skin blood flow following acute plasma volume reductions at altitude exposure, as suggested by the authors.

In 1987, Kolka et al. (44) compared local sweating and cutaneous blood flow responses to 60% altitude-specific VO_{2peak} at sea level and high altitude. They reported similar changes in esophageal temperature between conditions; however, exercise was set as a percentage of altitude-specific VO_{2peak} and the resulting differences in metabolic heat production between sea

level and high altitude may have confounded the influence of hypoxia on core temperature. The same change in core temperature for a lower rate of metabolic heat production potentially indicates that thermoregulation might actually have been impaired. The lower thermosensitivity of sweating and skin blood flow responses in hypoxia found in this study could be thought to support this notion, although it is known that metabolic heat production per unit of body surface area influences local sweating rate (9). Since exercise was performed at altitude-specific $\%VO_{2peak}$, heat production was accordingly lower in in the high altitude condition. A similar study performed two years later, again by Kolka et al. (43), during exercise at different intensities and ambient conditions reported supporting evidence in regards to decreased sensitivity of sweating. Measurements of whole-body sweat rates were added to this study and were lower at high altitude compared sea level, probably due to a slightly lower metabolic rate. Conversely, the change in esophageal temperature was greater in the high altitude condition despite lower metabolic heat production.

Kacin et al. (35) demonstrated that when exercise is performed at a fixed percentage of altitude-specific VO_{2peak} rectal temperature rises to a lesser degree in hypoxia compared to normoxia, but when exercise is performed at a fixed workload (and therefore VO_2) between the two conditions rectal temperature responds similarly. Interestingly, in this study it was also reported that LSR from the forehead was greater in hypoxic conditions than in normoxic at the same absolute workload but not different between hypoxic and normoxic conditions when exercise was performed at altitude-specific $\%VO_{2peak}$. The authors suggested these results could be explained by non-thermal factors such as increased physical strain, which is supported by a more recent study that found the forehead LSR response in unfit individuals to be approximately

double that of fit individuals despite exercising at the same rate heat production (and E_{req}), while WBSL and forearm LSR were similar between groups (8).

More recently, Miyagawa et al. (54) performed an extensive study of thermoregulatory and cardiovascular responses to exercise between normoxia and both normobaric hypoxia and hypobaric hypoxia. Similar results were found between both hypoxic trials suggesting that hypobaria had minimal effects, which strengthens the ability to apply the conclusions of the current thesis to a broader range of hypoxic and barometric conditions. The study by Miyagawa et al. (54) reported slightly greater increases in esophageal temperature by ~0.1°C during the hypoxic trials compared to normoxia, despite a similar sweating response. However, sweating was only measured as LSR from the chest, which cannot be extrapolated as a whole-body response and may be different in other regions of the body. Furthermore, the authors noted reciprocal changes in cutaneous perfusion and evaporative heat loss in the hypobaric trial in line with that found by Greenleaf et al (27). Importantly, Miyagawa et al. (54) also directly measured forearm vascular conductance, to get an estimate of skin blood flow, and found that it was attenuated in hypoxic trials due to greater reductions in plasma volume (by ~200 mL) compared to normoxia and possibly redistribution of blood flow towards the muscles (5). While workload was fixed in this study, VO_2 was slightly different between normoxia and hypoxia which could have resulted in different rates of metabolic heat production.

Several studies have also examined localized physiological responses to hypoxia exposure. One such study measured forearm sweating in hypobaric hypoxia following pilocarpine iontophoresis to induce the drive for sweating. Under hypoxic conditions the authors reported that forearm LSR was attenuated by about 16%, which was attributed to a peripheral effect of hypoxia on the sweat gland itself (17). However, in almost half of the subjects LSR was

the same or actually higher in hypoxia, and skin temperature, while not significantly different, was 1.2°C lower in hypoxia. In 1958, Black and Roddie (2) measured forearm blood flow at rest and reported that it was increased during short periods of hypoxic breathing. The mechanism suggested to be responsible for this response was a reduction in forearm vascular resistance stemming from hypocapnia related more to hyperpnea, rather than direct effects of hypoxia. More recently, Simmons et al. (72) corroborated these findings in a study concluding that both hypoxia and hypocapnia independently result in peripheral vasodilation but that hyperpnea is not a mediating factor. Rowell et al. (69) also measured forearm blood flow during periods of hypoxic breathing, but while exercise was being performed, and no effects of hypoxia were evident in this case. In agreement with previous studies, Sagawa et al. (70) showed that forearm blood flow is higher during hypoxia in thermoneutral conditions; however, the combination of hypoxia and passive heat stress abolished the differences in forearm blood flow between normoxia and hypoxia.

Although there is evidence for a vasodilatory response to hypoxia (2, 51, 72), which appears elevate skin blood flow during hypoxic exposure in comparison to normal oxygen conditions at rest and in thermoneutral conditions, some conflicting evidence suggests that exercise in hot conditions, as Greenleaf et al. (27) suggested and as shown in the study by Miyagawa et al. (54), may reduce skin blood flow during acute exposures to sustained hypoxia. Despite the fact that this reduction is likely caused by decreases in plasma volume (51, 54) and not hypoxia *per se*, evaluations of thermoregulation from a whole-body heat balance perspective should be primarily concerned with absolute responses – in this case a lower rate of blood flow to the skin from which heat can potentially be shed to the environment.

2.3 Summary

The current state of the relatively small body of literature pertaining to the influence of hypoxia on human thermoregulation is highly inconsistent, specifically in regards to skin blood flow and sweating responses. Although there are some differences between normobaric hypoxia and hypobaric hypoxia (mainly in evaporative efficiency due to low vapour pressure at high altitudes), it appears as though physiological responses to both conditions are quite similar. While some of the controversies surrounding sweating and its sensitivity might be explained by the exercise intensities chosen for certain studies (43, 44), others are less easily explained, such as the reported forehead sweating response to hypoxia (35). The discrepancies reported in the skin blood flow responses to hypoxia are a much more complicated matter to dissect. For years, the only method available with which skin blood flow could be estimated was plethysmography – a method inherently dependent on assumptions that muscle blood flow remains unchanged (15, 19). However, more recent evidence has demonstrated that muscle blood flow can increase with local heating (31) and during exercise in hypoxia (5). Newer technology (e.g., laser-Doppler flowmetry) may help reconcile these inconsistencies, but it is certainly not without limitations.

The experiment of this thesis aims to provide clear evidence of the thermoregulatory responses to hypoxia during exercise from a whole-body perspective. First, we will set exercise at a fixed heat production to eliminate biases stemming from differences in VO_{2peak}, and second, we will not only take two measurements of core temperature but we will also measure local responses of both sweating and skin blood flow—using laser-Doppler flowmetry—at multiple sites. Therefore, heat production, $\%VO_{2peak}$, and all heat loss responses will be accounted for in this study.

CHAPTER 3: METHODS & RESULTS

3.1 Thesis Article: To be submitted to the Journal of Applied Physiology and formatted accordingly.

Hypoxia-induced manipulations of relative exercise intensity do not alter steady-state thermoregulatory responses or maximal heat loss capacity during exercise

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Running head: Hypoxia and thermoregulation

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ABSTRACT

This study sought to determine the independent influence of hypoxia on thermoregulatory responses to exercise in compensable and uncompensable hot conditions. Eight participants completed three experimental trials of cycling in either normoxia (21% O_2) or hypoxia (13% O_2) in order to manipulate relative exercise intensity (%VO_{2peak}), since VO_{2peak} was reduced by ~30% in hypoxia. When trials were matched for %VO_{2peak}, changes in core temperature and local sweat rates (LSR) were significantly lower in the hypoxic trial as a result of a lower rate of metabolic heat production (H_{prod}) in order to maintain a similar %VO_{2peak} compared to normoxia. However, when H_{prod} was fixed between normoxic and hypoxic trials the systematic differences in core temperature and LSR were eliminated. Conversely, at a fixed H_{prod} skin blood flow (SkBF) was greater in hypoxia compared to normoxia by ~40%. Despite improvements in SkBF, the potential for maximum heat loss was unaffected during an incremental humidity ramp protocol, resulting in no difference between normoxia and hypoxia in the critical ambient vapour pressures at which core temperature inflected upwards. These data further demonstrate, using a within-subjects design, that metabolic heat production, irrespective of large differences in %VO_{2peak}, determines thermoregulatory responses during exercise. Furthermore, this study suggests that the influence of large differences in skin blood flow on heat dissipation may be lesser than previously thought.

INTRODUCTION

The physiological responses to hypoxia are well documented with increases in heart rate and respiratory rate among the primary acute responses that serve to maintain systemic oxygen delivery despite low arterial oxygen saturation. While important, some of these physiological adjustments may influence the thermoregulatory responses to heat stress particularly during exercise. For example, hypoxia may reduce plasma volume and blood flow (37) which could potentially impair skin blood flow – the primary medium for transporting heat from the core to the periphery, where it can ultimately be dissipated to the environment via radiation/convection and the evaporation of sweat. Hypoxia has previously been demonstrated to exert a vasodilatory effect on cutaneous blood vessels (46) which results in greater forearm blood flow at rest (2); however, during exercise other studies have reported no effect of hypoxia (43) or even attenuations of forearm blood flow (37).

Secondary to drastic reductions of VO_{2peak} in hypoxia (30, 32), relative exercise intensity ($\%VO_{2peak}$) is much higher for a given rate of heat production. Given the traditional logic that core temperature (45) and sweating (13) during exercise are determined by $\%VO_{2peak}$, a higher core temperature and sweat rate would be expected in hypoxia relative to the same rate of heat production in normoxia. However, the evidence for such a phenomenon is weak in compensable environments (1, 14, 37) and has not yet been investigated in uncompensable environments. Moreover, observations of sweating responses to exercise in hypoxia are highly variable. Studies employing pharmacological induction of sweating (11) and exercise at altitude-specific $\%VO_{2peak}$ (27, 28) have reported lower thermosensitivities of local sweat rates in hypoxic conditions, but exercise at a fixed absolute workload resulted in no differences in sweating between normoxia and hypoxia (37). It is also possible that greater sweat rates might occur in

glabrous skin regions (e.g., forehead) in hypoxia (20, 29) due to greater perceptual strain associated with the higher $\%VO_{2peak}$ (6).

Jay et al. (18) recently demonstrated (using a between-groups design) under normoxic conditions that core temperature in compensable conditions is determined by heat production per unit mass, not relative exercise intensity. Moreover, local sweat rates in compensable environments are determined by the evaporative requirements for heat balance (E_{req}) relative to body surface area (7), with the possible exception of the forehead (6). To further substantiate the aforementioned studies (7, 18) hypoxia may be used to alter $\%VO_{2peak}$ during exercise, which will allow for a within-subject assessment of the influence of $\%VO_{2peak}$ and heat production on core temperature and local sweat rates, respectively. Furthermore, maximal rates of heat loss have previously been determined using an incremental humidity ramp protocol (21, 24, 42), which increases the ambient vapour pressure in a stepwise fashion with constant ambient temperature and heat production. Above a critical ambient vapour pressure (P_{crit}) the maximal rate of heat loss possible for that environment will be surpassed by the heat loss requirements to maintain heat balance and an upward inflection of core temperature will then occur. Therefore, environments with ambient vapour pressures above P_{crit} do not permit the maintenance of heat balance and core temperatures will rise continuously (i.e., uncompensable).

The objectives of the current studies were therefore twofold. We assessed 1) whether hypoxia exerts an independent influence on core temperature and heat loss responses (i.e., sweating, skin blood flow) at both fixed heat production (and therefore E_{req}) and fixed $\%VO_{2peak}$ exercise in compensable conditions; and 2) whether hypoxia independently alters maximal rates of heat loss in uncompensable conditions and causes a shift in P_{crit} for core temperature. We hypothesized that 1) changes in core temperature and sweating are determined by the rate of

metabolic heat production and E_{req}, irrespective of hypoxia-induced differences in $\%VO_{2peak}$ and any concomitant alterations of skin blood flow; and 2) hypoxia-induced augmentations of skin blood flow are not effective at increasing skin temperature or sweat rates, and therefore maximal rates of heat loss, resulting in no effect on P_{crit} for core temperature compared to normoxia.

METHODS

Ethical Approval

The experimental protocol was approved by the Health Sciences and Science Research Ethics Board at the University of Ottawa (H09-14-12) and conformed to the *Declaration of Helsinki*. All participants in the study voluntarily provided written informed consent and completed a Physical Activity Readiness Questionnaire (PAR-Q) and American Heart Association/American College of Sports Medicine Health/Fitness Facility Pre-participation Screening Questionnaire prior to participation.

Participants

Based on the mean effect sizes of changes in core temperature from previous studies (6, 27) the minimum required sample size to determine significant differences ($\alpha = 0.05$, $\beta = 0.8$) in rectal temperature was seven (G*power v3.1.5; (16)). Therefore, eight (1 female) non-heat acclimated, healthy and active participants: 1.75 m (1.71-1.79 m), 70.2 kg (65.5-75.0 kg), 25 y (22-28 y), 54 mL/kg/min (48-60 mL/kg/min), were recruited to participate in the study. The participants reported no history of cardiovascular, respiratory, metabolic, or neurological disorders. All participants were asked to refrain from consuming any alcohol or caffeine, as well as performing any strenuous activity, 24 hours prior to testing. The participants were also asked

to maintain similar habits, such as sleep and diet, the night before and the day of experimental sessions, which were all separated by at least 48 h.

Experimental Design

The study consisted of five laboratory visits in total: two preliminary trials and three experimental trials. During each preliminary session, height, body mass, and maximal oxygen consumption (VO_{2peak}) were measured once in hypoxia (13% O_2) and once in normoxia (21% O_2). The maximal tests to determine VO_{2peak} were performed on a semi-recumbent cycle ergometer (Lode, Corival, Groningen, Netherlands) and began at 100 W and increased by 20 W every minute thereafter until physical exhaustion or until the rate of oxygen uptake attained a plateau, based on the recommendations from the Canadian Society of Exercise Physiology (8). The two VO_{2peak} tests were performed on separate days and in a counterbalanced order between participants.

Each of the three experimental trials was performed in a climate-controlled chamber. Prior to each trial, urine specific gravity (USG) was measured to ensure that the participants were below the cut-off value for euhydration (<1.025) (22). The first two trials were performed in a counterbalanced order and consisted of 90 min of cycling at a fixed H_{prod} of ~7 W/kg in either normoxia (21% O_2; NORM) or hypoxia (13% O_2; HYP1). The first 45 min (Part 1) were completed in a compensable environment (34.4 ± 0.2°C, 46 ± 3% RH) to compare steady-state thermoregulatory responses. The second 45 min (Part 2) were conducted to determine maximal heat loss potential using an incremental humidity protocol (+4% RH every 7.5 min) at the same ambient temperature. Maximal heat loss potential was indicated by the ambient humidity value at which esophageal temperature inflected upward during the incremental humidity protocol (critical vapour pressure; P_{crit}). During a third trial (13% O_2; HYP2), 45 min of cycling was

completed to compare steady-state thermoregulatory responses at an intensity corresponding to the same $\%VO_{2peak}$ as in NORM but a lower metabolic heat production. Once all equipment (see *Instrumentation* below) was in place and functioning, the participant rested in a seated position for a 30-min baseline period. In all experimental trials, there was a ~45 min post-exercise rest period during which the participant was de-instrumented and measurements of maximum skin blood flow were recorded under normoxic conditions.

Heat Balance Parameters

Oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were measured using indirect calorimetry (Vmax Encore, Carefusion, San Diego, CA). Metabolic energy expenditure (M) was subsequently estimated using Equation 1. Metabolic heat production (H_{prod}) was calculated by subtracting the rate of mechanical work (W) from M, as follows:

. $$M = VO_2 \frac{\left(\frac{RER - 0.7}{0.3} e_c\right) + \left(\frac{1 - RER}{0.3} e_f\right)}{60} \times 1000 \text{ (W)} \quad [1]$$

$$H_{prod} = M - W \text{ (W)} \quad [2]$$

Where RER is the respiratory exchange ratio (VCO_2:VO_2), and e_c and e_f are the caloric equivalents per litre of oxygen for the oxidation carbohydrates (21.13 kJ) and fats (19.62 kJ), respectively.

Heat losses via convection were determined by:

$$C = h_c\left(T_{sk} - T_a\right) \text{ [W]} \quad [3]$$

$$h_c = 8.3v^{0.6} \text{ [W·K}^{-1}\text{]} \quad [4]$$

Where h_c refers to the convective heat transfer coefficient ($W \cdot K^{-1}$) and is practical for a seated subject facing an air velocity of 0.2-4.0 $m \cdot s^{-1}$ (38), T_{sk} is the mean temperature of the skin (°C), T_a is the temperature of the ambient air in the environment (°C), and v is the air velocity ($m \cdot s^{-1}$).

Radiative heat losses were calculated as follows:

$$R = h_r (T_{sk} - T_a) \text{ [W]} \quad [5]$$

$$h_r = 4\varepsilon\sigma \cdot \frac{BSA_r}{BSA} \cdot [\frac{T_{sk}+T_r}{2} + 273.15]^3 \text{ [W}\cdot\text{K}^{-1}\text{]} \quad [6]$$

Where h_r refers to the radiative heat transfer coefficient ($W \cdot m^{-2} \cdot K^{-1}$) and T_r refers to the mean radiant temperature of the environment (°C), which is assumed to be equivalent to T_a, ε is the weighted area emissivity of the clothing body surface area assumed to be 0.95 (ND), σ is the Stefan-Boltzmann constant (5.67×10^{-8} $W \cdot m^{-2} \cdot K^{-1}$), and BSA_r/BSA is the effective radiative area of the body (ND) equal to 0.70 for seated subjects (39).

Total respiratory heat losses can be calculated by adding convective (C_{res}; Eq. 7) and evaporative (E_{res}; Eq. 8) respiratory heat loss (3, 15):

$$C_{res} = \frac{V_E \rho C_P (T_e - T_i)}{60} \text{ [W]} \quad [7]$$

$$E_{res} = \frac{V_E \rho (H_e - H_i)}{60} h_v \text{ [W]} \quad [8]$$

Where V_E refers to the rate of ventilation (L/min), ρ refers to the density of the air (kg/m^3), C_P refers to the specific heat capacity of dry air (kJ/kg·K), T_e refers to the temperature of the expired air (assumed to be 37°C), T_i refers to the temperature of the inspired air, which is equivalent to ambient air (°C), H_e refers to the humidity ratio of expired air (g/kg), H_i refers to

the humidity ratio of inspired air (g/kg), and h_v refers to the latent heat of vaporisation of water (J/kg·K).

The required amount of evaporative heat loss to maintain heat balance (E_{req}) can be calculated as:

$$E_{req} = H_{prod} - (C + R + C_{res} + E_{res}) \text{ [W]} \quad [9]$$

Instrumentation

Rectal temperature (T_{re}) was monitored using a pediatric thermistor (TM400, Covidien, Mansfield, MA, USA) inserted approximately 20 cm past the anal sphincter. Esophageal temperature (T_{es}) was also measured using a pediatric thermistor inserted through the nasal passage and into the esophagus with the bottom of the probe resting at approximately the level of the right atrium (33).

Skin temperature (T_{sk}) was measured at four sites (40) using thermistors integrated into heat flow sensors (2252 Ohms, Concept Engineering, Old Saybrook, CT, USA). The heat flow sensors were placed onto the skin using double-sided adhesive discs and surgical tape (Transpore, 3M, London, ON, Canada). All thermometry data were recorded using a National Instruments data acquisition unit (model NI cDAQ-9172) at a sampling rate 0.2 Hz. Data were simultaneously displayed and recorded in spreadsheet format on a personal computer (Dell Inspiron 545) with LabVIEW software (National Instruments, TX, USA).

Local sweat rates (LSR) were measured from ventilated capsules placed on the skin of the upper back, forearm, and forehead. Influent anhydrous air flowed through the capsule at a rate of 1.00 $L \cdot min^{-1}$. Flow rates were measured using an Omega FMA-A2307 flow rate monitor (Omega Engineering, Stamford, CT). The vapour content of the effluent air was measured using

capacitance hygrometers (Series HMT333, Vaisala, Helsinki, Finland). LSR values were calculated using the recorded flow rate and the difference in vapour content of the influent and effluent air, normalized to the area of skin under the capsule (expressed in $mg \cdot cm^{-2} \cdot min^{-1}$). The onset of sweating and the relationship of sweat rates to changes in esophageal temperature were determined using linear segmental regression.

In addition to LSR, whole-body sweat losses (WBSL) were estimated from the difference of pre- and post-exercise body mass measurements (Combics 2, Sartorius, Mississauga, ON, Canada), corrected for metabolic and vapour mass losses from respiration (36).

Heat-activated sweat gland density (HASGD) was determined using the iodine paper method (12) adjacent to the forearm sweat capsule. Sweat expulsions (i.e., the number of activated sweat glands) produced dark purple spots on the paper which were counted using Image J software (41). Forearm LSR was divided by HASGD to determine sweat gland output (SGO) expressed in $\mu g \cdot cm^{-2} \cdot min^{-1} \cdot gland$.

Blood pressure was monitored with an automated unit (Tango M2, SunTech, Raleigh, NC, USA) and a 3-lead ECG setup (Q-Stress v3.3, Quinton, Bothell, WA, USA). Mean arterial pressure (MAP) was calculated from the addition of 1/3 systolic blood pressure and 2/3 diastolic blood pressure. As an index skin blood flow (SkBF), red blood cell flux was measured (Periflux System 5000, Perimed, Järfälla, Sweden) on the forearm and upper back using laser-Doppler flowmetry. SkBF is expressed in arbitrary perfusion units (AU) and as a percentage of maximum SkBF, which was determined during 45 min of normoxic post-exercise local heating of the measurement area (~1 cm^2) to 41°C. Additionally, cutaneous vascular conductance (CVC) was calculated as SkBF/MAP; CVC values were also normalized to maximum values. The onset of

rises in skin blood flow and the relationship of the slope in comparison to changes in esophageal temperature were determined using linear segmental regression. Oxygen saturation (SpO_2) and heart rate (HR) were recorded every 5 s with a Rainbow SET pulse oximeter (Radical-7, Masimo, Irvine, CA, USA).

One blood sample of ~6 mL was taken at 0, 45, and 90 min of exercise, and was analyzed for hematocrit (Hct) and hemoglobin (Hb) using a photometer (HemoPoint H2 Meter, StanBio Laboratory, Boerne, TX, USA) and microcuvettes (Alere, Orlando, FL, USA). Each draw was replaced with an equivalent volume of 0.9% NaCl saline solution. Changes in plasma volume (ΔPV) were determined using the method described by Dill and Costill (10).

Ratings of perceived exertion (RPE) were taken at rest and every 15 min during exercise using a Borg scale (6-20).

Statistical Analysis

For Part 1, two-way repeated measures ANOVAs, with the independent factors of condition (2 levels: NORM, HYP1/HYP2) and time (four levels: 0, 15, 30, 45 min) were used to analyze the dependent variables of T_{sk}, ΔT_{es}, ΔT_{re}, LSR_{arm}, LSR_{back}, LSR_{head}, mean SkBF (AU and %max), mean CVC (AU and %max), HR, MAP, RPE, and SpO_2. Separate ANOVAs were performed to compare fixed H_{prod} trials and trials matched for $\%VO_{2peak}$. Two-way ANOVAs were performed again with the same variables for Part 2, using the independent factors of condition (NORM or HYP1) and time (seven levels: 0, 15, 30, 45, 60, 75, 90 min). When a significant interaction between time and condition was detected, individual time points were compared using *t*-tests with a Holm-Bonferonni correction. Partial eta squared values (η_p^2) are reported as measures of effect sizes. Mean values throughout the trials for $\%VO_{2max}$, H_{prod},

workload, onsets and thermosensitivities of sweating and SkBF, HASGD, SGO, and changes in PV were compared using a paired-sample Student's *t*-test. For Part 2, P_{crit} for T_{es} was determined using segmental linear regression and then compared using a paired-sample Student's *t*-test. All data are reported as means with 95% confidence intervals. Figures depict 95% confidence intervals for within-subject variation (5) Alpha was set at the P=.05 level. All statistical analyses were performed with Prism GraphPad v6.0 for Windows (La Jolla, CA, USA).

RESULTS

Workload, Exercise Intensity, and Heat Production

Mean values for H_{prod}, E_{req}, workload, and $\%VO_{2peak}$ for both parts of the study are presented in Table 1. Hypoxia induced a 27% reduction of VO_{2peak} from 3.81 L/min (3.31-4.25 L/min) in normoxia to 2.74 L/min (2.49-2.99 L/min) in hypoxia ($P < .001$, $d = 1.92$).

PART 1*:* By design, there was no difference in heat production ($P = .20$, $d = 0.49$) or E_{req} ($P = .17$, $d = 0.73$) in the fixed H_{prod} trials between NORM and HYP1 (Table 1), while workload was slightly lower in HYP1 than NORM ($P = .03$, $d = 0.61$); however, $\%VO_{2peak}$ was significantly greater in HYP1 compared to NORM ($P < .001$, $d = 2.46$). Conversely, when the trials were matched for $\%VO_{2peak}$, heat production ($P < .001$), E_{req} ($P < .001$), and workload ($P < .001$) were all significantly lower in HYP2 compared to NORM.

PART 2: By design, H_{prod} ($P = .27$) and E_{req} ($P = .31$) were not different between NORM and HYP1 but workload was slightly lower in HYP1 ($P = .01$). In HYP1 $\%VO_{2peak}$ was significantly greater than in NORM ($P < .001$).

Core and Skin Temperatures

Hypoxia and thermoregulation

PART 1: During the fixed H_{prod} trials, changes in T_{es} over time (Figure 1A) were not different between conditions (P = .97, η_p^2 < .01) with a ΔT_{es} after 45 min of 0.64°C (0.48-0.79°C) in NORM and 0.63°C (0.43-0.83°C) in HYP1. There was also no interaction between time and condition on changes in T_{re} (P = .98, η_p^2 < .01) with a ΔT_{re} after 45 min of 0.76°C (0.63-0.89°C) in NORM and 0.75°C (0.59-0.91°C) in HYP1 (Figure 1B). In contrast, when exercising at a matched $\%VO_{2peak}$ (but different H_{prod}), changes in T_{es} over time (Figure 1A) were significantly smaller in HYP2 compared to NORM (P = .02, η_p^2 = .21), with a 45-min ΔT_{es} of 0.50°C (0.30-0.71°C) in HYP2, while changes in T_{re} over time (Figure 1B) were also smaller in HYP2 compared to NORM (P = .03, η_p^2 = .20), with a 45-min ΔT_{re} 0.56°C (0.41-0.71°C) in HYP2. The change in T_{sk} over time was not different between all three trials (P = .54, η_p^2 = .07) with 45-min ΔT_{sk} values of 0.63°C (0.45-0.81°C) in NORM, 0.58°C (0.45-0.70°C) in HYP1, and 0.50°C (0.37-0.64°C) in HYP2.

PART 2: During the incremental humidity protocol, changes in T_{es} over time were not different between conditions (P = 0.99, η_p^2 < .01; Figure 5A), nor was there an interaction between time and condition on changes in T_{re} (P = 0.99, η_p^2 < .01). The changes in T_{sk} over time were not different between all three trials (P = 0.35, η_p^2 = .07) with mean values throughout part 2 of the trial of 34.49°C (34.31-34.67°C) in NORM and 34.66°C (34.50-34.82°C) in HYP1. Additionally, P_{crit} for the inflection of T_{es} (Figure 5B) was not different between conditions (NORM = 3.67 kPa, 95% CI: 3.42-3.91 kPa; HYP1 = 3.46 kPa, 95% CI: 3.19-3.73 kPa; P = .22).

Sweating

PART 1: During the fixed H_{prod} trials, LSR on the forearm (Figure 2A) did not respond differently over time between conditions (P = .19, η_p^2 = .12) with values after 45 min of 1.21

mg/cm^2/min (1.09-1.34 mg/cm^2/min) in NORM and 1.28 mg/cm^2/min (1.14-1.42 mg/cm^2/min) in HYP1. There also no significant interaction between time and condition on LSR of the upper back ($P = .88$, $\eta_p^2 = .02$) with values after 45 min of 1.06 mg/cm^2/min (0.94-1.18 mg/cm^2/min) in NORM and 1.05 mg/cm^2/min (0.83-1.27 mg/cm^2/min) in HYP1 (Figure 2B), nor did an interaction exist between time and condition on LSR of the forehead ($P = .93$, $\eta_p^2 = .01$) with LSR values after 45 min of 1.01 mg/cm^2/min (0.76-1.26 mg/cm^2/min) in NORM and 1.03 mg/cm^2/min (0.81-1.25 mg/cm^2/min) in HYP1 (Figure 2C). However, in the $\%VO_{2peak}$-matched trials LSR was attenuated in HYP2 on the forearm ($P < .001$, $\eta_p^2 = .50$) with LSR after 45 min of 0.77 mg/cm^2/min (0.63-0.91 mg/cm^2/min) (Figure 2A). LSR on the upper back was also attenuated in HYP2 ($P < .001$, $\eta_p^2 = .33$) with values after 45 min of 0.76 mg/cm^2/min (0.63-0.88 mg/cm^2/min) in HYP2 (Figure 2B), as was forehead LSR ($P = .02$, $\eta_p^2 = .24$) with values after 45 min of 0.62 mg/cm^2/min (0.41-0.82 mg/cm^2/min) in HYP2 (Figure 2C).

The mean onset threshold for LSR was not different between all trials ($P = .30$, $\eta_p^2 = .06$), NORM: 0.14°C (0.07-0.22°C); HYP1: 0.21°C (0.13-0.28°C); HYP2: 0.18°C (0.12-0.25°C), nor was the relationship between the slope of mean LSR and ΔT_{es} ($P = .45$, $\eta_p^2 = .06$), NORM: 1.50 mg·cm^{-2}·min^{-1}·°C^{-1} (1.11-1.89 mg·cm^{-2}·min^{-1}·°C^{-1}); HYP1: 1.93 mg·cm^{-2}·min^{-1}·°C^{-1} (1.03-2.83 mg·cm^{-2}·min^{-1}·°C^{-1}); HYP2: 1.39 mg·cm^{-2}·min^{-1}·°C^{-1} (0.73-2.06 mg·cm^{-2}·min^{-1}·°C^{-1}). Onset thresholds are displayed in Table 3 and thermosensitivities are displayed in Table 4.

Heat activated sweat gland density and sweat gland output are displayed in Table 5. During fixed H_{prod} trials, HASGD was not different between NORM and HYP1 ($P = .51$), while HASGD was lower in HYP2 when matched for $\%VO_{2peak}$ ($P = .01$). Conversely, SGO was not

different between conditions in both fixed H_{prod} trials (P = .64) and when matched for $\%VO_{2peak}$ (P = .48).

PART 2: LSR on the forearm did not change differently over time between NORM and HYP1 (P = .52, η_p^2 = .06) during the incremental humidity protocol, with values of 1.56 mg/cm^2/min (1.50-1.62 mg/cm^2/min) in NORM and 1.50 mg/cm^2/min (1.32-1.68 mg/cm^2/min) in HYP1 at 90 min (Figure 6A). LSR on the upper back (P = .98, η_p^2 = .01) also did not respond differently over time with end-exercise values of 1.43 mg/cm^2/min (1.31-1.54 mg/cm^2/min) in NORM and 1.40 mg/cm^2/min (1.18-1.62 mg/cm^2/min) in HYP1 (Figure 6B), nor did LSR on the forehead (P = .99, η_p^2 = .01) with end-exercise values of 1.36 mg/cm^2/min (1.14-1.59 mg/cm^2/min) in NORM and 1.34 mg/cm^2/min (1.14-1.54 mg/cm^2/min) in HYP1 (Figure 6C). WBSL in Part 2 were not different between trials after 90 min of exercise (P = .63), NORM: 1036 g (951-1134 g); HYP1: 1060 g (966-1154 g).

Heat activated sweat gland density and sweat gland output are displayed in Table 5. During fixed H_{prod} trials, HASGD was not different between NORM and HYP1 (P = .26). SGO was also not different between conditions in fixed H_{prod} trials during part 2 (P = .08).

Skin Blood Flow

PART 1: There was no main effect of hypoxia or interaction between time and condition on mean SkBF (P = .71, η_p^2 = .03) or CVC (P = .46, η_p^2 = .06) in AU during either the fixed H_{prod} trials or the $\%VO_{2peak}$-matched trials (Figure 3A, 3C). There was also no significant interaction between time and condition in the fixed H_{prod} trials when AU values were normalized to a percentage of maximum ($\%SkBF_{max}$: P = .28, η_p^2 = .09; $\%CVC_{max}$: P = .21, η_p^2 = .10); however, there tended to be a main effect of hypoxia resulting in greater mean $\%SkBF_{max}$ (P = .09, η_p^2 =

.50) and %CVC_{max} (P = .08, η_p^2 = .53) (Figure 3B, 3D). There was also no main effect of hypoxia or interaction between time and condition on mean %$SkBF_{max}$ (P = .61, η_p^2 = .04) and %CVC_{max} (P = .65, η_p^2 = .04) in the %VO_{2peak}-matched trials (Figure 3B, 3D). Maximum SkBF was not different between conditions (P = .14, η_p^2 = .18) with values after ~45 min of local heating of 312 AU (242-381 AU) in NORM, 235 AU (185-285 AU) in HYP1, and 325 (287-362 AU).

The mean onset threshold for SkBF was not different between all trials (P = .54, η_p^2 = .05), NORM: 0.22°C (0.11-0.32°C); HYP1: 0.29°C (0.15-0.43°C); HYP2: 0.25°C (0.19-0.31°C), nor was the relationship between the slope of mean SkBF and ΔT_{es} (P = .47, η_p^2 = .06), NORM: 152%max·°C^{-1} (23-81%max·°C^{-1}); HYP1: 81%max·°C^{-1} (37-124%max·°C^{-1}); HYP2: 61%max·°C^{-1} (42-80%max·°C^{-1}). Onset thresholds are displayed in Table 3 and thermosensitivities are displayed in Table 4.

PART 2: There was no main effect of hypoxia or interaction between time and consition during the incremental humidity protocol on mean SkBF (P = .88, η_p^2 = .03) or CVC (P = .49, η_p^2 = .07) in AU (Figure 7A, 7C); however, hypoxia elevated %$SkBF_{max}$ (P < .05, η_p^2 < .14) and %CVC_{max} (P = .01, η_p^2 = .18) to a greater extent over time than in NORM by ~40% at end-exercise (Figure 7B, 7D).

Cardiovascular and Hematological Measurements

Mean HR, MAP, SpO_2, Hb, Hct, and ΔPV values for both studies are all displayed in Table 2.

Hypoxia and thermoregulation

PART 1: In the fixed H_{prod} trials, the HR response was greater over time in HYP1 compared to NORM ($P < .001$, $\eta_p^2 = .48$) with mean values ~22 bpm higher (Figure 4A), MAP was not different between conditions ($P = .90$, $\eta_p^2 = .01$), SpO_2 decreased over time in HYP1 compared to NORM ($P < .001$, $\eta_p^2 = .50$) with mean values ~20% lower in HYP1 (Figure 4B), and reductions in PV after 45 min of exercise tended to be greater in HYP1 compared to NORM ($P = .06$). In the $\%VO_{2peak}$-matched trials, hypoxia had no effect on HR ($P = .44$, $\eta_p^2 = .06$), MAP ($P = .88$, $\eta_p^2 = .02$), or ΔPV ($P = .17$), but SpO_2 decreased over time in HYP2 with mean values ~20% lower than in NORM ($P < .001$, $\eta_p^2 = .48$).

PART 2: During the incremental humidity protocol, the HR response was also greater in HYP1 than in NORM ($P < .001$, $\eta_p^2 = .48$) with mean values ~22 bpm higher in HYP1, hypoxia had no effect on MAP ($P = .96$, $\eta_p^2 = .02$), SpO_2 significantly decreased over time ($P < .001$, $\eta_p^2 = .37$) in HYP1 with mean values ~20% lower than NORM, and ΔPV was not different between NORM and HYP1 at end-exercise ($P = .12$).

Ventilatory Responses and Respiratory Heat Losses

PART 1: During the fixed H_{prod} trials, mean VO_2 ($P = .30$) and RER ($P = .80$) were not different between NORM and HYP1, while the rate of ventilation ($P < .001$) and respiratory heat losses ($P < .001$) were both greater in HYP1 compared to NORM. Conversely, when matched for $\%VO_{2peak}$, mean VO_2 ($P < 0.01$) was lower in HYP2 compared to NORM, while RER tended to be lower in HYP2 ($P = .05$) and the rate of ventilation ($P = .01$) and respiratory heat losses ($P = .02$) were both significantly different lower in HYP2 than in NORM.

Hypoxia and thermoregulation

PART 2: During the incremental humidity protocol, mean VO_2 (P = .34) and RER (P = 1.00) were not different between NORM and HYP1, while the rate of ventilation (P < .001) and respiratory heat losses (P < .001) were both greater in HYP1 compared to NORM.

Ratings of Perceived Exertion

PART 1: In the fixed H_{prod} trials, RPE values (Borg) were higher over time in hypoxia (P = .04, η_p^2 = .18) with mean values of 11 (10-12) in NORM and 13 (12-14) in HYP1. Conversely, when exercising at a matched $\%VO_{2peak}$ RPE values were lower over time in HYP2 (P < .01, η_p^2 = .29) with a mean value of 10 (9-10).

PART 2**:** During the incremental humidity protocol, RPE values were greater over time in HYP1 (P = .02, η_p^2 = .17) with mean values of 12 (11-13) in NORM and 14 (12-15) in HYP1.

DISCUSSION

Part 1 of this study used a novel approach to demonstrate within-subjects that exercise at a fixed rate of metabolic heat production—irrespective of hypoxia-induced differences in $\%VO_{2peak}$—eliminates systematic differences in thermoregulatory outcome measures of core temperature and sweating. Furthermore, it has been demonstrated for the first time that skin blood flow is potentially elevated to a greater extent in hypoxia compared to normoxia during exercise at a fixed H_{prod}.

Such large differences in VO_{2peak} for a given subject between normoxia and hypoxia allow for a unique situation in which the role of $\%VO_{2peak}$ on changes in core temperature and sweating can be assessed without confounding factors associated with other between-group differences (e.g., mass, BSA, body fat %) (7, 11). Recently, Jay et al. (19) demonstrated that

differences in aerobic capacity between groups of high and low fitness do not influence changes in core temperature or thermoregulatory sweating during exercise matched for H_{prod}. However, when exercise was normalized for $\%VO_{2peak}$, significantly larger changes in core temperature occurred in the high fitness group as a result of their requirement to sustain much higher workloads—and therefore H_{prod}—than their less fit counterparts in order to attain a given $\%VO_{2peak}$. The current study lends support to Jay et al. (19) by manipulating $\%VO_{2peak}$ for a given absolute H_{prod} (NORM vs. HYP1) and by changing H_{prod} for a given $\%VO_{2peak}$ (NORM vs. HYP2) using hypoxia. It was found that despite differences in $\%VO_{2peak}$ of almost 20% (45% vs. 62%), core temperature (Figure 1) and sweating (Figure 2) were unaffected by hypoxia during exercise at a fixed H_{prod}. Conversely, to match $\%VO_{2peak}$ in hypoxia to normoxia, H_{prod} was lowered, resulting in smaller changes in rectal and esophageal temperatures (Figure 1) as well as attenuations of LSR in hypoxia at all sites (Figure 2). This demonstrates that setting exercise as a percentage of VO_{2peak} leads to systematic differences in the thermoregulatory responses. When H_{prod} was fixed there were no differences (with very small effect sizes) in thermoregulatory responses, which indicates that this is a more appropriate way to set exercise intensity when thermoregulatory responses are primary outcomes (7).

A study by Saltin & Hermansen in 1966 (45) presented an explanation of the inter-individual variability of core temperature responses to exercise, which was widely interpreted as evidence for the long-held notion that relative exercise intensity (i.e., $\%VO_{2max}$) primarily determines changes in core temperature during exercise. Accordingly, previous assessments of thermoregulation in simulated high altitude (i.e., hypoxia) have used the approach of comparing thermoeffector responses at altitude-specific $\%VO_{2peak}$. Kolka et al. (27, 28) found that when exercising at 60% of altitude-specific VO_{2peak} the steady-state forearm sweat rate was attenuated

in the high altitude trials (4575 m). However, the metabolic rates, and therefore H_{prod}, at high altitude in these studies were also lower in order to maintain similar $\%VO_{2peak}$ to the sea-level conditions. Recent evidence has demonstrated that LSR is determined by E_{req} in W/m^2 (7), which is primarily driven by heat production; therefore we can confidently attribute the LSR observations from Kolka et al. (27, 28) not to hypoxia *per se* but to differences in heat production stemming from a reduced VO_{2peak} at high altitude/hypoxia. Additionally, Kolka et al. (27, 28) reported reductions in the slopes of sweating and skin blood flow over esophageal temperature at high altitude. However, results from the current study demonstrate that onset thresholds for sweating and skin blood flow (Table 3), as well as thermosensitivities of sweating and skin blood flow (Table 4) were not different between normoxic and hypoxic conditions. Rather, the lower LSR in the $\%VO_{2peak}$-matched hypoxic trial (HYP2) was mediated by a lesser activation of sweat glands not differences in individual sweat gland output (Table 5). Therefore, the results from Kolka et al. (27, 28) are likely confounded by altitude-specific work rates.

In line with the results of the current study, others have reported no effect of hypoxia on core temperature during exercise at fixed absolute workloads (1, 14, 20, 29, 37) and concurrently no difference in LSR between normoxia and hypoxia (37). In contrast to the results of the current investigation, two studies have reported a significantly higher LSR on the forehead during exercise in hypoxia compared to normoxia at fixed absolute workloads (20, 29). It is noteworthy that while previous studies fixed workloads between normoxia and hypoxia, they did not report heat production. In the current study, workloads were dissimilar between NORM and HYP1 at a fixed heat production (Table 1), most likely due to decrements in mechanical efficiency. Although the exact mechanism leading to greater forehead sweating in hypoxia remains unknown, it was suggested that the central drive for sweating may have been potentiated by

greater perceived strain relating to non-thermal factors such as increased heart rate and dyspnea due to hypoxia. Greater forehead LSR have also been observed in normoxic conditions only between groups of low and high aerobic fitness, independently of E_{req}, which was also associated with greater perceptual strain (6). The cause of the inconsistency between LSR on forehead (Figure 2C) in the current study and in others is not clear; however, it might be speculated that perceptual strain under hypoxia in the current study was not sufficiently high to induce greater sweating from eccrine glands. The hypoxic workloads (~90 W; Table 1) and RPE [13] in the current study were much lower compared to Kounalakis et al. (29) who reported workloads of approximately 150 W and RPE values of 16, while Cramer et al. (6) reported workloads and RPE similar to that of the current study and observed greater forehead LSR nonetheless. Additionally, Kacin et al. (20) observed elevated systolic arterial pressure in hypoxia which indicates a greater sympathetic response that may have driven higher sweat output from eccrine glands (e.g., forehead); however MAP in the current study was similar between normoxia and hypoxia.

While SkBF and CVC in arbitrary units (Figure 3A, 3C) were not different between any of the trials, $\%SkBF_{max}$ and $\%CVC_{max}$ (Figure 3B, 3D) tended to be elevated to a greater extent during exercise at a fixed H_{prod} in hypoxia compared to normoxia (NORM vs. HYP1), but there were no differences in $\%SkBF_{max}$ or $\%CVC_{max}$ during $\%VO_{2peak}$-matched trials (NORM vs HYP2). Although evidence for a vasodilatory effect of hypoxia exists (2, 46), other studies report either no effect (43) or reductions (37) of skin blood flow during exercise in hypoxia. Interestingly, HR (Figure 4A) responded in a similar fashion to SkBF with significant elevations in HYP1 compared to NORM, but no differences between HYP2 and NORM. In addition to conflicting observations of skin blood flow between this study and relevant literature, it is also noteworthy that muscle blood flow is influenced by hypoxia (4, 16), therefore a measurement

technique not reliant on assumptions of muscle blood flow—such as laser-Doppler flowmetry used in the current study—might be better suited to make assessments of cutaneous perfusion rather than the oft-used measurement of forearm blood flow. It is, however, important to note that there are many limitations associated with laser-Doppler flowmetry, including differences in placement between trials and movements during exercise that could possibly affect the measurements. Future studies should therefore continue to investigate the independent influence of hypoxia on SkBF. Moreover, future studies should aim to develop a more reliable measure of skin blood flow that does not rely on assumptions of muscle blood flow—such as occlusion plethysmography—or that is less delicate and variable than laser-Doppler flowmetry.

Part 2 of this study was novel in that it examined the influence of hypoxia on the maximal potential for heat loss (i.e., the limit of physiological compensability). It has often been reported that hypoxia alters skin blood flow (28, 34, 37, 44, 46) and that impairments of SkBF occur in certain clinical populations, including the elderly (17, 23, 35, 49) and diabetics (25). Traditionally, skin blood flow is viewed as an important thermoregulatory response, and as such impairments of skin blood flow should lead to attenuations of heat loss capacity (26, 48). Conversely, recent studies have examined the effectiveness of interventions to augment cutaneous vasodilation (31, 47) and therefore SkBF, which following the logic that applies to impairments of SkBF should improve maximal heat loss capacity and defend against perturbations of heat balance.

One way in which the importance of SkBF for heat dissipation can be tested is with an incremental humidity ramp protocol. Historically, such a protocol has been used to identify critical environmental limits (21, 24) for work or exercise, but this approach has also been successfully used to test the effectiveness of an intervention on rates of maximal heat loss (42). It

would be expected that attenuated SkBF would supply less of the required heat and fluid for heat exchange at the skin, resulting in an earlier critical ambient vapour pressure (P_{crit}) value due to the rate of heat production surpassing maximal rates of heat loss sooner. Likewise, augmentations of SkBF might be expected to enhance the supply of heat and fluid through the blood to the skin and subsequently improve the rate of maximal heat loss to an extent that P_{crit} could potentially be delayed.

In the present study there were no differences in P_{crit} (Figure 5) values between normoxia and hypoxia, indicating that hypoxia does not independently influence thermoregulatory responses in uncompensable conditions. Despite augmentations of $\%SkBF_{max}$ and $\%CVC_{max}$ (Figure 3B, 3D) by ~40% at end-exercise, heat loss at the skin is driven by skin-air temperature and vapour pressure gradients. Given the similar responses of skin temperatures and the constant ambient temperature, skin-air temperature gradients were unaffected by alterations of skin blood flow of this magnitude. Wingo et al. (50) reported that LSR was attenuated with supra-physiological reductions of skin blood flow achieved via pharmacological intervention; however, whole-body sweat losses from our study demonstrate that sweating was not influenced by more physiologically relevant decreases in SkBF. Therefore, alterations of skin blood flow in the current study appear not to affect maximal heat loss capacity, which suggests that previous postulations may have overstated the importance of skin blood flow for heat dissipation.

Conclusions

This study demonstrates that hypoxia does not independently influence core temperature or sweating responses to steady-state exercise despite greater skin blood flow. Additionally, we used a novel within-subject approach to show that exercise set by $\%VO_{2peak}$ does not determine

changes in core temperature or local sweat rates, while an approach using metabolic heat production and E_{req}, irrespective of differences in $\%VO_{2peak}$, eliminate systematic differences in thermoregulatory responses. Furthermore, it was identified for the first time that hypoxia-induced augmentations of skin blood flow do not alter maximal rates of heat loss in uncompensable conditions or influence P_{crit} during an incremental humidity ramp protocol.

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APPENDIX: Tables and figures.

Table 1. Workload, heat production, and relative exercise intensity during cycling in three trials: NORM (normoxia; 21% O_2), HYP1 (fixed H_{prod} hypoxia; 13% O_2), and HYP2 (matched $\%VO_{2peak}$ hypoxia; 13% O_2).

	Workload (W)	$\%VO_{2peak}$	H_{prod} (W)	H_{prod} (W/kg)	E_{req} (W/m^2)
			PART 1		
NORM	90 (86-94)	45 (39-50)	471 (445-497)	6.7 (6.3-7.1)	236 (226-247)
HYP1	87 (84-90)	62 (57-66) †	488 (476-508)	7.0 (6.7-7.3)	246 (239-252)
HYP2	60 (55-66)*	48 (45-51)	384 (357-410)*	5.5 (5.1-5.9)*	188 (173-204)*
			PART 2		
NORM	89 (86-93)	45 (40-51)	480 (454-507)	6.9 (6.5-7.3)	251 (237-264)
HYP1	86 (83-89) †	63 (60-67) †	499 (474-525)	7.2 (6.9-7.5)	262 (249-275)

H_{prod}, heat production; E_{req}, evaporative requirements for heat balance. *Significantly different from HYP1 ($P < 0.05$). *Significantly different from HYP2 vs. NORM ($P < 0.05$). †Significantly different from HYP1 vs. NORM ($P < 0.05$).

Table 2. Cardiovascular and hematological measurements during cycling in three trials: NORM (normoxia; 21% O_2), HYP1 (fixed H_{prod} hypoxia; 13% O_2), and HYP2 (matched $\%VO_{2peak}$ hypoxia; 13% O_2).

	HR (bpm)	MAP (mmHg)	SpO_2 (%)	Hb (g/dL)	Hct (%)	ΔPV (%)
			REST			
NORM	66 (57-75)	89 (83-95)	97 (96-98)	14.5 (14.2-14.8)	43 (42-44)	-
HYP1	74 (65-83) †	89 (82-95)	84 (81-87) †	14.6 (14.2-15.1)	43 (42-44)	-
HYP2	74 (66-82) *	88 (84-93)	82 (79-84) *	14.5 (14.1-15.0)	43 (42-44)	-
			PART 1			
NORM	113 (100-125)	92 (84-101)	96 (96-97)	15.1 (14.7-15.5)	44 (43-45)	-6.1 (2.8-9.5)
HYP1	134 (125-144) †	93 (87-100)	76 (74-79) †	15.4 (14.9-16.0)	45 (44-47)	-9.5 (7.2-11.7)
HYP2	119 (108-130)	89 (83-95)	76 (75-78) *	14.9 (14.5-15.4)	44 (42-45)	-4.3 (1.5-7.5)
			PART 2			
NORM	123 (110-136)	90 (84-96)	96 (95-96)	15.4 (14.9-15.8)	45 (44-46)	-9.1 (5.1-13.1)
HYP1	145 (134-156) †	91 (82-99)	77 (76-79) †	15.7 (15.2-16.2)	46 (44-48)	-11.7 (9.8-13.7)

HR, heart rate; MAP, mean arterial pressure; SpO_2, oxygen-hemoglobin saturation; Hb, total hemoglobin; Hct, hematocrit; PV, plasma volume. *Significantly different from HYP1 ($P < 0.05$). *Significantly different from HYP2 vs. NORM ($P < 0.05$). †Significantly different from HYP1 vs. NORM ($P < 0.05$).

Table 3. Onset thresholds of thermoeffector responses during cycling in three trials: NORM (normoxia; 21% O_2), HYP1 (fixed H_{prod} hypoxia; 13% O_2), and HYP2 (matched $\%VO_{2peak}$ hypoxia; 13% O_2).

	NORM	HYP1	HYP2
	Sweating, Δ°C		
Arm	0.14 (0.05-0.23)	0.18 (0.12-0.25)	0.19 (0.12-0.26)
Back	0.14 (0.05-0.23)	0.18 (0.08-0.28)	0.15 (0.08-0.23)
Head	0.12 (0.05-0.19)	0.25 (0.09-0.41)	0.22 (0.15-0.29)*
	Skin blood flow, Δ°C		
Arm	0.18 (0.10-0.26)	0.30 (0.17-0.43)	0.24 (0.17-0.31)
Back	0.26 (0.11-0.41)	0.27 (0.12-0.43)	0.26 (017-0.34)

*Significantly different from HYP2 vs. NORM ($P < 0.05$).

Table 4. Thermosensitivities of thermoeffector responses during cycling in three trials: NORM (normoxia; 21% O_2), HYP1 (fixed H_{prod} hypoxia; 13% O_2), and HYP2 (matched $\%VO_{2peak}$ hypoxia; 13% O_2).

	NORM	HYP1	HYP2
	Sweating, $mg \cdot cm^{-2} \cdot min^{-1} \cdot °C^{-1}$		
Arm	1.93 (1.36-2.49)	1.82 (1.04-2.59)	1.35 (0.66-2.04)
Back	1.68 (1.10-2.25)	1.96 (1.01-2.90)	1.38 (0.75-2.00)
Head	1.60 (1.04-2.17)	2.44 (1.49-3.39)	1.51 (0.66-2.35)
	Skin blood flow, $\%max \cdot °C^{-1}$		
Arm	85 (29-140)	99 (39-159)	58 (18-97)
Back	28 (14-41)	60 (27-93)	64 (38-90)

Table 5. Heat-activated sweat gland density (HASGD) and sweat output per gland (SGO) during cycling in three trials: NORM (normoxia; 21% O_2), HYP1 (fixed H_{prod} hypoxia; 13% O_2), and HYP2 (matched $\%VO_{2peak}$ hypoxia; 13% O_2).

	Active glands per cm^2 (#)	SGO ($\mu g \cdot cm^{-2} \cdot min^{-1} \cdot gland^{-1}$)
	Part 1	
NORM	93 (73-113)	13.2 (9.5-17.0)
HYP1	101 (70-132)	12.6 (9.0-16.2)
HYP2	70 (52-88)*	12.0 (10.8-13.2)
	Part 2	
NORM	109 (88-130)	14.0 (11.1-16.8)
HYP1	112 (70-132)	13.6 (10.3-16.8)

*Significantly different from HYP2 vs. NORM ($P < 0.05$).

Table 6. Ventilatory responses and respiratory heat losses during cycling in three trials: NORM (normoxia; 21% O_2), HYP1 (fixed H_{prod} hypoxia; 13% O_2), and HYP2 (matched $\%VO_{2peak}$ hypoxia; 13% O_2).

	VO_2 ($L \cdot min^{-1}$)	RER (ND)	V_E ($L \cdot min^{-1}$)	$C_{res} + E_{res}$ (W)
		REST		
NORM	0.35 (0.31-0.38)	0.88 (0.79-0.98)	10.8 (9.1-12.5)	11 (9-12)
HYP1	0.42 (0.34-0.50) †	0.81 (0.76-0.86)	12.0 (10.2-13.8)	11 (7-14)
HYP2	0.39 (0.34-0.44)*	0.83 (0.79-0.88)	11.6 (10.1-13.1)	12 (10-13)
		PART 1		
NORM	1.64 (1.56-1.71)	0.90 (0.87-0.92)	37.5 (35.1-40.0)	35 (33-36)
HYP1	1.68 (1.61-1.75)	0.89 (0.87-0.92)	43.6 (41.4-45.7) †	41 (39-43) †
HYP2	1.30 (1.22-1.38)*	0.87 (0.82-0.91)	33.3 (30.9-35.6) *	32 (30-34) *
		PART 2		
NORM	1.67 ± 0.11	0.86 ± 0.05	38.1 ± 3.3	23 (21-25)
HYP1	1.72 ± 0.13	0.86 ± 0.04	44.6 ± 3.2†	27 (26-28) †

VO_2, rate of oxygen consumption; RER, respiratory exchange ratio; V_E, rate of ventilation; $C_{res} + E_{res}$, rate of respiratory heat losses via convection and evaporation. *Significantly different from HYP2 vs. NORM ($P < 0.05$). †Significantly different from HYP1 vs. NORM ($P < 0.05$).

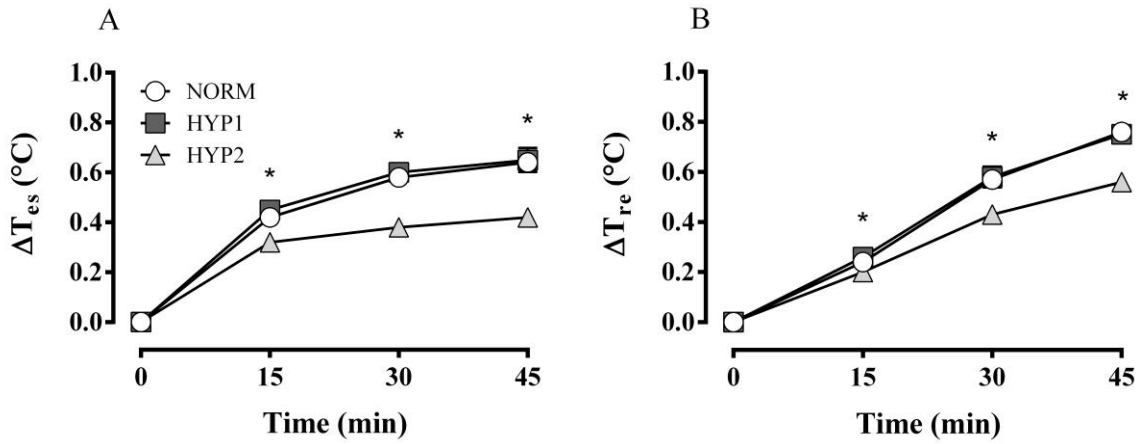

Figure 1. Changes in esophageal (A) and rectal (B) temperatures as a function of time during cycling in three trials: NORM (normoxia; 21% O_2), HYP1 (fixed H_{prod} hypoxia; 13% O_2), and HYP2 (matched $\%VO_{2peak}$ hypoxia; 13% O_2). *Significantly different HYP2 vs. NORM ($P < .05$).

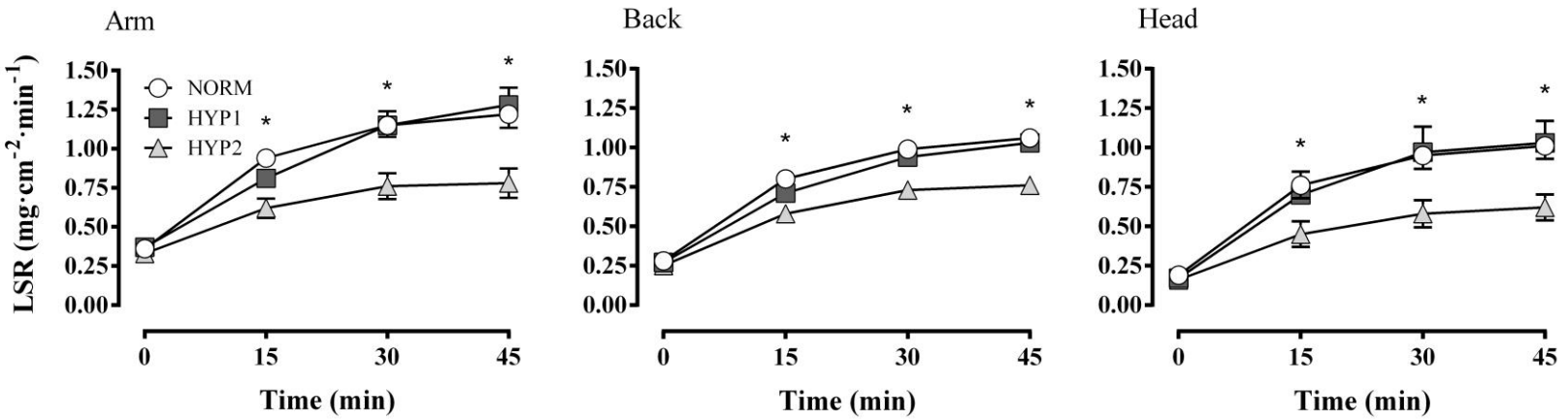

Figure 2. Local sweat rates (LSR) from the forearm, upper back, and forehead as a function of time during cycling in three trials: NORM (normoxia; 21% O_2), HYP1 (fixed H_{prod} hypoxia; 13% O_2), and HYP2 (matched $\%VO_{2peak}$ hypoxia; 13% O_2). *Significantly different HYP2 vs. NORM ($P < .05$).

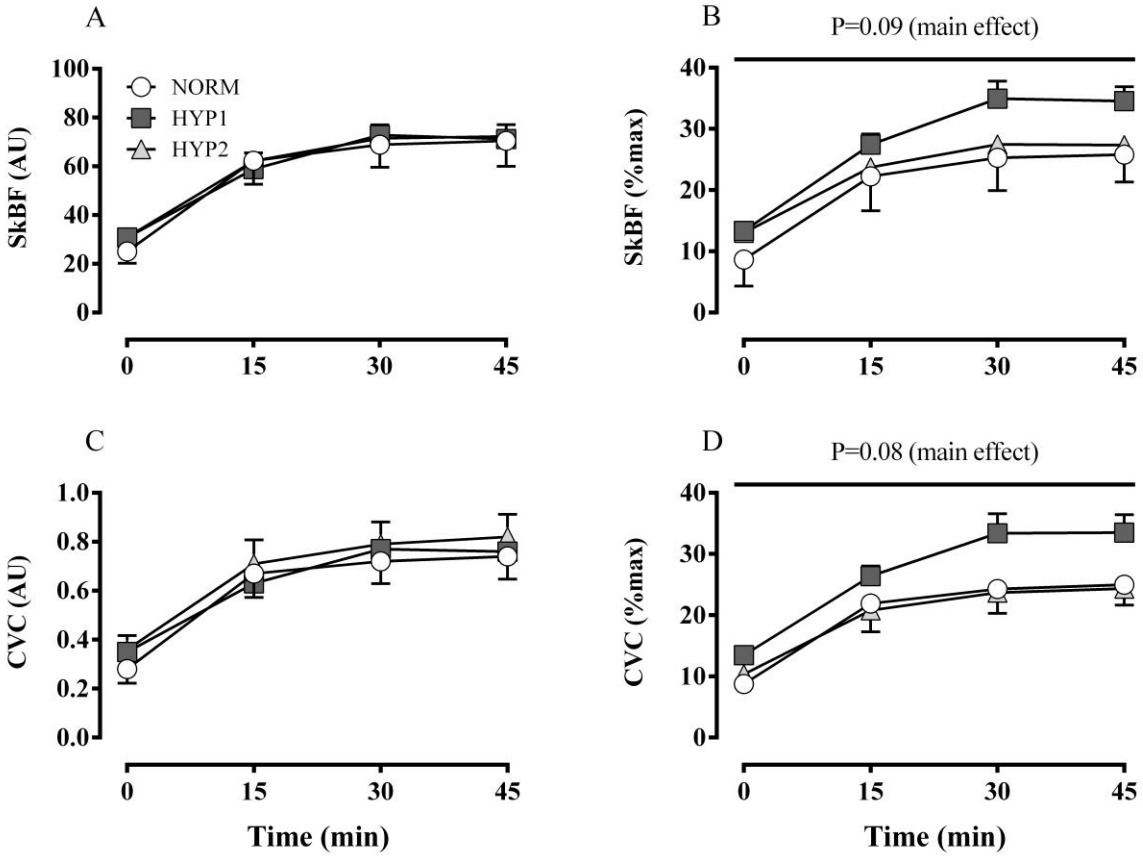

Figure 3. Mean response of skin blood flow (SkBF) and cutaneous vascular conductance (CVC) from the forearm and upper back in arbitrary units (AU; A,C) and as a percentage of maximum values (%max; B,D) as a function of time during cycling in three trials: NORM (normoxia; 21% O_2), HYP1 (fixed H_{prod} hypoxia; 13% O_2), and HYP2 (matched $\%VO_{2peak}$ hypoxia; 13% O_2).

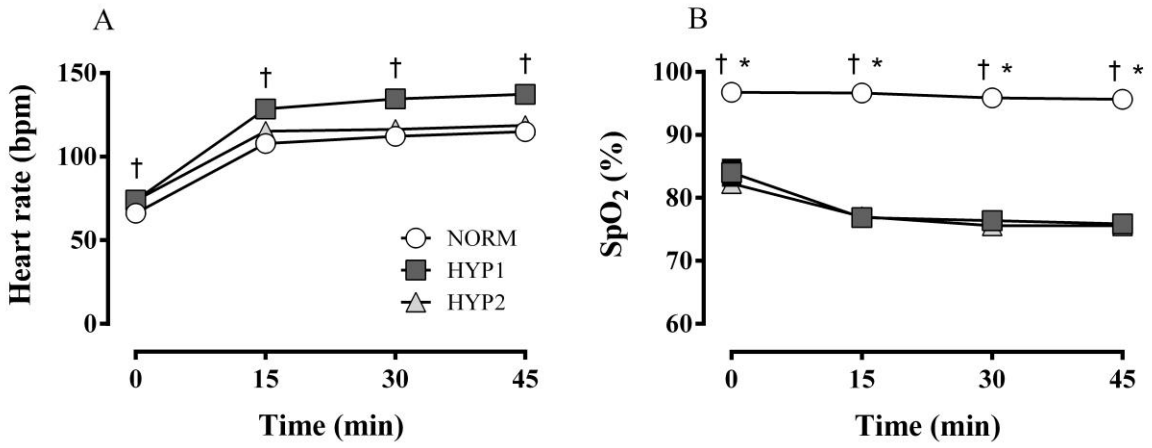

Figure 4. Heart rate (A) and oxygen-hemoglobin saturation (B) responses as a function of time during cycling in three trials: NORM (normoxia; 21% O_2), HYP1 (fixed H_{prod} hypoxia; 13% O_2), and HYP2 (matched $\%VO_{2peak}$ hypoxia; 13% O_2). *Significantly different from HYP2 vs. NORM ($P < 0.05$). †Significantly different from HYP1 vs. NORM ($P < 0.05$).

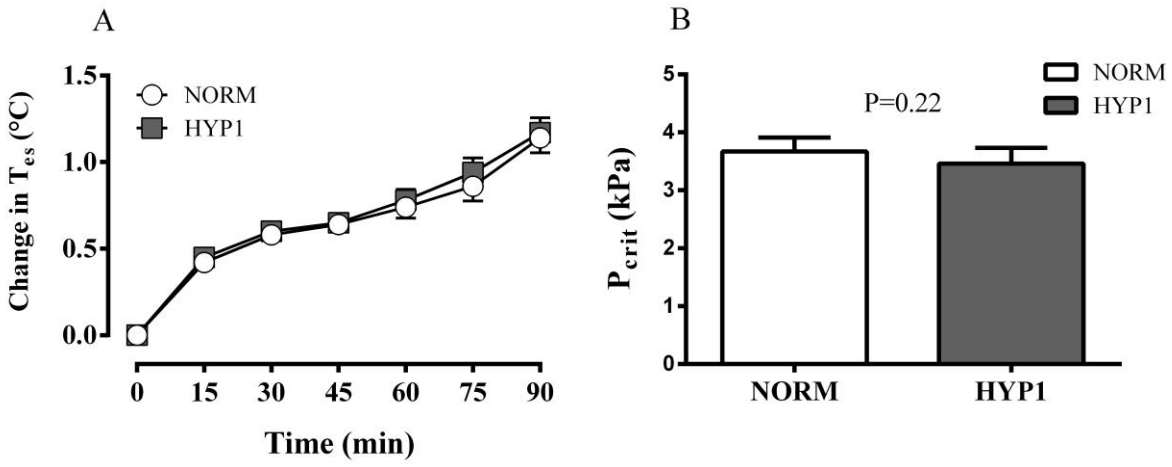

Figure 5. Changes in esophageal temperature (A) as a function of time during part 2; and the critical ambient vapour pressure (P_{crit}) for the inflection of esophageal temperature (B) between conditions of normoxia (NORM) and hypoxia (HYP1) at a fixed H_{prod}.

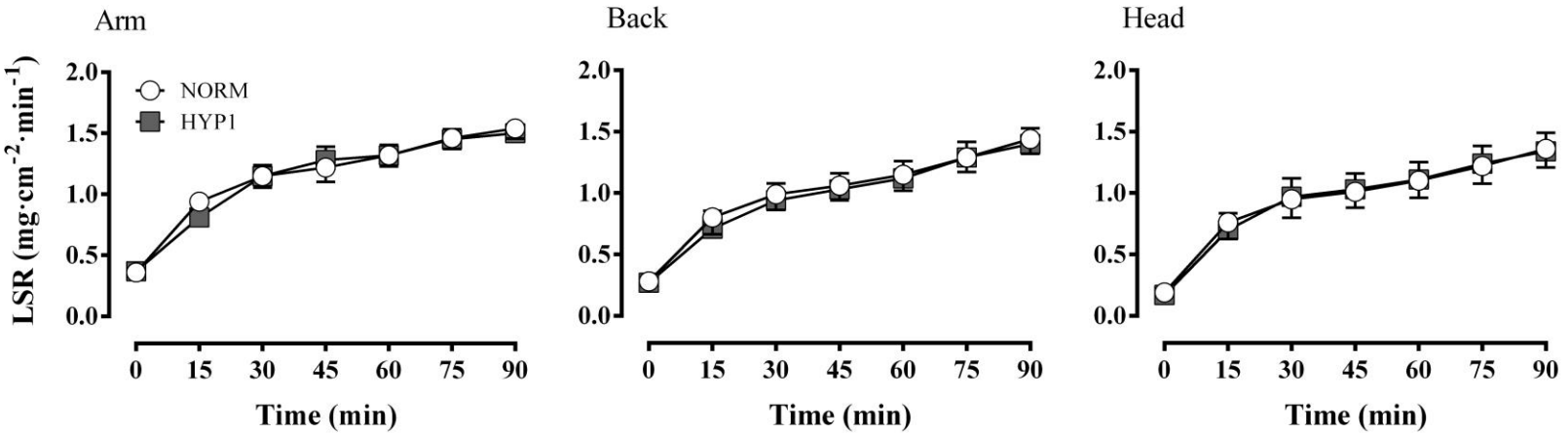

Figure 6. Local sweat rates (LSR) from the forearm, upper back, and forehead as a function of time during cycling between conditions of normoxia (NORM) and hypoxia (HYP1) at a fixed H_{prod} throughout part 2.

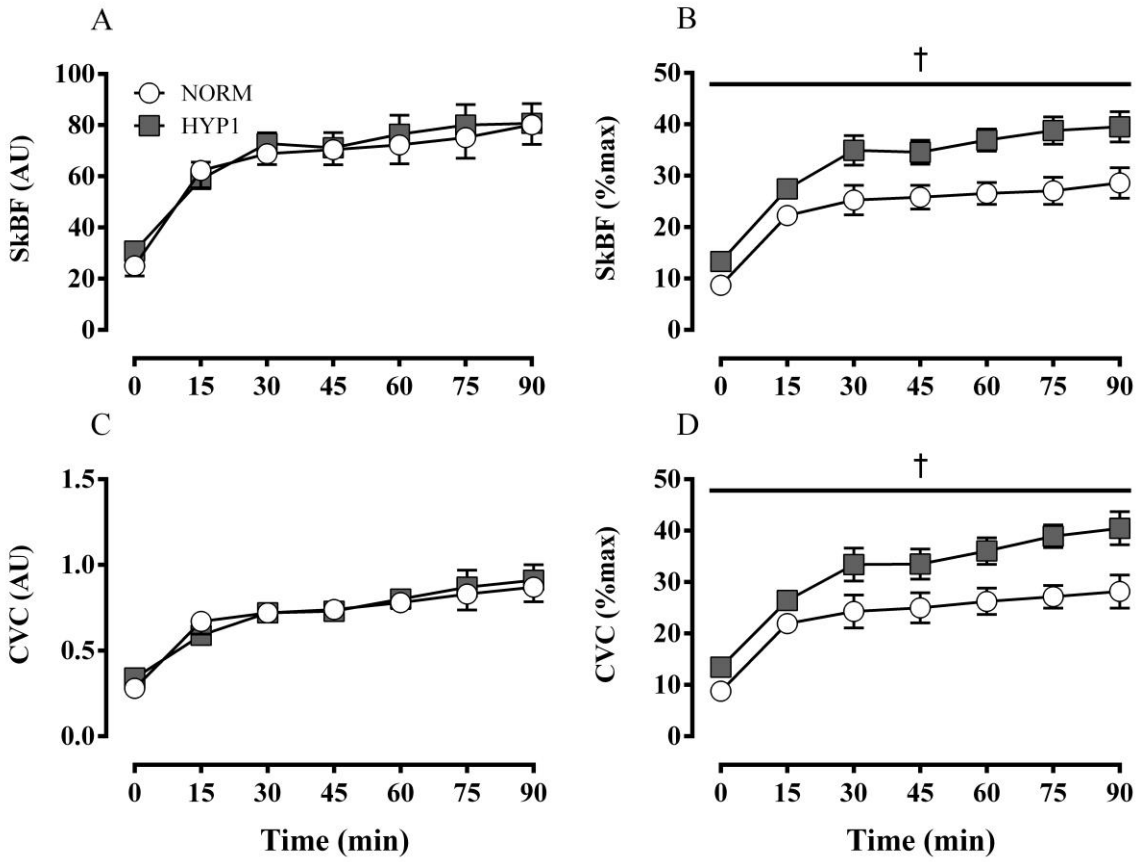

Figure 7. Mean response of skin blood flow (SkBF) and cutaneous vascular conductance (CVC) from the forearm and upper back in arbitrary units (AU; A,C) and as a percentage of maximum values (%max; B,D) as a function of time during cycling between conditions of normoxia (NORM) and hypoxia (HYP1) at a fixed H_{prod} throughout part 2. †Significant interaction NORM vs. HYP1 ($P < .05$).

CHAPTER 4: THESIS DISCUSSION

Previous works from our laboratory have elucidated the primary determinants of core temperature during exercise (10) and the appropriate method for selecting exercise intensity in between-groups experimental designs (9). These studies are supported by Part 1 of the current thesis, which used hypoxia to manipulate relative exercise intensity ($\%VO_{2peak}$) for a given rate of metabolic heat production. We concluded that heat production, irrespective of differences in $\%VO_{2peak}$, determines the changes in core temperature during exercise. While Cramer and Jay (9) demonstrated that between-groups studies of thermoregulatory responses should set exercise at a fixed H_{prod} relative to body mass, it is still generally acceptable for repeated measures experiments to set exercise according to $\%VO_{2peak}$. However, our current results suggest that caution should be taken when considering this approach for studies including factors that might affect VO_{2peak}, such as hypoxia (49), age (21), and exercise in the heat (79).

Another important finding from the current study was that hypoxia lead to significantly greater skin blood flow when exercising at the same rate of heat production, as very few studies have examined the skin blood flow response to exercise and acute hypoxia. Previously, Rowell et al. (69) demonstrated that cutaneous perfusion was not affected by hypoxia during exercise, while Kolka et al. (44) and Miyagawa et al. (54) reported attenuations of skin blood flow during exercise. Although the reason for the differences between these studies and the current study is unknown, it should be noted that the aforementioned studies quantified skin blood flow with measurements of forearm blood flow (FBF). Since muscle blood flow, which is important for estimations of FBF, increases during hypoxic exercise (5) the reliability of this measurement is questionable under these conditions. Our study measured skin blood flow using laser-Doppler

flowmetry and the results were in line with resting data from Simmons et al. (72) also measured by laser-Doppler.

Based on the maximal values of skin blood flow achieved during post-exercise local heating in our study, it could be contended that greater SkBF during HYP1 was a result of lower maximum SkBF by ~75 AU in this trial compared to NORM; however, this difference was not significant and was not consistent across all participants. Additionally, maximum SkBF following the other hypoxic trial (HYP2) was on par with the normoxic values, and it has previously been demonstrated that prolonged hypoxia increases maximum SkBF values compared to normoxia. While the duration of the exposure to hypoxia in our study was not prolonged, it would actually be expected that maximum SkBF would be higher in hypoxia not lower (47); therefore, we are confident that the differences between trials in maximum SkBF observed in our study can be attributed to day-to-day variability or some other random artifact.

Not only did our study determine the independent influence of hypoxia on skin blood flow, but it also contextualised the role of skin blood flow on heat balance. At similar levels of hypoxemia (~76% SpO_2) and thermal stress, skin blood flow did not respond similarly in both hypoxic trials (Figure 3). Rather, skin blood flow was significantly higher in HYP1 while HR (Figure 4A) and $\%VO_{2peak}$ were also higher than in NORM or HYP2. Conversely, NORM and HYP2, which were matched for $\%VO_{2peak}$, showed similar responses of HR and SkBF. Although undeniably important for supplying heat and fluid to the skin where it can be exchanged with the surrounding environment, these data apparently indicate that skin blood flow may actually be more closely associated with heart rate and relative exercise intensity than with other thermal indices such as core temperature or sweating.

Hypoxia and thermoregulation

Furthermore, we found that increases of SkBF by ~40% in hypoxia did not lead to greater maximal heat loss and as a result P_{crit} values between NORM and HYP1 were not different. This conflicts with previous studies which have suggested that impairments of SkBF due to age (52), hypertension (4), and skin grafts (12) have potentially serious implications for thermoregulatory capacity. Cramer et al. (unpublished data) also found that attenuations of skin blood flow, achieved by iso-osmotic dehydration, did not result in impairments of heat loss or earlier P_{crit} during a resting incremental humidity ramp protocol. Taken together, these data may suggest that physiologically relevant alterations of skin blood flow may not be as important for heat loss as previously thought. Therefore, future investigations should aim to determine whether skin blood flow should be considered as a thermoregulatory response, or rather a cardiovascular response.

The current thesis characterises the acute physiological responses to hypoxia in hot conditions. Therefore, future research might consider how these responses may differ under chronic exposure to hypoxia. For example, it is well noted that heart rate is acutely elevated in hypoxic environments; however, long-term adjustments might reduce heart rate to baseline levels. As such, it would be warranted to test whether hypoxia-induced elevations of skin blood flow are maintained in the absence of concomitant rises in heart rate. Moreover, investigations of hypoxia and cold exposure might discover more practical implications considering the natural occurrence of this environment. Future research questions should address the vasodilatory effect of hypoxia given the vasoconstrictor response that occurs in cold environments, as increases in skin blood flow in these conditions could exacerbate hypothermia.

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APPENDIX: Notices of ethical approval

File Number: H09-14-12 **Date (mm/dd/yyyy):** 10/16/2014

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

Ethics Approval Notice

Health Sciences and Science REB

Principal Investigator / Supervisor / Co-investigator(s) / Student(s)

First Name	Last Name	Affiliation	Role
Pascal	Imbeault	Health Sciences / Human Kinetics	Principal Investigator
Ollie	Jay	Health Sciences / Human Kinetics	Co-investigator
Geoff	Coombs	Health Sciences / Human Kinetics	Co-investigator
Nicholas	Ravanelli	Health Sciences / Human Kinetics	Co-investigator

File Number: H09-14-12

Type of Project: Professor

Title: Does an acute exposure to hypoxia alter heat dissipation during exercise in humans?

Approval Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
10/16/2014	10/15/2015	Ia

(Ia: Approval, Ib: Approval for initial stage only)

Special Conditions / Comments:
N/A

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File Number: H09-14-12 **Date (mm/dd/yyyy):** 10/16/2014

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Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
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During the course of the project, the protocol may not be modified without prior written approval from the REB except when necessary to remove participants from immediate endangerment or when the modification(s) pertain to only administrative or logistical components of the project (e.g., change of telephone number). Investigators must also promptly alert the REB of any changes which increase the risk to participant(s), any changes which considerably affect the conduct of the project, all unanticipated and harmful events that occur, and new information that may negatively affect the conduct of the project and safety of the participant(s). Modifications to the project, including consent and recruitment documentation, should be submitted to the Ethics Office for approval using the "Modification to research project" form available at: http://www.research.uottawa.ca/ethics/forms.html.

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Signature:

Protocol Officer for Ethics in Research
For Daniel Lagarec, Chair of the Health Sciences and Sciences REB

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Université d'Ottawa University of Ottawa
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Ethics Approval Notice

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Ollie	Jay	Health Sciences / Human Kinetics	Co-investigator
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File Number: H09-14-12

Type of Project: Professor

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10/16/2015	10/15/2016	Ia

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Signature:

Ethics Coordinator
For Catherine Paquet, Director of the Office of Research Ethics and Integrity

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Ethics Approval Notice

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Yannick	Plante		Assistant de recherche

File Number: H09-14-12

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