Developing an improved understanding of the biophysical and physiological determinants of steady-state sweating during exercise in the heat

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THESIS ABSTRACT

Four studies were performed to evaluate the independent influence of core temperature and heat acclimation on sweating responses when exercise is fixed for a given evaporative heat balance requirement (E_{req}) during compensable and uncompensable heat stress. By using circadian rhythm to modulate absolute core temperature, study 1 investigated whether absolute core temperature altered the steady-state sweat rate during compensable heat stress at a fixed E_{req}. Study 2 compared the influence of partial and complete heat acclimation on core temperature and sweating responses between a compensable and uncompensable heat stress condition. Study 3 quantified how maximum skin wettedness is altered with partial or complete heat acclimation. Study 4 determined whether aerobic fitness (i.e. maximum rate of oxygen consumption; VO_{2max}) per se independently alters the sweating and core temperature responses to uncompensable heat stress or if the frequent bouts of exercise-induced heat stress that accompany aerobic training are required to augment thermoregulatory capacity. Study 1 demonstrated that when absolute core temperature is different between AM and PM by ~0.2°C, steady-state sweat rates were the same for a fixed E_{req}. Only when a different level of E_{req} was attained, were differences in steady-state sweating observed. Moreover, steady-state sweat rates were similar despite differences in skin and core temperature when exercise intensity was matched to elicit a fixed E_{req} in two different ambient temperatures (23°C and 33°C). In study 2, neither partial nor complete heat acclimation altered the core temperature response to compensable heat stress despite a marginally greater sweat rate compared to an unacclimated state. However, the sudomotor adaptations associated with heat acclimation were evident during uncompensable heat stress and mitigated the rise in core temperature during 60 minutes of exercise compared to an unacclimated state. Study 3 determined that the biophysical parameter that defines the upper limit for evaporative heat loss, that is the maximum skin

wettedness achievable, increased following partial (0.84±0.08) and complete heat acclimation (0.95±0.05) compared to unacclimated (0.72±0.06) which directly explains the reduced change in core temperature reported in study 2 during uncompensable heat stress. Lastly, study 4 demonstrated that VO_{2max} per se does not alter the sudomotor responses to uncompensable heat stress. Rather, it is the repetitive exercise-induced heat stress experienced during aerobic training that induces a partial heat acclimation thereby mitigating the rise in core temperature during uncompensable heat stress. Taken together, when exercise is prescribed in a compensable environment, the steady-state sweat rate observed will be primarily determined by E_{req} independent of absolute core temperature, while heat acclimation will slightly increase the sweat rate despite providing no additional reduction in the change in core temperature. However, progressive heat acclimation increases the upper limit of compensability via a greater maximum skin wettedness thereby mitigating the rise in core temperature during uncompensable heat stress.

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PREFACE

The work presented in this thesis is my own, and I take full responsibility for the content. All thesis chapters were co-authored by Dr. Ollie Jay and Dr. Pascal Imbeault, and study 2 and study 2 were co-authored by Geoff Coombs. Study 3 was published in *Medicine & Science in Sports & Exercise*. At present, Study 2 has been offered a *de novo* submission following an initial round of the peer-review process to the *Journal of Applied Physiology*. Ethical approval was received for all studies from the University of Ottawa Health Sciences and Research Ethics Board and are included in Appendix A. The final accepted version of Study 3 can be found in Appendix B.

Furthermore, 8 non-thesis works have been included in the present thesis that were published during my graduate studies; (i) evidence to support the use of electric fans during heat waves in the *Journal of the American Medical Association* (Appendix C), (ii) our work evaluating the effects of acute acetaminophen ingestion on core temperature and sweating responses to exercise in the heat in the *Scandinavian Journal of Medicine & Science in Sports* (Appendix D), (iii) an invited discovery article discussing the benefits of fan use during extreme heat events in *Temperature* (Appendix E), (iv) an experimental study investigating the effects of hypoxia on heat loss responses during exercise in the *Journal of Applied Physiology* (Appendix F), (v) the independent effect of body morphology on the thermoregulatory responses to uncompensable heat stress in *Physiological Reports* (Appendix G), (vi) an evidence surrounding the possible relationship between sweating and skin blood flow during heat stress in the *American Journal of Physiology Regulatory, Integrative and Comparative Physiology* (Appendix H), (vii) the biophysical rationale to support the improved heat dissipation with a fan during high heat and humidity in the *International Journal of Biometeorology* (Appendix I), and (viii) our commentary

on the improbability that sweating can serve as a potential alterative to secrete persistent organic pollutants in *Environmental International* (Appendix J).

Permission was not required for republication of articles in a thesis for those published in the *Journal of Applied Physiology*, *Physiological Reports,* the *American Journal of Physiology Regulatory, Integrative and Comparative Physiology*, *Temperature*, *Environmental International*, and *Medicine and Science in Sports & Exercise* (See Appendix L). Republication permission was required for articles published in *Scandinavian Journal of Medicine & Science in Sports*, *Journal of the American Medical Association*, and the *International Journal of Biometeorology*.

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LIST OF ABBREVIATIONS AND SYMBOLS

Term	Description	Units
ADP	Adenosine diphosphate	[–]
A_r/A_D	Effective radiative area of the body	[ND]
ASGD	Activated sweat gland density	[glands·cm^{-2}]
ATP	Adenosine triphosphate	[–]
BSA	Body surface area	[m^2]
C	Rate of convective heat transfer	[W]
C_p	Specific heat capacity of the tissue	[kJ·kg^{-1}·^{o}C^{-1}]
C_{res}	Convective heat transfer of the respiratory tract	[W]
C_{sk}	Rate of convective heat transfer on the skin surface	[W]
E	Rate of evaporative heat transfer	[W]
e_c	Caloric equilvalent of carbohydrate	[kJ/L O_2]
e_f	Caloric equivalent of lipids	[kJ/L O_2]
E_{ff}	Evaporative efficiency	[%]
E_{max}	Maximum evaporative potential	[W, W/m^2]
E_{req}	Evaporative requirements for heat balance	[W, W/m^2]
E_{res}	Evaporative heat loss from the respiratory tract	[W]
E_{sk}	Evaporative heat loss from the skin surface	[W]
F	Fit	[–]
f_{cl}	Clothing area factor	[ND]
h	Heat transfer coefficient	[W·m^{-2}·K^{-1}]
h_c	Convective heat transfer coefficient	[W·m^{-2}·K^{-1}]
h_e	Evaporative heat transfer coefficient	[W·m^{-2}·kPa^{-1}]
HIIT	High intensity interval training	[–]
H_{prod}	Heat production	[W, W/m^2, W/kg]
h_r	Radiative heat transfer coefficient	[W·m^{-2}·K^{-1}]
HR_{max}	Max heart rate	[BPM]
HRR	Heart rate reserve	[%]
K	Rate of conductive heat transfer	[W]
k	Estimated thermal conductivity	[W·m^{-1}·K^{-1}]
K_{sk}	Rate of conductive heat transfer on the skin surface	[W]
LSR	Local sweat rate	[mg·cm^{-2}·min^{-1}]
M	Metabolic rate	[W]

P_a	Ambient water vapor pressure	[kPa]
P_{crit}	Critical vapour pressure limit to compensability	[kPa]
POA	Pre-optic area of the hypothalamus	[–]
POST-HA	Post heat acclimation (full heat acclimation)	[–]
POST-TRN	Post-training (partial heat acclimation)	[–]
PRE-TRN	Pre-training (unacclimated)	[–]
P_{sk}	Partial pressure of water vapour at the skin surface	[kPa]
$P_{sk,sat}$	Saturated water vapor pressure at skin temperature	[kPa]
R	Rate of radiative heat transfer	[W]
$R_{e,cl}$	Evaporative heat transfer resistance of clothing	[$m^2 \cdot kPa \cdot W^{-1}$]
R_{es}	Respiratory heat loss	[W]
RH	Relative humidity	[RH]
R_{sk}	Rate of radiative heat transfer on the skin surface	[W]
S	Heat storage	[W]
SGO	Sweat gland output	[$\mu g \cdot gland \cdot min^{-1}$]
T	Trained	[–]
T_a	Ambient temperature	[ºC]
T_b	Body temperature	[ºC]
T_{core}	Core temperature	[ºC]
T_{es}	Esophageal temperature	[ºC]
T_g	Black globe temperature	[ºC]
T_o	Operative temperature	[ºC]
T_r	Radiant temperature	[ºC]
T_{re}	Rectal temperature	[ºC]
TRP	Transient receptor potential	[–]
T_{sk}	Skin temperature	[ºC]
UF	Unfit	[–]
USG	Urine specific gravity	[ND]
UT	Untrained	[–]
v	Air velocity	[m/s]
VO_{2max}	Maximum rate of oxygen consumption	[ml/kg/min, L/min]
VO_{2peak}	Peak rate of oxygen consumption	[ml/kg/min, L/min]
W	External workload	[W]
WBSL	Whole-body sweat loss	[g, L]
WBSR	Whole-body sweat rate	[g/min, L/h]

Greek Symbols and their respective definitions

Term	Description	Units
Δ	Change from a reference point	[–]
σ	Stefan-Boltzmann constant	[$W \cdot m^{-2} \cdot K^{-4}$]
ω	Skin wettedness	[ND]
ω_{req}	Required skin wettedness for heat balance	[ND]
ω_{max}	Maximum skin wettedness	[ND]

CHAPTER 1: INTRODUCTION

It has been a longstanding notion that the steady-state sweat rate achieved during exercise is the result of attaining a given skin and core temperature (20, 130, 131, 136, 180), and can be independently modulated by an individual's aerobic training (69, 143, 147) and heat acclimation status (5, 109, 124, 146). However, recent evidence has proposed that the steady-state sweat rate observed during exercise is proportional to the evaporative requirements for heat balance (E_{req}) independent of aerobic fitness (99, 176).

By definition, E_{req} is the net difference between the heat energy generated by the body that is not transferred to mechanical work or biological processes, and the heat liberated via the dry heat transfer avenues of radiation, conduction, and convection. If clothing and climate enables 100% sweating efficiency (i.e. complete sweat evaporation) then manipulations of E_{req} via modulations of exercise intensity and ambient temperature will result in proportional changes in sweating (65). As such, it can be proposed that steady-state sweat rates are determined by E_{req} and not absolute core or skin temperature during compensable heat stress. Thus one aim of the present thesis is to compare steady-state sweat rate responses at a fixed E_{req} but in the presence of different absolute core temperatures using a circadian rhythm experimental model that alters absolute core temperature throughout different times of the day (10, 107).

Under conditions permitting the total evaporation of sweat from the skin, it has been shown that there is no difference in sweat losses between people unmatched for aerobic capacity when exercise is matched for E_{req} (99). During passive heat stress, a reduction in sweating efficiency (the ratio of sweat evaporated from the body and total sweat produced) occurs when the E_{req} exceeds 55% of the maximal evaporative (E_{max}) potential of the environment (41). During upright cycling in a hot and humid environment, reductions in sweating efficiency have been reported to

occur at a lower E_{max} (~30%) (4). Moreover, the reduction in sweating efficiency becomes greater as E_{req}/E_{max} ratio approached 1.00. A maximal skin wettedness (ω_{max}, complete skin surface coverage; 100%) can only be attained by heat acclimation and the literature suggests skin surface area sweat saturation is ~15% lower pre-acclimation (41). Contextually, having a higher ω_{max} will enable a greater maximum evaporative heat loss and extend the physiological compensability of a given activity/clothing combination to a hotter and/or more humid environment. However, this increase in ω_{max} has only been shown during passive heat acclimation (41) and not as a consequence of aerobic training. Pandolf (143) suggested little difference between the physiological adaptations of heat acclimation and aerobic training. Specifically, higher sweat rates have been observed in trained males using both heat stress (69, 147) and pharmacological (110) interventions, however whether this additional sweat secretion directly leads to greater evaporation or simply drips off the body is unknown. To our knowledge, no research thus far has attempted to assess whether the greater maximum sweat rates with training and heat acclimation may allow for improved sweat distribution and ultimately facilitate a greater ω_{max}, which is another aim of the present thesis.

While the benefits of a greater ω_{max} attained through a graded heat acclimation may be most evident during heat stress which challenges the upper limits of heat dissipation, it remains unclear whether these physiological adaptations will provide a greater evaporative heat loss and a smaller rise in core temperature during heat stress where E_{req} can be achieved (e.g. compensable heat stress). During compensable heat stress, heat production can be counterbalanced completely through sweat evaporation, thus it would seem unlikely that heat acclimation, either partial or complete, would alter the steady-state sweat rate response to compensable heat stress unless evaporative efficiency was lower with acclimation. The majority of studies (5, 13, 45, 59, 88, 89,

135, 156) evaluating the sudomotor adaptations to heat acclimation have employed an uncompensable heat stress prior to heat acclimation that often becomes compensable following the intervention due to the greater ω_{max}, thus contributing to the consistent conclusion in the literature that heat acclimation reduces the core temperature response to heat stress due to greater evaporation from the skin surface. In fact, no study to date has assessed the thermoregulatory responses to *compensable* heat stress before and after heat acclimation.

Lastly, it has been suggested that individuals with a high maximal absolute or relative rate of oxygen consumption, have a greater capacity for sweat production and therefore heat dissipation (particularly via evaporation) (77, 94, 128, 161). Indeed, an inverse relationship has been reported between aerobic capacity and the time required for the acquisition of complete heat acclimation suggesting that a progressively greater aerobic fitness induces partial heat acclimation (142). However, the acquisition of a high aerobic capacity may be secondary to aerobic training, or a host of other non-modifiable factors including, but not limited to, genetics (27, 104). As such, it remains unclear whether aerobic fitness per se (i.e. VO_{2max}) independently alters the upper limit for physiological compensability or if the augmented thermoregulatory responses previously observed in uncompensable environments (43, 167) with aerobic training are due to a partial acclimation occurring secondary to frequent bouts of exercise-induced heat stress with regular aerobic training.

1.1 Rationale and statement of the problem

Traditionally, it has been thought that the observed steady-state sweat rate during exercise in a compensable environment is determined by absolute core and skin temperatures (20, 130, 131, 136, 180). However, more recent evidence has demonstrated that steady-state sweat rate is determined by $E_{req;}$ in a compensable environment - a physical variable which is unaffected by core temperature; and sweating may be increased until heat balance is achieved - integrated

centrally as the absence of a rate of change in core and/or skin temperature. In support, studies manipulating skin temperature have observed interruptions in sweat secretion following rapid changes in skin temperature (17, 108, 117, 118, 199) or rhythmic warming and cooling of the skin (112). Most notably, Kondo et al. (105) reported temporary delays in sweat secretion occurred simultaneously to an absence of change in skin temperature suggesting the liberation of heat via evaporation of sweat from the skin surface independently acted as an afferent feedback signal.

In addition to the potential influence of absolute core temperature on steady-state sweat rates, both acclimation and training, or a combination of both, may modify the sweating response via an earlier sweating onset, increased sensitivity, and increased glandular capacity. These physiological modifications may give an advantage to such individuals when under heat stress via an increased maximum skin wettedness which will expand the prescriptive zone and consequently reduce the risk of heat illness. However, to date, the current state of knowledge has yet to quantify the physiological modification of ω_{max}, if any, between untrained and trained subjects through a longitudinal design. Moreover, it remains unclear whether aerobic fitness, in the absence of training, predisposes an individual to present with partial heat acclimation characteristics.

Thus, the studies presented in this thesis were designed to i) examine if the local and whole-body sweating response to heat stress are modulated at a fixed E_{req} by differences in core temperature induced by using a circadian rhythm experimental model, ii) identify whether aerobic training can independently alter ω_{max} and if it is equal to values attained following heat acclimation (i.e. 1.00), iii) evaluate whether partial or complete heat acclimation alters the sweating and core temperature response to compensable as well as uncompensable heat stress, and iv) to determine if a greater aerobic fitness, in the absence of training, independently alters the thermoregulatory responses to an uncompensable environment.

1.2 Objectives

The studies presented in the following thesis aim to address these primary research questions:

Study 1:

1. Does E_{req} independently determine steady-state sweat rates in the presence of a different absolute core and/or skin temperature?

Study 2:

2. Are the sweating and core temperature adaptations associated with heat acclimation evident in a compensable environment, or only in an uncompensable environment?

Study 3:

3. Do changes in maximal aerobic capacity through physical training independently alter ω_{max}?
4. Can these differences in ω_{max} with training be modified further with heat acclimation?

Study 4:

5. Does a higher aerobic fitness or frequent physical training, which potentiates partial heat acclimation secondary to repeated heat stress associated with exercise, explain the altered core temperature and sweating responses to uncompensable environments?

1.3 Hypotheses

It is hypothesized that:

Study 1:

1. Steady-state sweat rate during compensable heat stress is similar at a fixed E_{req} even with differences in absolute core temperature.

Study 2:

2. The change in core temperature and the sweating response to compensable heat stress will be similar irrespective of acclimation status, however partial and/or complete heat acclimation will reduce the rise in core temperature and increase sweat rate during uncompensable heat stress.

Study 3:

3. An increase in maximal aerobic capacity following a period of aerobic training will significantly increase ω_{max} compared to pre-training values due to a greater sweat coverage secondary to peripheral modifications.
4. ω_{max} following 10 days of heat acclimation after an aerobic training regime will result in a significantly greater ω_{max} than following aerobic training.

Study 4:

5. A higher aerobic fitness per se does not alter the sweating and core temperature response in an uncompensable environment. Rather, the partial heat acclimation associated with frequent training, which can result in a higher aerobic fitness, does alter the core temperature and sweating responses to uncompensable environments.

1.4 Implications

The studies within this thesis will provide greater understanding of physiological factors that determine the sweating and core temperature response during exercise in compensable and uncompensable environments. The findings from these studies will directly impact heat stress policies for occupational settings and athletic competition by providing empirical evidence to promote the health and safety of personnel during the two means of heat stress (e.g. compensable and uncompensable). Moreover, the importance of aerobic training in comparison to a higher aerobic fitness on sweating responses may help to promote regular and frequent exercise practices in working

populations who experience periods of uncompensable heat stress (e.g. miners, firefighters). Lastly, examining the sweating response to different absolute core temperatures for a fixed E_{req} may improve the current understanding of thermoregulatory responses in compensable conditions and provide clear evidence to support the unbiased comparisons of steady-state sweating responses between individuals by fixing heat stress to elicit a given E_{req} and not the attaining of an absolute core temperature.

1.5 Limitations and delimitations

The application of these findings will be limited to healthy males and females, aged 18-39 with VO_{2max} values ranging from ~35 to 70 $ml \cdot kg^{-1} \cdot min^{-1}$, body mass between 60 to 100 kg, and a body surface area (BSA) with 1.6 to 2.4 m^2. As such, these findings cannot be extrapolated to children or middle-aged to elderly adults, or individuals with impaired thermoregulatory function.

CHAPTER 2: Literature Review

Sections of this literature review have been accepted for publication as a chapter in the book entitled "Heat Stress in Sport and Exercise: Thermophysiology of Health and Performance" expected for release on February 19th, 2019 by Editor Dr. Julien Periard and the Publishing company Springer. The final accepted version can be found in Appendix K.

2.1 Conceptual Heat Balance

The ability to maintain body temperature within a narrow range during acute or chronic exposure to environmental extremes is paramount for optimal human performance, and ultimately, survival. Changes in body temperature during exercise, and heat or cold exposure are managed by physiologically modulating heat exchange between the skin surface and the surrounding environment via sensible (convection (C), radiation (R), and conduction (K)), and insensible (evaporation (E)) heat transfer.

The fundamental law of human heat balance illustrates that internal metabolic heat production (M-W) must be balanced by an equal rate of net heat dissipation, i.e. combined sensible and insensible heat losses from the skin and respiratory tract to the surrounding environment to ensure a rate of body storage (S) of zero (i.e. heat balance):

$$(M - W) = (\pm K_{sk} \pm C_{sk} \pm R_{sk}) + (C_{res} + E_{res}) + E_{sk} \pm S \qquad [\text{in W}\cdot\text{m}^{-2}] \qquad (1)$$

Metabolic Heat Production (M-W): is the difference between metabolic rate (M) and the external work performed (W). In its most basic form, M is the amount of energy released by hydrolyzing adenosine triphosphate (ATP) into adenosine diphosphate (ADP) and an inorganic phosphate molecule. It follows that a proportion of the energy released from this process is then utilized to create W, however the human body is quite inefficient and usually about 75-95% of M does not ultimately contribute to W but instead is liberated internally as heat. Road cycling, which is one

of the most efficient sporting activities (~30% of M is used for W (194)), so at an external work load of 240 W a metabolic rate of approximately 840 W is required, with ~600 W of this energy released as heat (Figure 1). Running or walking is one of the least efficient activities especially on a flat surface when effectively no external work is performed and all metabolic energy is converted to heat. Carbohydrates and lipids are the two main substrates utilized by the body to produce ATP, and although ATP can be produced both anaerobically and aerobically within a cell, oxygen consumption is required to restore ATP pools. Thus, M can be estimated (138) by measuring the rate of oxygen consumption and carbon dioxide production using:

$$M = VO_2 \cdot \frac{\left[\left(\left(\frac{RER-0.7}{0.3}\right)\cdot e_c\right)+\left(\left(\frac{1.0-RER}{0.3}\right)\cdot e_f\right)\right]}{60} \cdot 1000 \qquad \text{[in W]} \qquad (2)$$

Where: VO_2 is the rate of oxygen consumption in $L \cdot min^{-1}$, RER is the ratio of carbon dioxide production to oxygen consumption, e_c is the caloric equivalent per liter of oxygen for the oxidation of carbohydrates (21.13 kJ), and e_f is the caloric equivalent per liter of oxygen for the oxidation of lipids (19.62 kJ). To collectively express *M*-*W* in $W \cdot m^{-2}$ it must be divided by the body surface area (BSA) of the individual using the Dubois and Dubois equation (56):

$$BSA = 0.202 \times \text{mass}^{0.425} \times \text{height}^{0.725} \qquad \text{[in m}^2\text{]} \qquad (3)$$

Where: mass of the person is in kg, and the height of the person in m.

Sensible Heat Transfer from the Skin (± K_{sk} ± C_{sk} ± R_{sk}): is the sum of conduction (K_{sk}), convection (C_{sk}), and radiation (R_{sk}). These three avenues of heat transfer abide by the second law of thermodynamics whereby heat energy moves from an area of high concentration to low concentration (e.g. from high to low temperature). During active or passive heat stress, the prevailing temperature gradients for sensible heat transfer may be minimal or even negative, which

leads to sensible heat gain through one or more avenues at ambient temperatures above skin temperature (i.e. 35 to 36°C) (Figure 1).

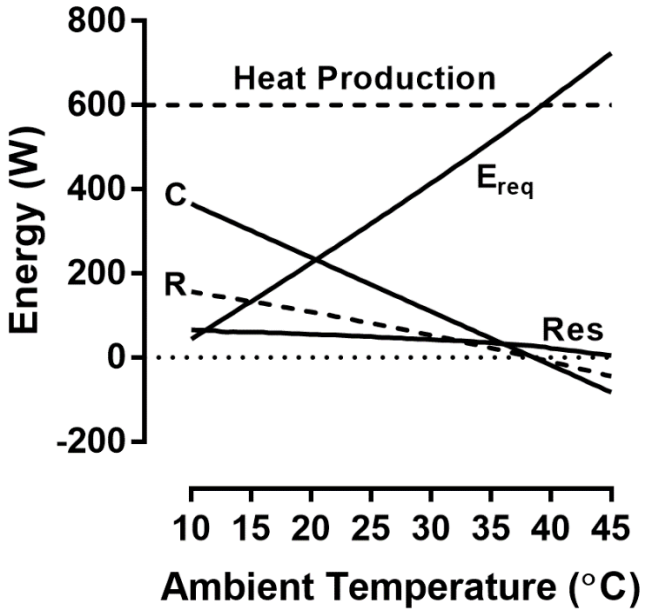

Figure 1 An example of partitional heat exchange for an exercising individual on an upright ergometer across an air temperature range of 10 – 45°C. $\mathbf{E_{req}}$ evaporative requirements for heat balance; **C** conduction; **R** radiation; $\mathbf{R_{es}}$ respiratory heat loss.

Conduction (K_{sk}): is the transfer of heat energy through direct contact between the skin and a solid object. From a whole-body heat balance perspective, particularly human heat stress conditions, K is generally assumed to be negligible, with the primary means for sensible heat transfer via convection and radiation. However, when a solid object is in direct contact with the skin (e.g. a cold metallic wall), conductive heat transfer can be calculated as:

$$K = kA\,(T_2 - T_1)/L \qquad [\text{in } W \cdot m^{-2}] \qquad (4)$$

Where: *k* is the estimated thermal conductivity of the object in contact with the skin, A is the total surface area of contact between the skin and solid (in m^2), (T_2-T_1) is the absolute temperature

difference between the skin and the solid's external surface, and L is the thickness of the solid object in contact with the skin surface.

Radiation (R_{sk}): Heat exchange by radiation is the electromagnetic energy transfer between a relatively cool and warm body. Radiative heat loss from the skin for a nude person can be derived using:

$$R_{sk} = h_r\,(T_{sk} - T_r) \qquad [\text{in } W\cdot m^{-2}] \qquad (5)$$

Where: T_{sk} is mean skin temperature (in °C), T_r is mean radiant temperature (in °C), and h_r is the radiative heat transfer coefficient (in $W\cdot m^{-2}\cdot K^{-1}$), which is estimated using:

$$h_r = 4\varepsilon\sigma \frac{A_r}{A_D}\left[273.2 + \frac{T_{sk} + T_r}{2}\right]^3 \qquad [\text{in } W\cdot m^{-2}\cdot K^{-1}] \qquad (6)$$

Where: ε is the emissivity of the body surface (usually assumed to be 0.95), σ is the Stefan-Boltzmann constant ($5.67\text{x}10^{-8}$ $W\cdot m^{-2}\cdot K^{-4}$), A_r/A_D is the effective radiative area of the body (m^2) which can be estimated as 0.70 or 0.73 for a seated or standing person (57), respectively, and $T_{sk} + T_r$ is the sum of mean skin temperature and mean radiant temperature. Mean radiant temperature is assumed to be equal to ambient air temperature when indoors without any substantial sources of radiation. However, in other environments, e.g. outdoor sun exposure, mean radiant temperature of the environment must be estimated using black globe temperature (T_g) measured with a standard 150 mm diameter black globe thermometer placed in a similar location as the exposed individual (e.g. in direct sunlight). T_g will vary depending on the time of day and year due to differences in the angle between the sun and the horizon. However, when interested in calculating radiative heat transfer for an individual wearing clothing, a black globe thermometer may overestimate the effect of a radiative source (particularly the sun) and should therefore be similar in color to the clothing worn by the individual. Lastly, air velocity (*v*) in m/s near the black globe thermometer must be

measured as greater airflow will alter T_g for a given amount of radiant heat energy. According to ISO 7726:1998 (97) mean radiant temperature (T_r) can be derived as follows:

If v < 0.15 m/s:

$$T_r = [(T_g + 273)^4 + \frac{0.25 \cdot 10^8}{\varepsilon} \cdot \left[\frac{T_g + T_a}{d}\right]^{0.25} \cdot (T_g - T_a)\ ]^{0.25} - 273 \qquad [\text{in °C}] \qquad (7)$$

If v ≥ 0.15 m/s:

$$T_r = [(T_g + 273)^4 + \frac{1.1 \cdot 10^8 v^{0.6}}{0.44} \cdot (T_g - T_a)\ ]^{0.25} - 273 \qquad [\text{in °C}] \qquad (8)$$

Convection (C_{sk}): is the transfer of heat promoted by typical air movement. It is directly proportional to the temperature difference between the skin surface and the ambient environment, and air velocity passing across the skin. A warm surface such as the skin can also produce natural convection when a person is still, where the boundary layer movement is a result of differing air density arising from a temperature gradient (e.g. warm air rises). Alternatively, and more commonly, forced convection pushes air across the skin surface (e.g. a fan) or convection is self-generated as a person moves through an air mass. Convective heat transfer for a nude person can be estimated using (144):

$$C_{sk} = h_c\,(T_{sk} - T_a) \qquad [\text{in W}\cdot\text{m}^{-2}] \qquad (9)$$

Where: T_{sk} is mean skin temperature (˚C); T_a is ambient air temperature (˚C); and h_c is the convective heat transfer coefficient (in $W\cdot m^{-2}\cdot K^{-1}$). For natural convection in still conditions, this value can be assumed to be 3.1 $W\cdot m^{-2}\cdot K^{-1}$ (123). If air velocity is >0.2 m/s, but <4.0 m/s, the convective heat transfer coefficient can be estimated using:

$$h_c = 8.3v^{0.6} \qquad [\text{in W}\cdot\text{m}^{-2}\cdot\text{K}^{-1}] \qquad (10)$$

Where: *v* is the mean air velocity around the body in m/s. During physical activity, it may be more practical to consider the mean relative air flow across the body surface rather than the mean

ambient air velocity. Moreover, the magnitude of self-generated airflow can influence the convective heat transfer coefficient. For example, independent of clothing and equipment, position-specific rates of locomotion alter the self-generated air flow, and consequently probably the level of heat strain, experienced by American Football players (53, 73). Alternatively, self-generated convection during outdoor cycling (>20 km/h) will in most cases be far greater than in most laboratory settings (52). As such, specific equations have been derived for estimating the convective heat transfer coefficient during different modalities of human movement (Table 1).

Table 1. Estimations of the convective heat transfer coefficient (h_c) for common modalities of exercise.

Exercise Modality	**Equation/ Constant h_c ($W \cdot m^{-2} \cdot K^{-1}$)**	**Comments**
Stationary cycle ergometer (50 RPM)	5.4	Ambient air flow <0.2 m/s (139)
stationary cycle ergometer (60 RPM)	6.0	Ambient air flow <0.2 m/s (139)
Outdoor cycling	$h_c = 8.4 v_{speed}^{0.84}$	v_{speed}: cycling velocity (m/s) (52)
Walking/Running	$h_c = 8.3 v_{loc}^{0.531}$	v_{loc}: speed of locomotion (m/s) (139)
Treadmill exercise	$h_c = 8.3 v_{loc}^{0.391}$	v_{loc}: speed of locomotion (m/s) (139)

All convective heat transfer coefficients presented have been developed for thermal stress at approximately sea level. The relationship between barometric pressure (P_b) and convective heat transfer can be integrated into equation 9 as follows (64):

$$C_{sk} = h_c (T_{sk} - T_a) (P_b/760)^{0.55} \quad [\text{in } W \cdot m^{-2}] \quad (11)$$

If clothing is worn, combined sensible heat transfer via convection and radiation ($C_{sk} + R_{sk}$) can be estimated using:

$$C_{sk} + R_{sk} = \frac{(T_{sk} - T_o)}{\left(R_{cl} + \frac{1}{h \cdot f_{cl}}\right)} \quad [\text{in W}\cdot\text{m}^{-2}] \quad (12)$$

Where: T_o is operative temperature (in °C):

$$T_o = \frac{(h_r T_r + h_c T_a)}{(h_r + h_c)} \quad [\text{in °C}] \quad (13)$$

And: h is the combined heat transfer coefficient (in $W\cdot m^{-2}\cdot K^{-1}$), i.e. $h_c + h_r$; and f_{cl} is the clothing area factor defined as the surface area of the clothed body divided by the surface area of the nude body and estimated using (119):

$$f_{cl} = 1 + \left[\frac{0.31 \cdot R_{cl}}{0.155}\right] \quad [\text{ND}] \quad (14)$$

Where: R_{cl} is the dry heat transfer resistance of clothing (in $m^2\cdot°C^{-1}\cdot W^{-1}$), which can be obtained from normative tables (95, 119) such as the International Standardisation Organisation (ISO) 9920 standard.

Respiratory Heat Exchange (C_{res} + E_{res}): Respiratory heat exchange occurs through the convective heat transfer (C_{res}) between inhaled air and the lungs, and evaporative heat loss from the respiratory tract (E_{res}) due to the saturation of air with water vapour when entering the lungs. Net respiratory heat exchange can be estimated using (11):

$$C_{res} + E_{res} = [0.0014M \bullet (34 - T_a)] + [0.0173M \bullet (5.87 - P_a)] \quad [\text{in W}\cdot\text{m}^{-2}] \quad (15)$$

Where: M is metabolic heat production in $W\cdot m^{-2}$, T_a is air temperature in °C, and P_a is the ambient water vapor pressure in kPa.

The rate of respiratory heat loss is dependent on the temperature and humidity of inspired air (120, 183) and minute ventilation (29, 126). As such, the amount convective heat transfer through respiration during exercise in the heat compared to the cold is minimal due to the small temperature gradient between ambient and core temperature. Additionally, the amount of evaporative heat loss

via respiration is dependent on the humidity gradient between the lungs and the air, and the rate of ventilation which is assumed to have a linear relationship with the rate of metabolic energy expenditure (up to 80% of maximum oxygen consumption; (126)).

Evaporation from skin surface (E_{sk}): The evaporation of sweat (or water) from the skin surface is the largest modifiable avenue of heat loss from the body. During heat stress, sweating becomes the predominant factor for determining whether heat balance is obtained, and when air temperature equals skin temperature and dry heat loss is eliminated, evaporation becomes the only avenue for dissipating metabolic heat at the skin surface (137). The latent heat lost for every gram of sweat that completely evaporates from the skin is 2.426 kJ (189). As such, evaporative heat loss can be estimated using body mass changes corrected for metabolic and respiratory mass losses, as well as any ingested fluids, but only under conditions that permit complete evaporation (15). Arguably the most accurate method for estimating evaporative heat loss is direct calorimetry, which measures the difference in absolute water vapor pressure between influent and effluent of an enclosed air space (178). However, once again the complete evaporation of all sweat from the skin is a necessity and is typically achieved in a calorimeter by ensuring a high and turbulent air mass flow (152). Under combinations of climate and activity that yield incomplete sweat evaporation from the skin surface, evaporative efficiency (i.e. the proportion of secreted sweat that actually evaporates; (4)) can be roughly estimated. It is known that as the sweat saturation level of the skin reaches a maximum, evaporative efficiency rapidly declines (4, 40, 72). First described by Gagge (62), sweat saturation levels can be expressed as a "skin wettedness" value (ω), which is physiologically defined as the fraction of the skin surface that is covered in sweat. It follows that reductions in evaporative efficiency have been reported when ω>0.50 during passive heat stress (41), and when ω>0.30 during upright cycling (4). Mathematically, the ω value required (for heat balance; ω_{req})

is defined as the ratio of the evaporative requirement to maintain heat balance (E_{req}) relative to the maximum evaporative capacity in the ambient environment (E_{max}):

$$\omega_{req} = {E_{req}}/{E_{max}} \quad [ND] \quad (16)$$

By rearranging the conceptual heat balance equation (equation 1), and assuming a rate of body heat storage (S) of zero, E_{req} can be estimated as follows:

$$E_{req} = (M - W) - (\pm K_{sk} \pm C_{sk} \pm R_{sk}) - (C_{res} + E_{res}) \quad [\text{in W}\cdot\text{m}^{-2}] \quad (17)$$

E_{max} is determined by the water vapour pressure gradient between the skin and the air, as well as air speed, clothing properties, and the maximum proportion of the skin that can be physiologically saturated with sweat (ω_{max}):

$$E_{max} = \omega_{max} \frac{(P_{sk,sat} - P_a)}{\left(R_{e,cl} + \frac{1}{h_e \cdot f_{cl}}\right)} \quad [\text{in W}\cdot\text{m}^{-2}] \quad (18)$$

Where: ω_{max} is maximum skin wettedness, which can reach 1.00 for a fully heat acclimated person but only 0.72 in an untrained, non-heat acclimated individual (149); $P_{sk,sat}$ is the saturated water vapour pressure at skin temperature (in kPa); P_a is the water vapour pressure measured in ambient air (in kPa); $R_{e,cl}$ is the evaporative heat transfer resistance of clothing (in $\text{m}^2\cdot\text{kPa}\cdot\text{W}^{-1}$); f_{cl} is the clothing area factor (equation 14); and h_e is the evaporative heat transfer coefficient (in $\text{W}\cdot\text{m}^{-2}\cdot\text{kPa}^{-1}$).

Values for $P_{sk,sat}$ can be derived using Antoine's equation (181) as follows:

$$P_{sk} = \text{EXP}\left[18.956 - \frac{4030.18}{T_{sk}+235}\right] \quad [\text{in kPa}] \quad (19)$$

Values for the h_e can be estimated using h_c (from equation 10/Table 1) as follows:

$$h_e = 16.5 h_c \quad [\text{in W}\cdot\text{m}^{-2}\cdot\text{K}^{-1}] \quad (20)$$

Values for evaporative efficiency (E_{eff}) (i.e. as a fraction of secreted that evaporates from the skin) can be subsequently estimated for a given level of ω_{req} using (96):

$$E_{eff} = 1 - \frac{\omega_{req}{}^2}{2} \quad \text{[ND]} \quad (21)$$

Evaporative efficiency can also be estimated by directly measuring the mass of dripped sweat trapped in an oil pan placed on a scale directly underneath the participant. However this technique had been primarily reported during passive heating (41) and is difficult to implement during exercise.

Evaporative heat loss from the skin surface (E_{sk}) can then be estimated using:

$$E_{sk} = (WBSL \times 2.426) \times E_{eff} \quad \text{[in kJ]} \quad (22)$$

Where: WBSL is whole-body sweat loss over a fixed exercise time (in g).

It is important to acknowledge that the approach described above is especially limited for individuals wearing layered clothing outfits. While trapped sweat can indeed still evaporate, the effective latent heat of vaporization of this sweat (which is usually assumed to be 2.426 $kJ \cdot g^{-1}$) has been shown to decline dramatically (by up to ~80%) depending on the material properties and most importantly the number of clothing layers (82). As such, E_{sk} from measured sweat losses, even if sweat trapped in clothing is accounted for, could be overestimated by more than 4-fold.

Heat Storage (S): Heat storage occurs when an imbalance arises between metabolic heat production and the parallel rate of net heat dissipation via sensible and evaporative heat transfer. Typically, at rest in a temperate environment, humans are in heat balance (i.e. S=0) as heat loss from sensible heat exchange via convection and radiation match resting metabolic rate without any requirement for evaporation other than passively through respiration. However, elevated rates of heat production following the onset of exercise under nearly all environmental conditions lead to a positive rate of heat storage. On the other hand, cold exposure without sufficient clothing insulation can cause high rates of convective and radiative heat loss that exceed metabolic heat

production leading to a negative heat imbalance and thus a negative rate of heat storage. Cumulatively over time sustained rates of positive or negative heat storage result in changes in internal (i.e. core) body temperature, which if left unchecked can become detrimental to human performance and ultimately health.

The change in heat storage required to alter core temperature is dependent on biophysical factors. Firstly, the body mass of an individual represents their heat sink. Changes in core temperature for an absolute amount of heat stored in the body are inversely correlated, i.e. a smaller rise in core temperature is observed with a larger body mass for a fixed heat storage (51, 150). Secondly, large differences in the specific heat of the tissues of the body (C_p) caused by marked differences in body composition can also alter core temperature despite a similar heat storage. A C_p of 3.47 $kJ \cdot kg^{-1} \cdot {}^{o}C^{-1}$ is assumed for the average person (67). However, owing to the different C_p of fat tissue (2.97 $kJ \cdot kg^{-1} \cdot {}^{\circ}C^{-1}$) and lean mass (3.64 $kJ \cdot kg^{-1} \cdot {}^{\circ}C^{-1}$) overall C_p can vary depending on adiposity. While small differences in C_p do not seem to meaningfully influence core temperature, it has been recently demonstrated that a ~20% difference in body fat percentage is sufficient to independently yield ~0.2-0.3°C greater rises in core temperature during moderate exercise in 28°C environment (9).

2.2 Thermoregulatory System

The human body maintains a core temperature of ~37.0˚C which is only a few degrees shy of its upper survival limit, however relatively far from its lower limit (158). Thus, it can be suggested that the physiological control of these pathways is most important for one's survival, and impairment may be fatal due to the proximity of the upper limit. The ability to survive during times of extreme heat stress, such as marches through the desert (3) or explorations into deep mining tunnels (78), is due to the complex physiological thermoregulatory system and its interaction with

the surrounding environment. To maintain core temperature, the human thermoregulatory system functions in a negative feedback mechanism where if the body stores excess heat, heat loss responses will be activated, and if the body becomes cold due to an internal heat debt, then heat will be actively conserved and excess internal heat will be generated.

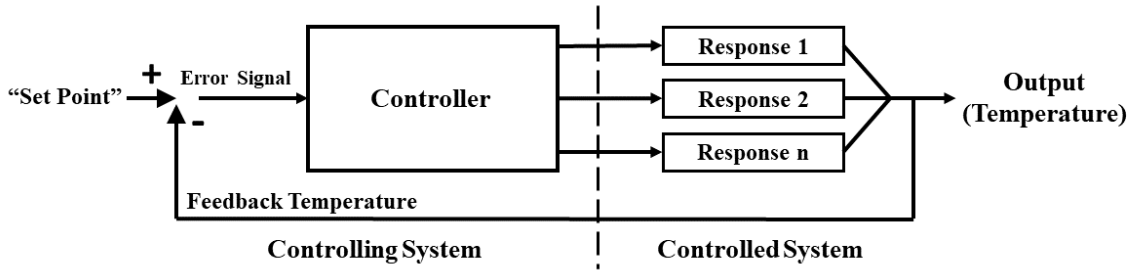

Figure 2 Schematic representing the principles of a set-point theory. Adapted from Satinoff (162). The afferent temperature is referenced against a "set-point" temperature and the net difference determines the up- or down- regulation responses activated by the controller to mitigate the rise or fall in the systems temperature.

There exist multiple theories to explain human thermoregulation and all agree that a negative feedback system exists to maintain homeostasis. The most practical and most utilized explanation involves the set point theory as represented in Figure 1. Afferent signals synapse onto a central integrator (denoted as the intersection between feedback temperature and set-point) that compares the multiple input signals to a *set point* or *reference*. The central integrator detects a difference (if any) and sends an error signal to control mechanisms to minimize the difference between afferent feedback and the reference.

Although simplistic, the true nature of how information (in this case, temperature) is detected and integrated is unknown. Current literature acknowledges the importance of the hypothalamus in thermoregulation. However, the integration and how it is transferred to heat loss or heat production responses remain inconclusive.

In an extension of the set point theory, Hammel (79) suggested that there exists an adjustable set point in which it is modified by the needs of the organism. Hammel states that the proportional controller permits "…its set point to be modified by skin temperature, core temperature, state of consciousness, etc. Indeed, it is a device by which the load error for driving a thermoregulatory response is achieved not by requiring the regulated hypothalamic temperature to deviate greatly from an invariant set point, but rather by offsetting the set point according to the needs of the organism (79)." This suggested paradigm of thermoregulatory control was further developed by Benzinger (22, 23) who hypothesized that the anterior hypothalamus strictly controls heat loss while the posterior hypothalamus controls heat gain. Simplistically, the anterior and posterior hypothalamus relay information between one another and due to increasing inhibition of one structure causes the equilibrium to shift towards the responses driven by the more excited structure.

More recent reconsiderations of thermoregulatory control both compliment the traditional set point theory while proposing that multiple feedback loops act to determine the thermoregulatory response to maintain homeostasis. Briefly, independent thermoeffector loops are activated when their respective threshold perturbation in temperature is exceeded (101, 158, 159). While each thermoeffector loop operates independently, multiple thermoeffector responses may be activated in parallel resulting in cumulative effector activity (159). Further, the term *set point* has been proposed to be substituted with *balance point* as this eliminates the idea of a unified system where a singular reference temperature determines the whole-body thermoregulatory response (157, 158). In addition to the classical negative feedback loop to thermoregulatory control, some thermoeffector loops may also integrate a feedforward aspect which serves to activate thermoregulatory responses in anticipation of pertubations in core temperature (101, 193).

For example, skin thermoreceptors may act as the feedforward component to these hypothesized thermoeffector loops as skin temperature has been shown to modulate the thermoregulatory response (117, 131, 199), with evidence that some skin thermoreceptors do not respond to absolute temperature, but rather the change in temperature (87). Alternatively, Houdas (90, 91) and Werner (191–193) have proposed that absolute core temperature may not be the primary regulator of thermoregulatory control, but rather absolute core temperature is the consequence of external or internal heat load due to disturbances in heat balance. In sum, the principle control mechanism for the thermoregulatory system is not fully understood.

Thermosensors: Free nerve endings are located throughout the epidermis and detect either warm or cold sensations. Recently, it has been suggested that the transient receptor potential (TRP) family of cation channels found on the free nerve endings may mediate thermal sensation on the skin (18, 106, 201). However no conclusive evidence exists (92, 145). The signals originating from the thermosensors (epidermis or organs) are conveyed through the lateral spinothalamic tract to the central integrator. Presently, the relative contribution of either peripheral or central thermosensors on whole body thermoregulation is unclear despite that both are integrated to make a response. Recent work by Cotter and Taylor (49) observed different local cutaneous thermosensitivities of sudomotor control throughout the body, illustrating the complexity of integration.

Central Integrator: The preoptic area (POA) of the hypothalamus serves as the central integrator of the thermoregulatory system. The POA integrates inputs from thermosensors and derives a necessary response to maintain homeostasis. The information arising from warm or cold sensitive neurons are translated by the hypothamalus by their firing rates, or rather their deviation from a neutral firing rate (80). Furthermore, warming and cooling of the POA stimulate heat loss and gain

responses, respectively (16, 134). As explained in Section 2.2, the central integrator may work as a dynamic equilibrium between posterior and anterior hypothalamus to create the most appropriate response to maintain homeostasis (21, 23, 79).

***Efferent Responses*:** Reflex physiological mechanisms aid the maintenance of body temperature within prescribed limits for human health by modifying heat balance. Autonomic increases in vascular conductance of the skin mediated by a cutaneous vasodilatation (79, 155), and eccrine sweating (22, 131), are observed in proportion to elevations in skin and/or core temperature during exercise and/or with heat exposure. Similarly, in the cold, a vasoconstriction response and shivering thermogenesis occur in proportion to reductions in skin and/or core temperature (79, 80, 193).

Sweating: Humans have both apocrine and eccrine sweat glands, with eccrine glands being the most abundant and important to human thermoregulation (195). The eccrine sweat gland consists of two main regions, the duct and secretory coil. The secretory coil contains three types of cells; clear cells, dark cells, and myoepithelial cells. The myoepithelial cells surround the secretory clear and dark cells. Dark and clear secretory cells line the lumen of the coil in a single layer of pseudostratified epithelium (127). The clear cells are suggested to be mainly responsible for sweat secretion due to the abundance of mitochondria (164) while dark cells seem to be precursors of clear cells and assist minimally in sweat secretion into the lumen (165). The duct participates in reabsorption of solutes and as the rate of sweat excretion increases, the rate of reabsorption decreases (173, 195). Eccrine sweat glands are innervated by post ganglionic C sympathetic fibers with acetylcholine being the primary neurotransmitter (46, 100). Excitation and contraction of myoepithelial cells, which are structurally similar to striated muscle, surrounding the secretory coil cause expulsion of sweat onto the skin surface (166).

Sweating was initially thought to be in response to high skin temperatures (63, 198) or core temperature, however it has been well established that it is integration of both (22, 24, 55, 132, 136) which signal heat loss requirements. During exercise, there exists a proportional control system of sweating through integrating skin and core temperature (130), with more recent evidence suggesting that muscle temperature may also be integrated as well (182). The sensitivity of the proportional control system may also be increased through acclimation and training (132) where the onset of sweating occurs at a lower absolute core temperature for a given skin temperature. In addition to thermal factors, non-thermal factors have suggested to affect the sweating response. The non-thermal factors have been summarized in the cited review by Shibasaki (169), and include mechanoreceptors, baroreceptors, osmoreceptors, and metaboreceptors.

Although sweat production is thought to be under proportional control, two factors can limit the amount of sweat that is evaporated to the environment – the process that actually permits heat dissipation from the body. Firstly, the gradient between ambient and skin surface water vapor pressure drive the potential for evaporation from the skin (30, 31). Secondly, air velocity can influence the potential for evaporation from the skin (2, 133) whereby greater air velocity increases the evaporative heat transfer coefficient and thus evaporative efficiency.

2.3 Integration of efferent responses to human heat balance

While at rest mean skin temperature (T_{sk}) is typically 33 to 34˚C. During heat stress, an initial vasodilatation causes an increase in T_{sk}, which alters the temperature difference between the skin surface and the ambient environment and thus increases sensible heat loss (or decreases sensible heat gain if $T_a > T_{sk}$) via convection (Equation 9) and radiation (Equation 5) (137). If net heat loss via convection and radiation (and the small heat losses via respiration) are not sufficient to balance the rate of internal heat production via metabolism (Equation 2), eccrine sweating must be initiated

to enhance evaporative heat loss from the skin. Once sweat is secreted from eccrine sweat glands and reaches the skin surface, the area of skin directly under the sweat is considered to be 100% saturated with water vapour (19). As such, the gradient between the partial pressure of water vapour at the skin surface (P_{sk}) and in ambient air (P_a), and therefore the rate of evaporative heat loss, is increased by sweating. As sweat gland output increases, skin wettedness (ω) increases until reaching a maximum theoretical value of 1.00 when the entire surface area of the body that is available for evaporation (typically equal to total body surface area in healthy humans) is completely covered in sweat. This level of ω is only possible in fully heat acclimated individuals (96). The ability to saturate ~15-25% more of the skin surface following heat acclimation (as described more in the following section) permits an extension of the range of compensable conditions for a given ambient temperature and humidity. Whole-body sweat rate is regulated to ensure that, if possible, a steady-state core temperature is attained (192). It follows that for thermal equilibrium to be possible a rate of heat storage of zero must be achieved. As such whole-body sweat rate is effectively controlled to ensure heat balance, or more specifically the evaporative heat requirement for heat balance (E_{req}) (Equation 17) (66). The relationship between whole-body sweat rate and E_{req} becomes non-linear however once decrements in evaporative efficiency (Equation 21) are observed; i.e. when E_{req} is approximately > 50% of E_{max} (Equation 18).

As skin surface sweating is autonomically controlled via a feedback loop using afferent signals from thermoreceptors throughout the body (38), sweating cannot commence without a "load error", i.e. a rise in internal temperature (37, 80), which in almost all circumstances requires heat storage. There is therefore a delay in the physiologically mediated changes in skin surface heat dissipation relative to the heat production, which results in a transient heat imbalance. The duration of this imbalance is determined by i) the rate at which sweating, and skin blood flow rise

relative to increases in core and skin temperature; and ii) the maximum physiological capacity of the person to increase sweat production and skin blood flow. The longer this imbalance between heat production and net heat dissipation lasts, the greater S will be for a particular person, and the greater the rise in internal tissue temperatures.

At the attainment of heat balance, recent studies have demonstrated that the amount of sweat secreted onto the skins surface and subsequently evaporated is strongly associated with the evaporative requirements for heat balance when exercising in a compensable condition (i.e. heat balance is achieved) with 100% sweating efficiency (51, 66). The relationship between sweating and E_{req} has been demonstrated for both local sweat rates and E_{req} relative to surface area (in W/m^2, (51)) and between whole body sweat rate and absolute E_{req} (in W, (66)). The robustness of the relationship between sweating and E_{req} is maintained even when dry heat exchange is manipulated through increasing ambient temperature (66). Thus, thermal equilibrium during exercise is attained by counterbalancing the net heat production with dry and evaporative heat transfer.

This theory for sweating based on the physical properties for heat balance has yet to be dissociated from the classical theory of thermoregulatory control. That is, a desired steady state sweat rate will be achieved following the attainment of a given absolute core and skin temperature (11, 81, 82, 86, 114). The more recent E_{req} and sweating relationship would suggest that the steady state sweat rate when heat balance is achieved irrespective of absolute core and skin temperature, which was first speculated by Houdas et al. (90, 91) and further refined by Werner (191, 193). Rather, continuous increases in sweat rate are produced until heat balance is achieved; integrated centrally as the absence of a rate of change in core and/or skin temperature, and characterizing the "load error" hypothesis previously described and would negate the requirement of an adjustable "set-point" temperature (79). In extension of this hypothesis, Kondo et al. (105) observed a

temporary interruption in sweat secretion following the absence of change in local skin temperature, suggesting the potential for skin cooling (possibly by the heat liberated via evaporation of sweat from the skin) to independently act as an afferent feedback signal. This observation is further supported by studies employing a passive heat stress model followed by rapid skin cooling (17, 108, 117, 118, 199), or when skin temperature is warmed and cooled in a rhythmic fashion (112). The control of sweating becomes further complicated by more recent work suggesting that body morphology may better explain the relative contributions of sweating and vascular responses to heat loss (140).

Acute manipulations of core and/or skin temperature via the application of heat or cold to the body will independently induce thermoregulatory responses to counterbalance the acute heat or cold stress (26, 113, 186, 197). Alternatively, circadian rhythm results in core temperature varying by up to 0.5°C between early morning and late afternoon (10, 153) and thus provides a potential model for evaluating the independent influence of absolute core temperature on steady-state sweat rates when E_{req} is matched at separate times of day. The circadian rhythm of internal temperature in humans has been extensively documented (10, 107), however the underlying mechanism responsible for the diurnal variation remains unclear. In general, the diurnal variation in core temperature has been suggested to arise from changes in; i) physical activity throughout the day (75, 153, 170) and/or ii) adjustments in cutaneous vasodilation which consequently alter the dry heat loss pathways from the body surface (107, 174, 175). Indeed, previous studies have proposed that circadian rhythm alters the absolute core temperature for the initiation of sweating and cutaneous vasodilatation (6, 174, 179, 190), with limited evidence to support a greater steady-state sweat rate in the afternoon compared to the morning (185). However, Wenger et al. (190) observed a similar change in core temperature prior to the onset of sweating and cutaneous

vasodilation in the evening compared to morning. As such, it may be interpreted that thermoregulatory responses are activated following a given perturbation in core temperature and not the attainment of an absolute core temperature, independent of circadian rhythm. Further, the exercise protocol employed by Waterhouse et al. (185) which demonstrated an altered steady-state sweating response as a result of circadian rhythm did not match for E_{req} between exercise bouts which may explain the differences observed. Taken together, any independent influence of circadian rhythm on steady-state sweating responses to heat stress may be eliminated if evaluated between conditions matched for E_{req}. **Chapter 3.1 will attempt to evaluate whether E_{req} determines the steady-state sweat rate, regardless of the absolute core temperature by using the circadian rhythm model to manipulate core temperature.**

Compensable and Uncompensable heat stress: Heat stress risk, in terms of the magnitude of core temperature rise is greatly dependent on the physiological compensability of the individual in the given environment. While body temperatures will plateau at an elevated level if heat balance is attainable (compensable), body temperatures will continue to rise without a plateau occurring if heat balance is not possible (uncompensable). Uncompensable heat stress can occur because i) metabolic heat production is too high, and/or ii) the physiological capacity to sweat has been reached, and/or iii) the environment/clothing prevents a sufficiently high rate of heat dissipation from the skin even with maximum sweating. In the context of the previously described heat balance components, whether a given heat exposure is compensable or not is determined by, 1) the amount of evaporation required for heat balance (E_{req}); and 2) the maximal evaporative capacity of the environment (E_{max}): i.e. if $E_{req} \leq E_{max}$ = *Compensable*; if $E_{req} > E_{max}$ = *Uncompensable*.

The E_{req} and E_{max} for a given exposure are determined by both environmental conditions and physiological characteristics. A lower E_{req} is observed as i) T_a and T_r become cooler; ii) *v* becomes

greater apart from when $T_a > T_{sk}$; iii) M-W is lower; and iv) T_{sk} is higher. On the other hand, a higher E_{max} is observed as i) P_a becomes drier; ii) *v* becomes greater; iii) body surface area of the person is greater; and iv) $R_{e,cl}$ of clothing worn is lower. Generally speaking therefore, the cooler, windier, and drier an environment is, the more likely it will lead to compensable heat stress especially if levels of physical activity are low and/or clothing with a low evaporative resistance is worn. Nevertheless, numerous combinations of activities and climate can yield uncompensable heat stress. Even activities with a low metabolic heat production can be uncompensable if the climate is sufficiently hot, humid, and still. Similarly, activities with high rates of metabolic heat production can be uncompensable even in relatively temperate climates. Moreover, for a fixed set of environmental characteristics, the more mean skin temperature can be increased through elevations in skin blood flow, and the greater the skin wettedness that can be achieved, the more likely an individual will a) avoid uncompensable heat stress and a continued increase in core temperature; and b) limit the magnitude of heat storage and therefore the increase in core temperature as exercise continues.

A resting thermoneutral core temperature is ~37.0±0.5˚C, but elevations as little as ~2˚C can elevate the risk of heat exhaustion (114). The risk of heat stroke becomes greater once core temperature exceeds 40-41°C and in severe cases can prove potentially life-threatening. Eventually the denaturing of body proteins occurs followed shortly by death at body temperatures above 42 to 43ºC (114). Even moderate elevations in core temperature alongside elevated skin temperature and sensations of discomfort can potentially influence worker performance during cognitive tasks (172) and lead to unsafe behaviour (148).

2.4 Interventions influencing thermoregulatory function and heat balance

Physical Training*:* Physically trained people demonstrate greater secretory activity of the sweat gland during pilocarpine iontophoresis (35) and an observable increased sweat rate after an 8 week high intensity training program during a heat tolerance test (69). Moreover, recent evidence suggests that training causes peripheral adaptations to the sweat gland; increased cholinergic responsiveness (196) and earlier onset time for sweating following direct stimulation of muscarinic receptors (110). Although the current state of literature suggests that training may induce morphological and/or physiological changes to the sweat gland, it has not yet been shown whether these greater maximal sweat rates result in a greater heat dissipation via evaporation. When aerobically fit and unfit individuals are matched for mass and heat production, no differences in WBSL are present in compensable conditions (99). However, when highly fit and moderately fit individuals are exercising in uncompensable conditions (i.e. heat stress combined with impermeable clothing ensembles), the change in core temperature is greater in fitter individuals in addition to having higher sweat rates (43).

Frequent physical training has long been postulated to provide similar thermoregulatory adaptations to heat acclimation with respect to sweat gland function provided certain criteria are met as summarized by Pandolf (143). The three most important criteria for similar physiological benefits between training in a cool environment and acclimation on performance during a heat tolerance test are: i) exercise intensity greater than 50% VO_{2max} (9), ii) exercise training programs lasting 8 to 12 weeks (70), and iii) training programs which cause large (>1.0°C) elevations in core temperature (85, 142).

However, little is known about the influence of aerobic training on ω_{max}; where E_{req} is equal to actual E_{max}, which has been shown to increase with passive (40) or active (103) heat acclimation.

Alber-Wallström & Holmer (4) provide observational evidence by stating, "…two of our subjects were athletes and their sweating more closely resembled that of an acclimatized subject." Havenith and Middendorp (83) lend support to these observations by suggesting "[the] influence of the VO_{2max} in both warm climates may reflect the better sweat distribution over the body, which was observed in trained subjects." Although trained individuals may have greater maximal sweat rates than untrained, no empirical evidence exists to suggest that this may contribute to greater distribution over the body surface, as is the case with acclimation (103).

Despite the body of literature to suggest a partial acclimation associated with aerobic training, recent work by Mora-Rodriguez et al. (128) assumed ω_{max} values for trained and untrained individuals to be equal to 1.0 and 0.85 of their theoretical E_{max} respectively. These observations are based on a passive heat acclimation study conducted on a rather small sample size (n=4) where fitness was not addressed - nor considered (41). The same passive heat acclimation evidence is used by the International Organization for Standardization (ISO) to create a predicted heat strain model (PHS, ISO:7933[2004]; (98)), which does not consider training status, but does characterizes the ω_{max} of an unacclimated or acclimated person as 0.85 and 1.00, respectively (115, 116). The PHS model is used to estimate the sweat rate and core temperature following exposure to a specific working condition based on physical factors and physiological assumptions (i.e. acclimation status). The absence of evidence to quantify the influence of training on ω_{max} may limit the validity of the quintessential PHS model (ISO:7933) commonly used to determine exposure times for occupations at greater risk for heat stress (i.e. firefighters and military). **Thus, it remains unclear whether frequent aerobic training permits an increase in maximum skin wettedness and will be evaluated in Chapter 3.3.**

In the absence of heat acclimation, it has been proposed that cardiorespiratory fitness may provide a similar advantage due to the assumption that an aerobically fit person is also partial acclimated, as supported by the inverse relationship between aerobic capacity and the time required for the acquisition of complete heat acclimation (142). Based on this evidence, it would stand to reason that the range of compensable conditions is augmented by simply having a greater aerobic capacity. However, aerobic capacity is simply the maximum rate of oxygen consumption, which can be influenced by other, non-modifiable, factors such as genetics (27, 104). Alternatively, an increase in aerobic capacity as a consequence of aerobic training is often characterized by frequent and repetitive bouts of exercise-induced heat stress (9, 69, 142, 147). For example, Selkirk and McLellan (167) provided evidence that perhaps body fatness and fitness may influence heat tolerance during uncompensable heat stress. However, they did not match for mass, BSA, and heat production, which have all been shown to influence heat loss (50, 99), making thus the comparison between fit and unfit (lean and non-lean) individuals difficult. Additionally, the change in rectal temperature between fit and unfit low fatness groups following 60 minutes of exercise were similar (suggesting similar changes in body heat content) yet absolute core temperature was different, which can be attributed to fit individuals having a lower resting core temperature (99). Although they provide observations that fit individuals may tolerate a higher core temperature during uncompensable heat stress while wearing semipermeable clothing, they do not provide evidence that fit individuals have an altered ω_{max}. As such, it may not be aerobic capacity per se that alters the upper limit of compensability, but rather the frequent and repetitive bouts of heat stress during aerobic training which modulate a partially heat acclimated state. Indeed, Corbett et al. (47) recently provided evidence to suggest that aerobic capacity did not influence the magnitude of the adaptive response to heat acclimation. **The aim of Chapter 3.4 is**

to examine whether aerobic capacity independently alters the upper limit for physiological compensability, or if it is the result of frequent aerobic training with its accompanying increase in aerobic capacity which modulates the thermoregulatory responses to uncompensable heat stress.

Heat Acclimation: The effects of repeated exposure on one's ability to tolerate and survive in hot environments has been well documented (3, 70, 78, 93, 109, 124, 142, 171). For example, Shaklee (1917) demonstrated that monkeys who were immediately exposed to long durations of solar radiation died within 40 minutes to 6 hours whereas monkeys who received 10-21 short exposures were able to live longer. Shaklee concluded that the monkeys were able to live longer due to their increased sweat rates compared to their unacclimatized counterparts. Although an animal model, the human response to acclimation is comparable (7, 34, 42, 109).

Acclimation in humans has been shown to enhance the sweating response through an increased sensitivity of central drive (109, 132), increased peripheral sweat gland function (33) and an increased sweat gland size and capacity (163). Furthermore, Ogawa and Sugenoya (141) observed an increased pulsation from sweat glands following heat acclimation, which may illustrate a change in central control of the sweating response. Moreover, it has been shown that acclimation will increase sodium ion reabsorption of the sweat gland duct (32). Candas et al.. (40, 41) quantified that a 10-day passive acclimation in a hot and humid environment can increase ω_{max} to 1.00 (the equivalent of a fully saturated skin surface) and Kenney and Zeman (103) demonstrated that the ω_{max} of unacclimated women was lower than acclimated. Heat acclimation has also been shown to reduce the magnitude of change in core temperature during an uncompensable heat tolerance test at a relative intensity (13) and similar rates of heat production (7, 8, 70). Although heat acclimation protocols have not been universally standardized, it has been

generally accepted that 7-14 days of repeated exercise bouts in a hot and humid environment will almost completely elicit the physiological changes (42, 70, 74, 168). While the physiological adaptations have been well documented, **it is unclear whether the increase in ω_{max} following heat acclimation will be similar or greater than following an aerobic training regime and will be evaluated in Chapter 3.3.**

Lastly, despite the physiological and biophysical benefits of heat acclimation during uncompensable heat stress, it has not yet been determined whether heat acclimation alters any thermoregulatory responses to exercise in compensable environments. During uncompensable heat stress which is normally conducted in a hot and humid environment, one is required to achieve their ω_{max} in order to liberate as much of the heat produced via evaporation of sweat from the skin's surface to mitigate the upward rise in core temperature. By definition, a compensable environment will not require a ω_{max}, and therefore heat balance will inevitably be achieved. In a compensable condition, it would be expected that thermoregulatory responses such as the change in core temperature and sweating would be similar between morphologically matched groups when prescribed the same absolute heat production (99). **However, no evidence exists to confirm whether thermoregulatory responses to compensable exercise conditions are altered following partial or complete heat acclimation and thus is the aim of Chapter 3.2.**

CHAPTER 3: METHODS AND RESULTS

3.1 Thesis Study #1

The diurnal variation in absolute core temperature does not alter the steady-state sweating response at a fixed evaporative heat balance requirement

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Abstract

The present study sought to determine whether the diurnal fluctuation in absolute core temperature alters the sweating response to exercise in thermoneutral (23°C) and warm (33°C) environments at a fixed evaporative requirement for heat balance (E_{req}). In the morning (0800h, AM) and afternoon (1600h, PM), eight males exercised on a semi-recumbent ergometer for 60 min at an E_{req} of 200 W·m^{-2} at different ambient temperatures (T_a, 23°C and 33°C), and a trial at a higher E_{req} (250 W·m^{-2}) at the same T_a (33°C), totaling 6 trials. Esophageal temperature (T_{es}), skin temperature (T_{sk}), local sweat rate (LSR) at the arm and upper-back, and whole-body sweat rate (WBSR) were measured. For the same E_{req}, steady-state T_{es} was higher in the PM (23°C AM: 37.4±0.1°C, PM: 37.6±0.2°C, P=0.001; 33°C 200 W·m^{-2} AM: 37.0±0.2°C, PM: 37.2±0.2°C, P<0.001; 33°C 250 W·m^{-2} AM: 37.3±0.2°C, PM: 37.45±0.20°C, P=0.001) while steady-state mean LSR (23°C AM: 0.73±0.23 mg·cm^{-2}·min^{-1}, PM: 0.68±0.23 mg·cm^{-2}·min^{-1}, P=0.18; 33°C 200 W·m^{-2} AM: 0.62±0.12 mg·cm^{-2}·min^{-1}, PM: 0.57±0.12 mg·cm^{-2}·min^{-1}, P=0.20; 33°C 250W·m^{-2} AM: 0.91±0.18 mg·cm^{-2}·min^{-1}, PM: 0.83±0.17 mg·cm^{-2}·min^{-1}, P=0.37) and WBSR (23°C 200W·m^{-2} AM: 10.5±1.6 g·min^{-1}, PM: 10.4±2.2 g·min^{-1}, P=0.70; 33°C 200 W·m^{-2} AM: 9.9±1.7 g·min^{-1}, PM: 10.1±2.1 g·min^{-1}, P=0.64; 33°C 250 W·m^{-2} AM: 13.8±1.5 g·min^{-1}, PM: 13.9±1.4 g·min^{-1}, P=0.46) were similar. For the same T_a (33°C) but different E_{req} (200 vs 250 W·m^{-2}), steady-state T_{es} (P<0.001),, mean LSR (P<0.001), and WBSR (P<0.001) were higher with a greater E_{req}. Again, when E_{req} was matched (200 W·m^{-2}) but different T_{sk} (23°C: 31.7±0.8°C vs 33°C: 33.7±0.4°C, P<0.001), steady-state LSR (P>0.17) and WBSR (P>0.93) remained similar. Collectively, these findings support that E_{req} determines steady-state sweating during compensable heat stress independently of differences in absolute T_{es} and T_{sk}.

Introduction

While the human thermoregulatory system maintains internal body temperature around 37°C at rest in a temperate environment, circadian rhythm results in an absolute core temperature that differs by up to 0.5°C between early morning and late afternoon (7, 33, 40). It is commonly assumed that the absolute core temperature attained during heat stress determines steady-state sweat rates (2, 3, 22, 24, 25, 27, 36). However, other evidence suggests that the evaporative requirements for heat balance (E_{req}) more specifically determine steady-state sweat rate irrespective of absolute core temperature (9, 13). It follows that the diurnal variation in absolute core temperature serves as a simple experimental model to test the question of whether absolute core temperature independently alter steady-state sweat rate during exercise at a fixed E_{req}.

During heat stress, the primary goal of the thermoregulatory system is to prevent rises in core temperature. I order to attenuate the rise in core temperature, heat balance must be achieved by counterbalancing heat gain with sufficient heat loss. By definition, E_{req} is the net difference between internal metabolic heat production and dry heat loss, and is therefore the rate of heat loss required via the latent evaporation of sweat from the skin surface to satisfy heat balance. As such, in a compensable environment with complete evaporation from the skin surface (i.e. no dripping sweat), steady-state sweat rate, that is the rate of sweat secreted on to the skin surface, must be determined by E_{req} (9, 13). Moreover, the relationship between steady-state sweat rate and E_{req} should remain even when E_{req} is matched between conditions with a lower heat production to offset the reduced dry heat loss occurring secondarily to a higher air temperature (13). However, it remains unclear whether the relationship between steady-state sweat rate and E_{req} remains alongside different absolute core temperatures.

Absolute core temperature and steady-state sweating

Wenger et al (41) and Stephenson et al. (35) each observed a rightward shift of the absolute core temperature associated with the onset of sweating, with similar thermosensitivities, in individuals who conducted an exercise bout in the afternoon compared to the morning. Additionally, the onset for sweating has been reported to occur earlier if exercise is conducted in a hot compared to a cool environment due to differences in skin temperature (24). While E_{req} may determine local and whole-body sweat rates once heat balance is achieved (i.e. at steady-state), a greater cumulative whole-body sweat loss would be expected over a fixed exercise time due to higher non-steady-state sweat rates if the onset for sweating is hastened due to differences in absolute core temperature and/or skin temperature.

Thus, the purpose of the present study was to determine whether differences in absolute core temperature occurring in the morning (AM) and afternoon (PM) alter sweating responses during exercise at a fixed E_{req} of 200 and 250 $W \cdot m^{-2}$ in a warm (33°C) environment. Further, heat production in an additional trial was increased to yield a fixed E_{req} of 200 $W \cdot m^{-2}$ in a cooler (23°C) environment in order to identify any role of skin temperature on steady-state sweat rate response at a fixed E_{req}. It was hypothesized that under all conditions that yielded a fixed E_{req}, steady-state sweat rates would be similar, irrespective of absolute core temperature (AM versus PM) or skin temperatures (air temperature of 23°C versus 33°C), but when exercise intensity was altered to yield different levels of E_{req} (200 $W \cdot m^{-2}$ versus 250 $W \cdot m^{-2}$) at the same air temperature steady-state sweat rates would be different. Additionally, it was hypothesized that while steady-state sweating would be unperturbed by differences in absolute core and skin temperature, greater cumulative whole-body sweat losses would occur over the total exercise time due to higher non-steady state sweat losses during the initial stages of exercise initiated by an earlier onset in

sudomotor activation in i) the afternoon compared to morning, and ii) in a 33°C compared to 23°C environment.

Methods

Ethical approval was obtained from the University of Ottawa Health Sciences Research Ethics Board (H04-17-20) conforming to the principles set forth in the Declaration of Helsinki 2013. All volunteers gave consent (verbal and written) prior to all experimental trials, and were required to fill out a Physical Activity Readiness Questionnaire and an American Heart Association Pre-participation Screening Questionnaire. An *a priori* power calculation was performed using G*Power 3.1.9.2 software to determine the sample size required for the present study. Using previously reported data where the primary outcome variables were similar to the present study (i.e. whole body sweat losses, local sweat rates, esophageal temperature), the minimum effect size reported to observe a difference an any outcome variable of 1.42 was used. Assuming a two-tailed t-test and 0.05 for both the α and β values as they respectively represent the probability of reporting a false positive or negative, a total of 9 participants were required to observe a difference, if any, between the primary outcome variables in the present study. To date, a total of 8 healthy males have completed all 6 trials (25.7±1.5 y, 76.43±7.14 kg, 1.78±0.06 m, 1.94±0.10 m^2).

Experimental protocol

In advance to all experimental sessions, participants were asked to abstain from caffeine, alcohol, and strenuous exercise for at least 12 h, and instructed to eat a light meal and drink ~500 mL of water 2 h before arrival. Participants completed a total of 6 experimental trials: i) an E_{req} of 200 $W \cdot m^{-2}$ at 23°C and 1.5 kPa, ii) an E_{req} of 200 $W \cdot m^{-2}$ at 33°C and 1.5 kPa, and iii) an E_{req} of

Absolute core temperature and steady-state sweating

250 $W \cdot m^{-2}$ at 33°C and 1.5 kPa, each at two separate times of day (0800 h and 1600 h). All testing was conducted on separate days a minimum of 24 h apart.

Upon arrival, participants self-inserted the rectal thermistor probe, provided a urine sample, and changed in to standardized shorts and shoes. Urine specific gravity (USG) was measured using a refractometer (Reichert TS 400, Depew, NY, USA) and no value exceeded 1.025 which is suggestive of pre-exercise dehydration (15). Participants then entered the climatic chamber set to the desired environmental conditions for the experimental trial where remaining instrumentation was then completed. After instrumentation, participants rested for 30 minutes (denoted as baseline) in order to equilibrate with the environment. At 25-min of baseline, participants were weighed using a balance scale accurate to the nearest ±2 g (Combics 2, Sartorius, Mississauga, ON, Canada) with all instrumentation wires affixed to an adjacent equipment cart using masking tape. Following completion of the baseline period, participants began 60-min of exercise on a semi-recumbent ergometer (Lode Corival, Groningen, the Netherlands) at a target intensity eliciting an E_{req} of 200 $W \cdot m^{-2}$ or 250 $W \cdot m^{-2}$. The rate of oxygen consumption required to achieve the target E_{req} was determined in advance of the experimental trials using the conceptual heat balance equation (see calculations) and was monitored in real-time using a breath-by-breath metabolic cart (Vmax Encore, CareFusion, Yorba Linda, CA). The participant's body mass was taken again at 45 mins and at the end of exercise.

Instrumentation

Ambient temperature and humidity within the climatic chamber were measured using a dew point mirror (473 Dew Point Mirror, MBW Calibration, Wettingen, Switzerland) adjacent to the participant. Rectal temperature (T_{re}) and esophageal temperature (T_{es}) were measured using pediatric grade thermistor probes (Mon-a-therm®, Mallinckrodt Medical, St. Louis, MO). The T_{re}

probe was inserted ~12 cm past the anal sphincter. The T_{es} probe was inserted through the nasal cavity into the esophagus to a maximum depth of 40 cm, estimated to be the region close to the left ventricle (19). Mean skin temperature was measured using surface thermistors (Concept Engineering, Old Saybrook, CT, USA) affixed to the skin using surgical tape (Transpore®, 3M, London, ON) and calculated as the weighted average between four regions (31): chest 30%, triceps 30%, thigh 20%, and calf 20%. All thermometric measures were sampled every 5 seconds (NI cDAQ-91722 module, National Instruments, Austin, TX) and displayed in real-time on a desktop computer using customized LabView software (v7.0, National Instruments, Austin, TX).

Ventilated sweat capsules were used to measure local sweat rates (LSR) of the upper back (inferior to the scapular spine and ~5 cm from the axilla) and forearm (mid-point of the anterior distal segment). Each 2.8-cm^2 capsule was supplied with anhydrous air at a continuous rate of 1.50 L/min and 1.35 L/min for the forearm, and back, respectively (Omega FMA-A2307, Omega Engineering, Stamford, CT). Capsules were secured to the skin using surgical tape. Independent factory-calibrated capacitance hygrometers (HMT333, Vaisala, Vantaa, Finland) analyzed the temperature and humidity of the outflowing air from each capsule. Local sweat rate of the back and forearm were then calculated as the product of absolute humidity and flow rate and expressed relative to the area under the capsule in milligrams per square centimeter per minute ($mg \cdot cm^{-2} \cdot min^{-1}$). Sudomotor thermosensitivity was determined for each trial using linear regression analysis of 1-min averages of LSR (arm and back, separately) with the change in mean body temperature (ΔT_b) defined as the weighted average between T_{es} (80%) and T_{sk} (20%) during the linear portion of the response (8, 37). Sudomotor onset times were defined as the intial rise in local sweat rate following the onset of exercise (in min).

Calculations

Absolute core temperature and steady-state sweating

Partitional Calorimetry: heat balance parameters were estimated via partitional calorimetry (29) and expressed relative to body surface area (BSA) estimated using the DuBois and DuBois equation (11). The conceptual heat balance equation was rearranged to estimate E_{req} prior to each condition using assumed values for skin temperature (T_{sk}=31°C in 23°C; and T_{sk}=33°C in 33°C (31)).

$$E_{req} = H_{prod} - (C + R + C_{res} + E_{res}) \; [W \cdot m^{-2}] \quad (1)$$

The rate of metabolic heat production (H_{prod}) was calculated by subtracting the rate of external work (in W) from metabolic energy expenditure (M). M was estimated using the following equation:

$$M = VO_2 \cdot \frac{\left(\left(\frac{RER - 0.7}{0.3}\right)e_c\right) + \left(\left(\frac{1.0 - RER}{0.3}\right)e_f\right)}{60 \cdot A_D} \cdot 1000 \; [W \cdot m^{-2}] \quad (2)$$

Where: VO_2 is the rate of oxygen consumption (L/min), e_c is the caloric equivalent per liter of oxygen for the oxidation of carbohydrates (21.13 kJ per L of O_2 consumed), e_f is the caloric equivalent per liter of oxygen for the oxidation of lipids (19.62 kJ per L of O_2 consumed), and respiratory exchange ratio (RER) is the ratio of carbon dioxide production and oxygen consumption (VCO_2/VO_2).

Convective heat exchange from the skin, *C*, was calculated as (29):

$$C = h_c \cdot (T_{sk} - T_a) \; [W \cdot m^{-2}] \quad (3)$$

Where: T_{sk} is mean skin temperature (in °C), T_a is ambient temperature (in °C), and h_c is the convective heat transfer coefficient (26):

$$h_c = 8.3 \cdot v^{0.6} \; [W \cdot m^{-2} \cdot K^{-1}] \quad (4)$$

Where: v is air velocity assumed to be equal to 1.2 $m \cdot s^{-1}$, A_D is body surface area (in m^2) estimated using the Dubois and DuBois equation (11).

Radiant heat transfer (R) was estimated by:

$$R = h_r \cdot (T_{sk} - T_r) \; [W \cdot m^{-2}] \quad (5)$$

Where: T_r is the mean radiant temperature (assumed to be equal to ambient temperature for indoor exposures) and h_r (radiant heat transfer coefficient) in $W \cdot m^{-2} \cdot K^{-1}$ is estimated using the following:

$$h_r = \varepsilon \cdot 4\sigma \cdot (A_r/A_D) \cdot ((T_{sk} + T_r)/2 + 273.15)^3 \; [W \cdot m^{-2} \cdot K^{-1}] \quad (6)$$

Where: ε is the area weighted emissivity of the body surface (0.95), σ is the Stefan-Boltzmann constant (5.67×10^{-8} $W \cdot m^{-2} \cdot K^{-14}$), A_r/A_D is the effective radiative surface area (ND) which can be estimated as 0.73 for a standing person (12), and $T_{sk} + T_r$ is the sum of the mean skin temperature and mean radiant temperature (°C), assumed to be equivalent to T_a (°C).

Respiratory heat loss was estimated using the following:

$$E_{res} + C_{res} = 0.0173 \cdot (H_{prod}) \cdot (5.87 - P_a) + 0.0014 \cdot (H_{prod}) \cdot (34 - T_a) \; [W \cdot m^{-2}] \quad (7)$$

Statistical analysis: All data are expressed as means±SD. Separate two-way ANOVAs were performed to compare the dependent variables (E_{req}, sudomotor thermosensitivity, and onset times for sweating, and the T_{re}, T_{es}, T_{sk}, $LSR_{arm,}$ LSR_{back}, and WBSR at steady-state) between the independent variables of time of day (two levels: AM vs PM) and condition (three levels: 23°C 200 $W \cdot m^{-2}$ of E_{req}, 33°C 200 $W \cdot m^{-2}$ of E_{req}, and 33°C 250 $W \cdot m^{-2}$ of E_{req}). Separate two-way ANOVAs were performed to compare dependent variables between the independent variables of time of day (two levels: AM vs PM) and E_{req} for the same air temperature (two levels: 33°C 200 $W \cdot m^{-2}$ of E_{req}, and 33°C 250 $W \cdot m^{-2}$ of E_{req}). Separate two-way ANOVAs were performed to

compare dependent variables between the independent variables of time of day (two levels: AM vs PM) and matched E_{req} between different air temperatures (two levels: 23°C 200 W·m^{-2} of E_{req}, 33°C 200 W·m^{-2} of E_{req}). A P-value less than 0.05 was considered as statistically significant, and the probability of a Type 1 error was maintained at 5% for all post hoc multiple comparisons using a Holm-Sidak correction factor. All statistical analyses were performed with GraphPad Prism (version 7.0, Graphpad Software, La Jolla, CA).

Results

AM vs PM – Matched E_{req}

Core and skin temperatures: Figure 1 illustrates the end-exercise core and skin temperature for all conditions. Steady-state T_{re} was lower in the morning compared to afternoon regardless of condition (23°C 200 W·m^{-2} AM: 37.82± 0.17°C, PM: 37.90±0.14°C, P=0.05; 33°C 200 W·m^{-2} AM: 37.32± 0.15°C, PM: 37.54±0.15°C, P=0.001; 33°C 250 W·m^{-2} AM: 37.57 ± 0.16°C, PM: 37.79±0.17°C, P=0.001, Fig. 1). In parallel with T_{re}, steady-state T_{es} was lower in the morning compared to afternoon for all three conditions tested (23°C 200 W·m^{-2} AM: 37.42± 0.16°C, PM: 37.60 ±0.20°C, P=0.001; 33°C 200 W·m^{-2} AM: 37.04± 0.19°C, PM: 37.23±0.21°C, P<0.001; 33°C 250 W·m^{-2} AM: 37.30 ± 0.19°C, PM: 37.45±0.20°C, P=0.001, Fig. 1). Steady-state mean T_{sk} was similar between matched conditions in the morning and afternoon during exercise in 23°C at a fixed E_{req} of 200 W·m^{-2} (AM: 31.75±0.78°C, PM: 31.84±0.71°C, P=0.88), 33°C at a fixed E_{req} of 200 W·m^{-2} (AM: 33.74±0.38°C, PM: 33.77±0.47°C, P=0.95), and 33°C at a fixed E_{req} of 250 W·m^{-2} (AM: 34.10±0.53°C, PM: 34.09±0.58°C, P=0.95, Fig. 1).

Steady-state sweating: Figure 1 demonstrates the end-exercise local sweat rate. The local sweat rate of the forearm was similar between morning and afternoon following 60 minutes of exercise at 23°C 200W·m^{-2} E_{req} (AM: 0.87±0.23 mg·cm^{-2}·min^{-1}, PM: 0.82±0.24 mg·cm^{-2}·min^{-1},

P=0.17), 33°C 200W·m^{-2} E_{req} (AM: 0.82±0.11 mg·cm^{-2}·min^{-1}, PM: 0.79±0.15 mg·cm^{-2}·min^{-1}, P=0.29), and 33°C 250W·m^{-2} E_{req} (AM: 1.11±0.21 mg·cm^{-2}·min^{-1}, PM: 1.05±0.24 mg·cm^{-2}·min^{-1}, P=0.15). Likewise, the local sweat rate of the upper back following 60 minutes of exercise was not different between morning and afternoon at 23°C and 200 W·m^{-2} E_{req} (AM: 0.54±0.27 mg·cm^{-2}·min^{-1}, PM: 0.49±0.25 mg·cm^{-2}·min^{-1}, P=0.49), nor 33°C 200 W·m^{-2} E_{req} (AM: 0.41±0.19 mg·cm^{-2}·min^{-1}, PM: 0.39±0.15 mg·cm^{-2}·min^{-1}, P=0.54), or at 33°C and 250 W·m^{-2} E_{req} (AM: 0.69±0.25 mg·cm^{-2}·min^{-1}, PM: 0.65±0.21 mg·cm^{-2}·min^{-1}, P=0.49). No difference in whole-body steady-state sweat rates (e.g. 46th to 60th minute, Figure 1) were observed between morning compared to afternoon for a fixed E_{req} of 200 W·m^{-2} at 23°C (AM: 10.5±1.6 g·min^{-1}, PM: 10.4±2.2 g·min^{-1}, P=0.70), an E_{req} of 200 W·m^{-2} at 33°C (AM: 9.9±1.7 g·min^{-1}, PM: 10.1±2.1 g·min^{-1}, P=0.64), and an E_{req} of 250 W·m^{-2} at 33°C (AM: 13.8±1.5 g·min^{-1}, PM: 13.9±1.4 g·min^{-1}, P=0.46).

Non-steady state sweating: Whole-body non-steady state sweat rates (e.g. 0-45th minute of exercise, Figure 4) were similar irrespective of time of day for 23°C 200 W·m^{-2} of E_{req} (AM: 9.3±1.7 g·min^{-1}, PM: 9.7±1.9 g·min^{-1}, P=0.70), 33°C 200 W·m^{-2} of E_{req} (AM: 9.0±0.5 g·min^{-1}, PM: 10.1±2.1 g, P=0.64), and 33°C 250 W·m^{-2} of E_{req} (AM: 13.8±1.5 g, PM: 13.9±1.4 g, P=0.46). Whole-body sweat rates for the 60 minutes of exercise were not different between morning compared to afternoon for a fixed E_{req} of 200 W·m^{-2} at 23°C (AM: 9.9±1.3 g·min^{-1}, PM: 10.0±1.5 g·min^{-1}, P=0.81), an E_{req} of 200 W·m^{-2} at 33°C (AM: 9.4±0.8 g·min^{-1}, PM: 9.7±1.1 g·min^{-1}, P=0.81), and an E_{req} of 250 W·m^{-2} at 33°C (AM: 13.5±1.2 g·min^{-1}, PM: 13.2±1.3 g·min^{-1}, P=0.81).

Onset and thermosensitivity: Table 1 illustrates the onset and thermosensitivities (LSR:T_b) for both arm and back local sweat rates. The onset time for sweating was similar between AM and PM for the arm at 23°C at 200 W·m^{-2} of E_{req} (P=0.99), 33°C at 200 W·m^{-2} of E_{req} (P=0.79), and 33°C at 250 W·m^{-2} of E_{req} (P=0.79). Again, the onset time for sweating was similar between AM

and PM for the back at 23°C and 200 $W \cdot m^{-2}$ of E_{req} (P=0.99), 33°C at 200 $W \cdot m^{-2}$ of E_{req} (P=0.78), and 33°C at 250 $W \cdot m^{-2}$ of E_{req} (P=0.99).

Moderate vs High E_{req} - Matched Air Temperature (33°C)

Core and skin temperatures: Figure 2 demonstrates the end-exercise core and skin temperature between conditions matched for air temperate (33°C) and within a time of day (AM or PM). End-exercise T_{re} was higher during the condition requiring 250 $W \cdot m^{-2}$ of E_{req} compared to 200 $W \cdot m^{-2}$ of E_{req} for AM (P=0.01) and PM (P=0.01) trials. Similarly, end-exercise T_{re} was higher during the conditions requiring 250 $W \cdot m^{-2}$ of E_{req} compared to 200 $W \cdot m^{-2}$ of E_{req} for AM (P=0.006) and PM (P=0.009) trials. Lastly, end-exercise T_{sk} was higher at 250 $W \cdot m^{-2}$ of E_{req} compared to 200 $W \cdot m^{-2}$ of E_{req} for AM (P=0.004) and PM (P=0.005) trials.

Steady-state sweating: Local sweat rate of the arm and back for conditions matched for air temperature (33C) but unmatched for E_{req} (200 $W \cdot m^{-2}$ vs 250 $W \cdot m^{-2}$) are presented in Figure 2. The local sweat rate of the arm was higher at steady-state (e.g. 60 minutes of exercise) with heat stress requiring 250 $W \cdot m^{-2}$ of E_{req} compared to 200 $W \cdot m^{-2}$ of E_{req} in the AM (P<0.001) and PM (P<0.001). Equally, the local sweat rate of the back was higher at steady-state with heat stress requiring 250 $W \cdot m^{-2}$ of E_{req} compared to 200 $W \cdot m^{-2}$ of E_{req} for both AM (P<0.001) and PM (P<0.001). Again, steady-state whole-body sweat rates were greater with heat stress resulting in 250 $W \cdot m^{-2}$ of E_{req} compared to 200 $W \cdot m^{-2}$ of E_{req} in the AM (P<0.001) and PM (P<0.001, Fig. 2).

Non-steady-state sweating: Non-steady-state whole-body sweat rates were greater with 250 $W \cdot m^{-2}$ of E_{req} compared to 200 $W \cdot m^{-2}$ of E_{req} in the AM (P<0.001) and PM (P<0.001, Fig. 4). As expected, whole-body steady-state sweat rates for the full duration of heat stress (0-60 minutes)

were greater with 250 $W \cdot m^{-2}$ of E_{req} in comparison to 200 $W \cdot m^{-2}$ of E_{req} in the AM ($P<0.001$) and PM ($P<0.001$, Fig. 4).

Onset and thermosensitivity: The onset time for sweating (Table 1) was similar between AM ($P=0.10$) and PM ($P=0.11$) for the arm when conditions were matched for air temperature (33°C) but different E_{req} (200 vs 250 $W \cdot m^{-2}$). However, an earlier onset time for sweating was observed for the back in the AM ($P<0.001$) and PM ($P<0.001$) for the same ambient temperature but different E_{req}.

23°C vs 33°C - Matched E_{req} (200 $W \cdot m^{-2}$)

Core and skin temperatures: The end-exercise core and skin temperature responses for conditions with matched E_{req} but different ambient temperatures can be found in Fig. 3. The end-exercise T_{re} was lower following 60 minutes of compensable heat stress in 33°C compared to 23°C in either the AM ($P<0.001$) or PM ($P<0.001$, Fig. 3) trials. Likewise, the end-exercise T_{es} was lower in 33°C compared to 23°C despite a similar E_{req} in the AM ($P<0.001$) and PM ($P<0.001$, Fig. 3). As expected, end-exercise mean T_{sk} was greater with a higher ambient temperature (33°C vs 23°C) while same E_{req} in the AM ($P<0.001$) and PM ($P<0.001$, Fig. 3) following 60 minutes of compensable heat stress.

Steady-state sweating: Steady-state local sweat rates of the arm and back are presented in Figure 3 for conditions matched for Ereq (200 $W \cdot m^{-2}$) but unmatched for ambient temperature (23°C vs 33°C) for trials conducted in the AM and PM. Despite the 10°C difference in ambient temperature, steady-state local sweat of the arm was similar when E_{req} was matched in the AM ($P=0.17$) and PM ($P=0.27$). Again, steady-state local sweat rate of the back was similar for the same E_{req} but different ambient temperatures in the AM ($P=0.20$) and PM ($P=0.22$) following 60

minutes of exercise in compensable conditions. Whole-body steady-state sweat rates were similar for the same E_{req} but different ambient temperatures in both the AM (P=0.93) and PM (P=0.93, Fig. 3).

Non-steady-state sweating: Non-steady-state whole body sweat rates were similar when matched for E_{req} despite a 10°C difference in ambient temperature in compensable conditions presented in the AM (P=0.44) or PM (P=0.44 Fig. 4). Lastly, whole-body sweat rates throughout the 60 minutes of compensable heat stress were similar when E_{req} was matched between conditions with different ambient temperatures in the AM (P=0.31) and PM (P=0.31 Fig. 4).

Onset and thermosensitivity: As expected, the onset time for sweating (Table 1) was earlier for the arm when conditions were matched for E_{req} (200 $W \cdot m^{-2}$) but different ambient temperatures (33°C vs 23°C) in the AM (P<0.001) and PM (P<0.001). Similarly, an earlier onset time for sweating was observed for the back in the AM (P<0.001) and PM (P<0.001) for the same E_{req} but different ambient temperatures (33°C vs 23°C).

Discussion

To our knowledge, this study is the first to demonstrate that E_{req} determines steady-state and non-steady state sweat rate despite differences in absolute core temperature that occur as a function of different times of the day, even with different combinations of air temperature and metabolic rate. When exercise was prescribed to elicit a fixed E_{req} (Table 1), the local and whole-body steady state sweat rate were similar regardless of differences in absolute core (AM vs PM, Fig. 1) or skin temperature secondary to differences in ambient temperature (23°C versus 33°C, Fig. 3). The slightly higher absolute core temperature in the afternoon did not evoke a greater sweat rate when exercise was fixed for a given E_{req} in comparison to when it was presented in the

morning. In sum, the present evidence suggests that absolute core temperature does not alter the whole-body and local steady-state sweat rates during compensable heat stress at a fixed E_{req}.

Since the work of Benzinger et al. (3, 4), it has been proposed that sweat rates are dependent on the absolute core temperature attained. More recently, the use of thermal clamp protocols (e.g. absolute core temperature is maintained at a desired level) have been employed to assess steady-state sweating across a range of morphologically dissimilar individuals (28, 30). Thus, the prevailing notion that heat loss responses are a consequence of the absolute core temperature attained has remained for the past five decades. However, the current observations do not seem to support this point of view. Rather, steady-state sweating responses during compensable heat stress seem to be predominantly determined by E_{req} and not absolute core temperature. In a combination of studies (9, 13), it has been concluded that whole body and local sweat rates are determined by the absolute (e.g. W) and relative (e.g. $W \cdot m^{-2}$) evaporative heat balance requirements, respectively. By design, the environmental conditions tested in the present study ensured that heat stress was both compensable and resulted in 100% sweating efficiency (e.g. no dripping sweat). For a fixed E_{req}, the steady-state local sweat rate of the upper back and arm were similar (Fig. 1,3), despite different absolute core temperatures in the morning relative to the afternoon (Fig. 1). In addition, no difference in both the non-steady state (0-45 min of exercise) and steady state (46-60 min) whole body sweat losses were observed within each morning and afternoon condition for a fixed E_{req} (Fig. 1, 4). However, when E_{req} was higher for the same ambient temperature (Fig. 2), steady-state local and whole body sweat rates were higher. Indeed, a marginally greater core and skin temperature was observed when E_{req} was higher (i.e. 250 $W \cdot m^{-2}$) for a matched ambient temperature (33°C) regardless of time of day (Fig. 2), as a result of the higher heat production (Table 2). The greater core and skin temperature observed was likely a result of the greater heat

production required to elicit an E_{req} of 250 W·m^{-2} compared to 200 W·m^{-2} (Table 2). To further eliminate the potential influence of core temperature on steady-state sweating, E_{req} was also matched between two environments differing by ~10°C but by increasing metabolic heat production to offset the greater dry heat losses in 23°C compared to 33°C (Table 2) at two different times of day (Fig. 3). In comparing these trials, again local and steady state sweat rates were similar despite the ~0.5°C greater absolute core temperature following exercise in 23°C and the ~4°C greater skin temperature at 33°C. The greater core temperature observed at 23°C compared to 33°C is supported by the ~2 W/kg greater rate of heat production (Table 2) required to elicit an E_{req} of 200 W·m^{-2} due to the greater dry heat loss in the cooler environment (23°C: 92 W·m^{-2} vs 33°C: 19 W·m^{-2}). While it may be argued that the greater skin temperature may have counterbalanced the lower core temperature observed at 33°C resulting in similar steady-state sweat rates as the 23°C environment supporting the integration of core and skin temperature on sweating (18, 23), steady-state sweat rates were similar irrespective of different steady-state core temperatures when comparing with the same conditions between AM and PM (Fig. 1). Thus, the present study design successfully enabled us to isolate the influence of E_{req} from differences in absolute core temperature, metabolic rate, and skin temperature.

It has been previously proposed that the circadian rhythm of resting core temperature in humans follows a diurnal pattern whereby ‘heat-gain’ occurs in the early morning, resulting in a reduced or delayed activation of thermoregulatory responses while their activation is hastened in the late afternoon to promote ‘heat loss’ (40). Waterhouse et al (38, 39) demonstrated that the absolute threshold for the onset of sweating appeared to happen at a lower core temperature in the morning compared to the evening, and the thermosensitivity, that is the relationship between changes in core temperature and sweat rate, were greatest in the late afternoon. In support,

Absolute core temperature and steady-state sweating

Stephenson et al. (35) observed a rightward shift (e.g. a higher core temperature) for the onset of sweating during exercise in temperate conditions (25°C) in the late afternoon in comparison to the morning. However, Wenger et al. (41) reported a similar change in mean body temperature prior to the onset of sweating with no change in sudomotor thermosensitivity between exercise conducted in the early morning or afternoon. The present study supports no alteration in the thermosensitivity or onset time for the initiation of sweating independent of time of day (between AM or PM) within all conditions tested despite a higher absolute core temperature in the afternoon compared to morning (Fig. 1). Unfortunately, the onset for upward rises in sweating occurred prior to changes in T_{es} which has been previously demonstrated to lag by ~3 minutes at the start of exercise in the heat (32) thus limiting our observations based to time and not a physiological afferent signal (e.g. core temperature).

The onset for sweating occurs earlier in hotter conditions (10, 22, 23) and should therefore result in a greater cumulative sweat loss, however this was not observed in the present study. Unexpectedly, non-steady state sweat losses were similar in the present study between conditions matched for the same E_{req} despite a 10°C difference in air temperature (Figure 4). Further, the earlier onset for sweating at 33°C compared to the 23°C condition which was matched for E_{req} was not large enough to influence the cumulative whole-body sweating response as previously thought (5, 20, 42). One plausible explanation is that the rate of sweating in the present study may not have been sufficient to demonstrate a difference in addition to the short ~ 3-minute delay in the onset of sweating in the 23°C condition compared to 33°C. As such, the differences in non-steady state sweat losses may be more apparent during heat stress requiring a greater E_{req}, however future evidence is required to confirm.

Perspectives

Absolute core temperature and steady-state sweating

Circadian rhythm has been typically believed to independently alter thermoregulatory control and thus investigators examining the thermoregulatory response to an intervention or between group comparisons are usually required to conduct studies at the same time of day to mitigate the introduction of systematic errors associated with an uncontrolled variable (16, 33). Indeed, a circadian rhythm for the expression of certain biomarkers and protein complexes has been previously reported (e.g. heat shock proteins, inflammatory markers, (6, 17, 34)), however their contribution to whole body thermoregulatory responses remain largely unclear (14, 21). Nevertheless, the present findings demonstrate that investigators may assess time-dependent changes in core temperature and sudomotor responses irrespective of time of day when absolute core temperature is not a primary outcome variable during compensable heat stress. Skin blood flow was not measured in the present study and so it remains unclear whether it is influenced by circadian rhythm as previously proposed (1, 39). However, if skin blood flow is in fact altered by circadian rhythm, it did not precipitate any measurable difference in the change in core temperature (a proxy of net heat storage) or in the local or whole-body sweat loss responses to compensable heat stress. Further evaluation is warranted to determine whether circadian rhythm alters the thermoregulatory responses in clinical populations (e.g. elderly, multiple sclerosis, spinal cord injuries).

Conclusion

Steady-state sweat rates were similar, irrespective of absolute core temperature (AM versus PM) or skin temperatures secondary to differences in air temperature (23°C versus 33°C) under conditions which elicited the same fixed E_{req}. As such, when exercise intensity was set to elicit different levels of E_{req}, steady-state sweat rates were higher with a higher $E_{req.}$ The onset for sudomotor activation and thermosensitivity was unaltered by circadian rhythm within a given

condition and thus no differences in the cumulative whole-body sweat losses were observed. Lastly, while the onset for sudomotor activation was hastened in at 33°C compared to a 23°C matched for the same E_{req}, the cumulative whole-body sweat rate was similar.

Author contributions. N.R., P.I., and O.J. were involved in conception and design of the experimental protocol. N.R. was responsible for data collection. Data analysis and interpretation was performed by N.R., P.I., and O.J. N.R. drafted the manuscript. O.J. critically revised the manuscript.

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Table 1. Thermosensitivity (LSR:T_b) of the arm and back and absolute onset time (in mins) for sweating following the following the initiation of exercise for each condition as defined by the predicted evaporative requirements for heat balance (E_{req}) in $W \cdot m^{-2}$.

		Thermosensitivity ($mg \cdot cm^{-2} \cdot min^{-1} \cdot K^{-1}$)			**Onset time (mins)**		
Predicted E_{req}		**23°C 200** $W \cdot m^{-2}$	**33°C 200** $W \cdot m^{-2}$	**33°C 250** $W \cdot m^{-2}$	**23°C 200** $W \cdot m^{-2}$	**33°C 200** $W \cdot m^{-2}$	**33°C 250** $W \cdot m^{-2}$
Arm	**AM**	0.85±0.16	1.10±0.49	0.98±0.28	7.67±0.82	3.67±2.88*	2.83±1.83
	PM	0.87±0.16	0.94±0.38	1.07±0.29	7.67±1.97	3.33±3.08*	2.50±1.64
Back	**AM**	0.74±0.37	0.99±0.80	0.86±0.45	7.83±0.75	5.33±2.88*	2.60±1.95†
	PM	0.77±0.46	0.85±0.56	0.98±0.56	8.13±2.01	4.83±2.79*	2.67±1.75†

*Significantly earlier than 23°C and 200 $W \cdot m^{-2}$ ($P<0.001$).

†Significantly earlier 33°C 200 $W \cdot m^{-2}$ ($P<0.05$).

Table 2. Mean calculated partitional calorimetric values expressed inWatts (W), or relative to total body mass ($W \cdot kg^{-1}$) or per surface area ($W \cdot m^{-2}$), for the experimental sessions conducted at 0800h (AM) and 1600h (PM).

	AM			**PM**		
Target E_{req}	**23°C 200 $W \cdot m^{-2}$**	**33°C 200 $W \cdot m^{-2}$**	**33°C 250 $W \cdot m^{-2}$**	**23°C 200 $W \cdot m^{-2}$**	**33°C 200 $W \cdot m^{-2}$**	**33°C 250 $W \cdot m^{-2}$**
M (W)	619±43*	443±41	635±43*	626±44*	444±44	649±40*
Work rate (W)	114±9*	63±8	106±7*	115±8*	65±7	106±10*
H_{prod} (W)	505±41*	381±37	528±43*	511±46*	380±40	543±41*
H_{prod} ($W \cdot kg^{-1}$)	7.2±0.7*	5.4±0.6	7.6±0.6*	7.3±0.8*	5.4±0.6	7.7±0.7*
E_{req} (W)	339±38†	348±43†	480±41	346±23†	344±45†	492±45
E_{req} ($W \cdot m^{-2}$)	190±20†	194±20†	269±17	194±12†	192±22†	275±22

M: Metabolic energy expenditure, **H_{prod}** Heat production, **E_{req}** the evaporative requirements for heat balance. *Significantly greater than 33°C 200 $W \cdot m^{-2}$ ($P<0.001$). †Significantly lower than 33°C 250 $W \cdot m^{-2}$ ($P<0.001$).

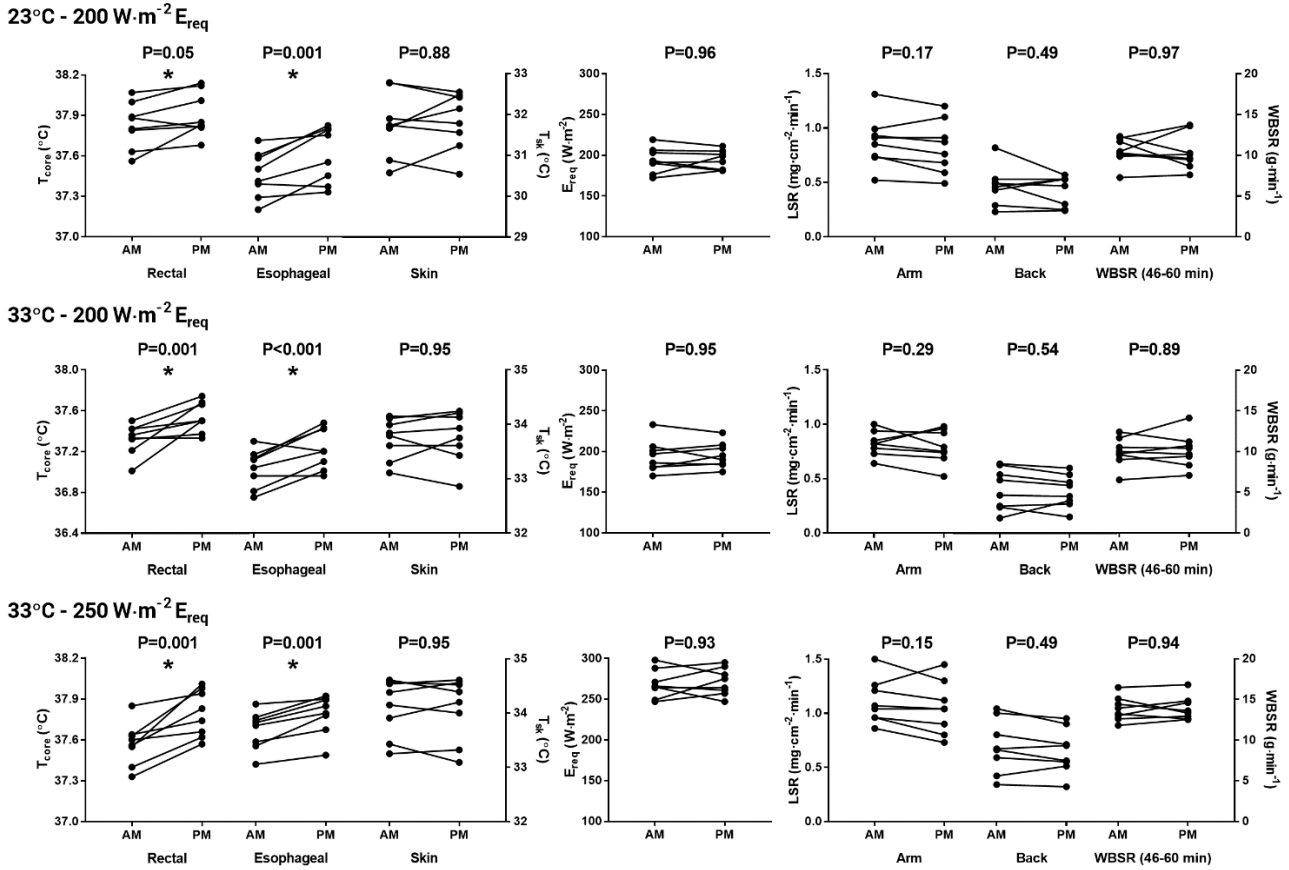

Figure 1. The absolute steady-state core (T_{core}: rectal and esophageal) and skin temperature (T_{sk}), evaporative requirements for heat balance (E_{req}), local sweat rate (LSR) of the arm and back, and steady-state (i.e. 46-60 min) whole-body sweat rate (WBSR) for all three conditions (top: 23°C, 200 W·m^{-2} E_{req}; middle: 33°C, 200 W·m^{-2} E_{req}; bottom: 33°C, 250 W·m^{-2} E_{req}) compared between AM (0800 h) and PM (1600 h). *Significant difference between AM and PM.

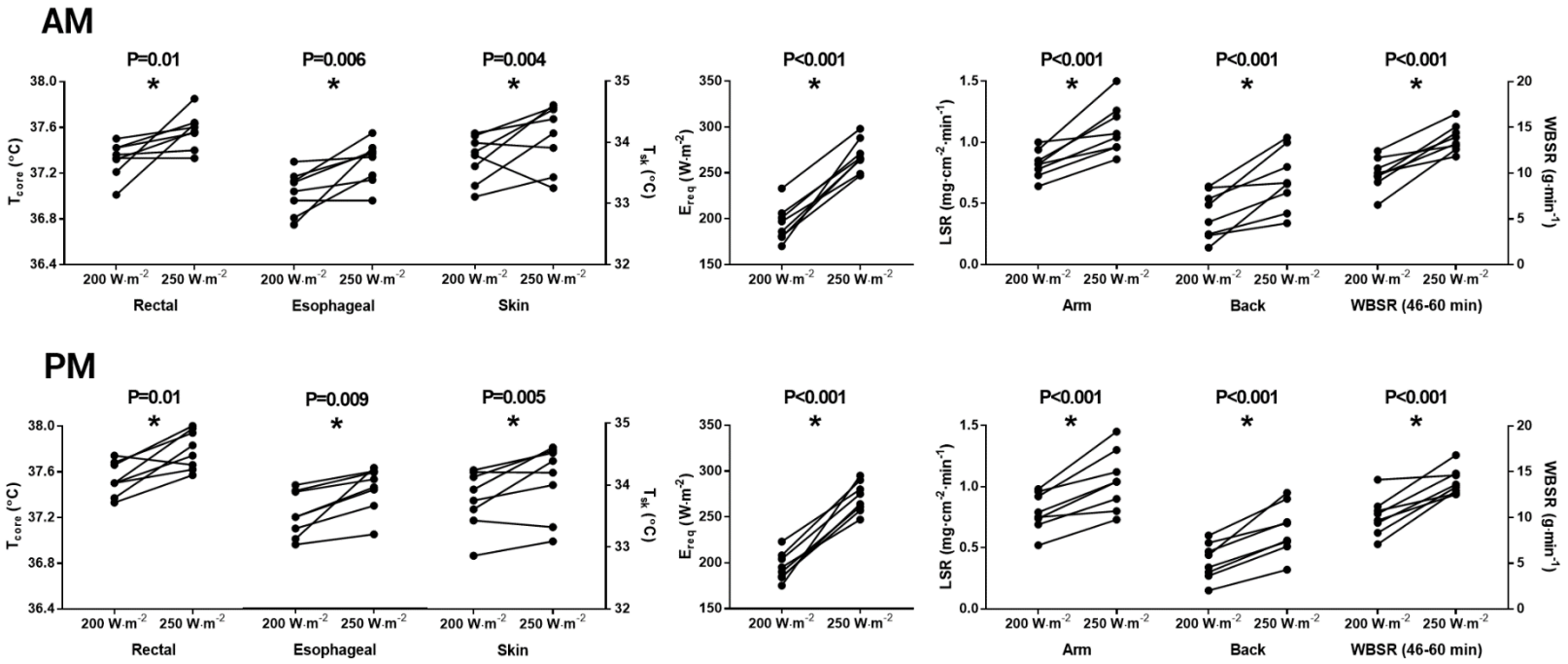

Figure 2. The absolute steady-state core (T_{core}: rectal and esophageal) and skin temperature (T_{sk}), evaporative requirements for heat balance (E_{req}), local sweat rate (LSR) of the arm and back, and steady-state (i.e. 46-60 min) whole-body sweat rate (WBSR) for conditions matched for ambient temperature (33°C) but unmatched for Ereq (200 W·m^{-2} vs 250 W·m^{-2}) within AM (0800 h, top) and PM (1600 h, bottom). *Significant difference between 200 W·m^{-2} and 250 W·m^{-2}.

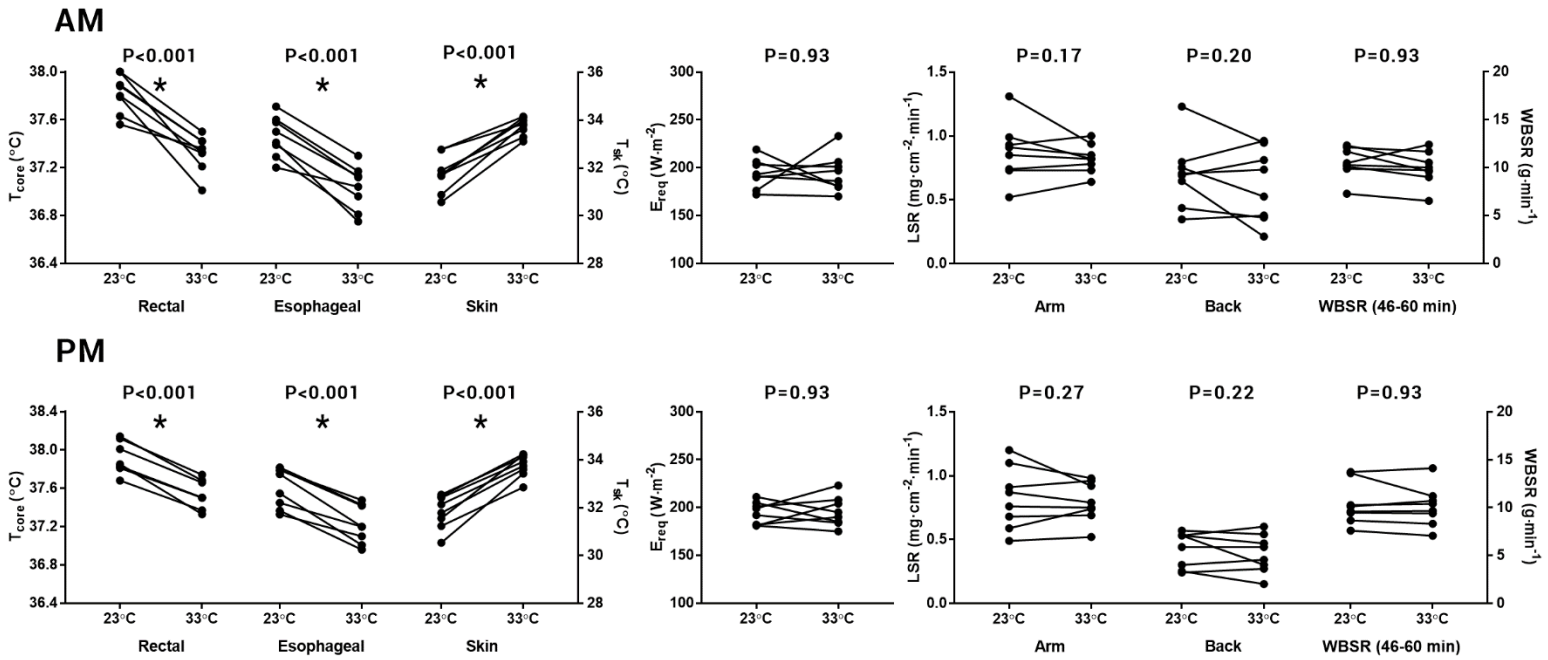

Figure 3. The absolute steady-state core (T_{core}: rectal and esophageal) and skin temperature (T_{sk}), evaporative requirements for heat balance (E_{req}), local sweat rate (LSR) of the arm and back, and steady-state (i.e. 46-60 min) whole-body sweat rate (WBSR) for conditions matched E_{req} (200 $W \cdot m^{-2}$) but unmatched for ambient temperature (23°C vs 33°C) within AM (0800 h, top) and PM (1600 h, bottom). *Significant difference between 23°C and 33°C.

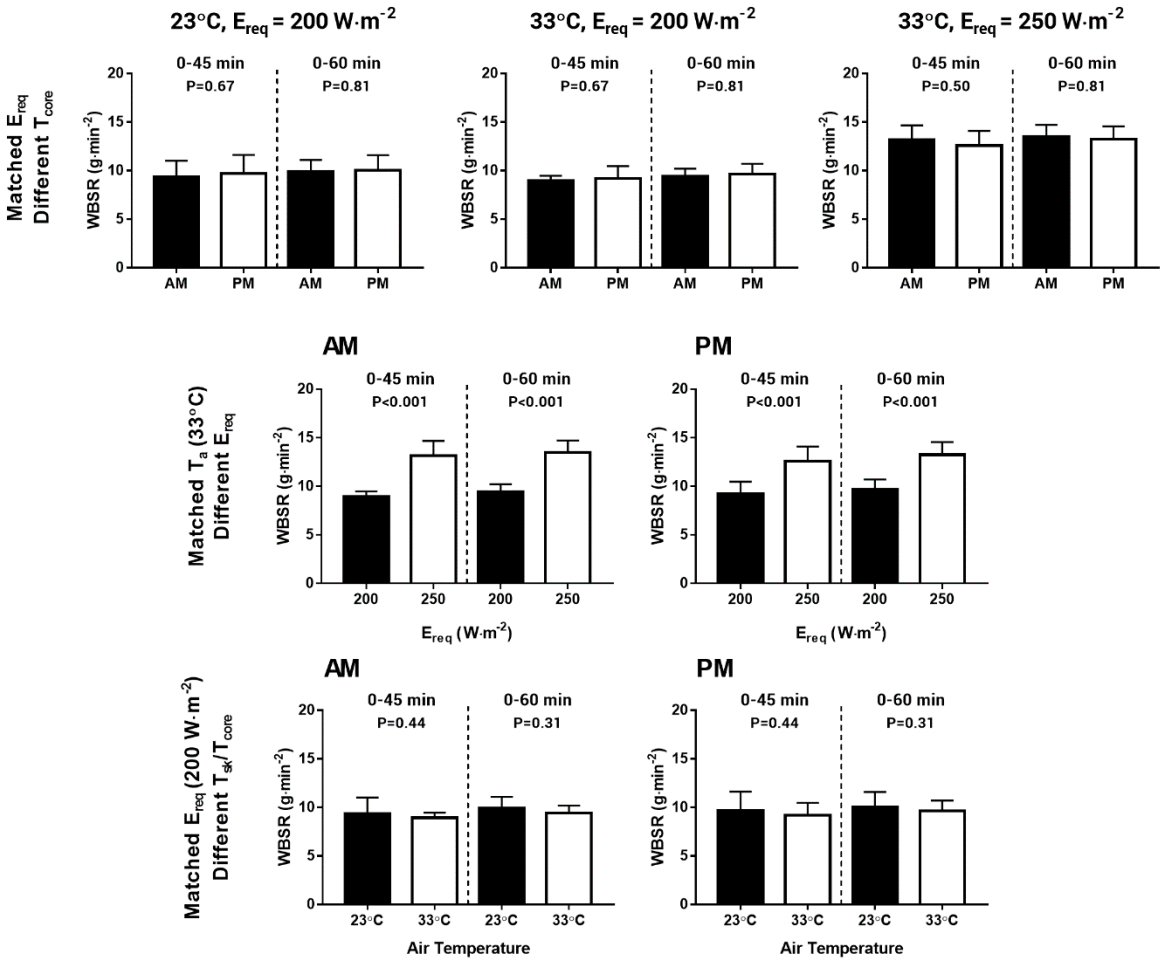

Figure 4. The non-steady-state (0-45 min) whole-body sweat rate (WBSR) and WBSR through exercise (0-60 min) compared between AM (0800 h) and PM (1600 h) for all conditions (top) with a different end-exercise core temperature (T_{core}), compared between different evaporative requirements for heat balance (E_{req}) with the same ambient temperature (T_a; 33°C) within AM and PM (middle), and compared between different skin (T_{sk}) and core (T_{core}) temperatures with the same E_{req} (bottom).

3.2 Thesis Study #2

Thermoregulatory adaptations with progressive heat acclimation are predominantly evident in uncompensable, but not compensable, conditions

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Running Title: *Heat acclimation and compensable heat stress*

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ABSTRACT

This study assessed whether, notwithstanding lower resting absolute core temperatures, alterations in time-dependent changes in thermoregulatory responses following partial and complete heat acclimation (HA) are only evident during uncompensable, and not compensable, heat stress. Eight untrained individuals underwent 8-weeks of aerobic training (i.e. partial HA) followed by 8-days of HA in 38°C/65%RH (i.e. complete HA). On separate days, participants completed a 45-min compensable (37°C/30%RH) and a 60-min uncompensable (37°C/60%RH) exercise bout pre-training (PRE-TRN), post-training (POST-TRN), and post-heat acclimation (POST-HA). Esophageal temperature (T_{es}), arm (LSR_{arm}) and back (LSR_{back}) sweat rate, and whole-body sweat rate (WBSR) were measured. For compensable heat stress, resting T_{es} was lower POST-TRN (36.74±0.27°C, P=0.05) and POST-HA (36.60±0.27°C, P=0.001) compared to PRE-TRN (36.99±0.19°C), however ΔT_{es} was similar in all trials (PRE-TRN:0.40±0.23°C; POST-TRN:0.42±0.20°C; POST-HA:0.43±0.12°C, P=0.97). While LSR_{back} was unaltered by HA (P=0.94), end-exercise LSR_{arm} was higher (P<0.001) POST-TRN (0.70±0.14 mg/cm^2/min, P<0.001) and POST-HA (0.75±0.16 mg/cm^2/min, P<0.001) compared to PRE-TRN (0.61±0.15 mg/cm^2/min). Despite the same evaporative heat balance requirement, steady-state WBSR (31st-45th min) was greater POST-TRN (12.7±1.0 g/min, P=0.02) and POST-HA (12.9±0.8 g/min, P=0.004), compared to PRE-TRN (11.7±0.9 g/min). For uncompensable heat stress, resting T_{es} was again lower POST-TRN (36.77±0.22°C, P=0.05) and POST-HA (36.62±0.15°C, P=0.03) compared to PRE-TRN (36.86±0.24°C). But, ΔT_{es} was smaller POST-TRN (0.77±0.19°C, P=0.05) and POST-HA (0.75±0.15°C, P=0.04) compared to PRE-TRN (1.10±0.32°C). Both LSR_{back} and LSR_{arm} increased with HA (P<0.007) supporting the progressively greater WBSR with HA (POST-TRN:14.4±2.4g/min, P<0.001; POST-HA:16.8±2.8g/min, P<0.001) compared to PRE-TRN

(12.7±3.2 g/min). In conclusion, despite a slightly augmented sweating during compensable heat stress, the thermal benefits associated with HA are primarily evident only when conditions exceed the physiological capacity to dissipate heat.

INTRODUCTION

It is well documented that repeated and frequent bouts of heat stress elicit a range of physiological adaptations, i.e. heat acclimation. In general, the acquisition of heat acclimation is conventionally defined by a greater sweat rate (1, 24, 28, 38), a lower core temperature (7, 47, 49), an "earlier" onset of sweating (25, 35, 43), and a more pronounced sudomotor thermosensitivity (13, 30), in comparison to an unacclimated state. Moreover, in the absence of environmental heat stress, evidence to date indicates frequent physical training, and not maximum aerobic fitness per se (17), can also result in a partial heat acclimation (34), however the combination of heat exposure and exercise are necessary for complete heat acclimation to develop (1, 49).

Higher whole-body (24, 28, 35) and local sweat rates (18, 47) during exercise in a hot environment following heat acclimation can clearly lead to a smaller rise in core temperature. However, these adaptations have been typically demonstrated with combinations of climate and exercise (4, 13, 47) that are physiologically uncompensable (2, 27), and are thus commonly assumed to occur in compensable conditions (4, 20, 43, 47). We have recently demonstrated that the upper limit of compensability is progressively elevated with partial (through regular aerobic training) and complete heat acclimation by virtue of the activation of a greater number of sweat glands per unit surface area permitting a greater skin surface sweat coverage (i.e. skin wettedness; (40)). However, this enhanced heat loss capacity may only be beneficial under conditions that challenge this upper limit, and it remains unclear how evident the hallmark thermoregulatory indicators of heat acclimation during exercise are (i.e. higher steady-state sweat rates and smaller elevations in core temperature) with submaximal heat loss requirements (i.e. compensable heat stress). Indeed, when exercise is conducted in physiologically compensable conditions it is well known that steady-state sweat rates are predominantly determined by the evaporative requirements

for heat balance (E_{req}), which are mostly governed by metabolic heat production (12, 14, 22). While a greater cumulative sweat loss throughout exercise would seem highly likely due to the earlier onset time for sudomotor activity following heat acclimation or partial acclimation during heat stress (43), a greater steady-state sweating response would not seem adaptively advantageous if the rate of evaporation required to balance metabolic heat production, and thus attain a steady-state core temperature, is already attained.

During uncompensable heat stress, the degree of uncompensability within a given person determines the change in core temperature over a fixed period of time (11, 41). By raising the upper limit of heat loss through augmentations of maximum skin wettedness (40) heat acclimation reduces the rate of heat storage and slows the rate of rise of core temperature compared to an unacclimated state. However, during exercise in a compensable environment, when this upper limit for heat loss is not challenged, the change in core temperature from baseline to steady-state will only be blunted following acclimation if the core temperature onset threshold for sweating (expressed as a change from baseline and not an absolute value) and/or sudomotor thermosensitivity are meaningfully changed. It follows that while absolute core temperature during exercise in a compensable environment is clearly much lower with heat acclimation, the change in core temperature from this altered baseline value may only be minimally influenced, if at all.

Thus, the purpose of the present study was to evaluate whether partial and then complete heat acclimation already reported with 8 weeks of physical training immediately followed by 8 days of heat acclimation only lead to smaller increases in core temperature and higher steady-state sweat rates during exercise in an uncompensable heat stress environment, but not in a compensable environment. It was hypothesized that while altered changes in core temperature and sweating are observed following partial and complete heat acclimation during exercise in an uncompensable

heat stress environment, similar changes in core temperature and steady-state sweating would be observed irrespective of acclimation status during compensable heat stress.

METHODS

Participants

Ethical approval was obtained from the University of Ottawa Health Sciences Research Ethics Board (H12-11-05) conforming to the principles set forth in the Declaration of Helsinki 2013. All volunteers gave both verbal and written consent prior to participation. Participants were required to fill out a Physical Activity Readiness Questionnaire and an American Heart Association Pre-participation Screening Questionnaire to assess whether they were sufficiently healthy to complete the required exercise protocols. All participants had no prior cardiovascular, neuromuscular, and/or respiratory medical condition which may be exacerbated with exercise, were non-smokers or at least 12 months without smoking, and initially reported less than 100 minutes of moderate intensity aerobic exercise per week.

Based on previously reported data (36), a power calculation (G*Power 3.1.9.2) suggested that a minimum of six participants were required to demonstrate a significant difference in the absolute esophageal temperature achieved following 60 minutes of uncompensable heat stress prior to (38.6±0.1°C) and following heat acclimation (38.4±0.1°C) in physically active individuals, with β- and α-values equal to 0.95 and 0.05, respectively. All participants commenced during the winter months to mitigate any potential influence of partial acclimation associated with seasonal variation (45, 50). A total of 8 people (6 males, 2 females) completed the study. Participant characteristics are reported in Table 1.

Experimental design

Heat acclimation and compensable heat stress

Participants completed an 8-week training intervention immediately followed by 8 consecutive days of heat acclimation. Participants completed two fitness assessments (pre- and post-training), and six separate exercise-heat stress trials: a compensable and uncompensable exercise-heat stress trial (i) pre-training (PRE-TRN) (ii) post-training (POST-TRN), and (iii) post heat acclimation (POST-HA).

The 8-week training intervention, 8-day heat acclimation protocol, and fitness assessments have been described in detail previously (40). Briefly, participants initially completed a fitness assessment to determine their maximum aerobic capacity (VO_{2max}) using a modified Bruce Treadmill Protocol (6). The results of the VO_{2max} test were used to determine the associated heart rate reserve (HRR) for a given intensity to more accurately prescribe training workloads to ensure the success of the training intervention to increase VO_{2max}. The training intervention consisted of 3 days per week of steady state exercise at an intensity equivalent to 70% of HRR for 60 minutes per session and 1 session per week of high intensity interval training lasting no more than 60 minutes including a self-paced warm up and cool-down (10 repeats of 90 seconds of recovery and 90 seconds at >90% of HRR). More than 2/3rd of the training was conducted on a treadmill while the remaining was conducted on an upright ergometer in an attempt to mitigate the risk of injury due to participating in heavy exercise. The training intervention resulted in 15±8% increase in VO_{2max} with no change in body mass (PRE:80.2±16.7 kg; POST: 78.9±15.5 kg, P=0.12) or estimated body surface area (PRE:2.0±0.2 m^2; POST: 1.9±0.2 kg, P=0.12), as previously reported (40). Within 48 h of completing the training intervention, maximum aerobic capacity was reassessed. On the following day, the POST-TRN compensable heat stress trial was conducted. Within 24hrs of completing the POST-TRN compensable heat stress trial, participants commenced an 8-day heat acclimation protocol wherein Day 1 and Day 8 were structured as the uncompensable

heat stress trial. On Days 2-7 participants completed 90 minutes of walking on a treadmill in a hot and humid environment (38°C and 65% relative humidity) at an intensity eliciting a clamped heart rate at 70% of HR_{max}, thus requiring progressive increases in workload throughout the heat acclimation protocol due to the rapid cardiovascular adaptations associated with heat acclimation (37). Within 24 h of completing the final uncompensable heat stress trial, the participants completed one final compensable heat stress test.

Compensable and Uncompensable heat stress trials

Participants were asked to avoid alcohol and caffeine for at least 12 h prior to testing and consume a light meal and drink ~500 mL of water at least 2 h prior to arrival to the laboratory. Participants were not permitted to eat any food or drink any fluid during any experimental trial. First, participants provided a urine sample upon arrival to analyze urine specific gravity (USG) to confirm adequate (<1.025; (23)) and similar hydration status prior to all experimental trials. Participants then self-inserted a pediatric grade rectal thermistor, changed in to standardized clothing (males: running shorts and athletic shoes, females: sports bra, running shorts, and athletic shoes), and entered the climatic chamber set to 37.5°C with either 30% RH (i.e. compensable trial) or 60% RH (i.e. uncompensable trial) for the remaining instrumentation. Following 30 minutes of rest denoted as "baseline", participants began walking on a treadmill at a fixed metabolic heat production (H_{prod}) of 450 W for 45 min (in the compensable trial) or 60 minutes (in the uncompensable trial). The combination of exercise intensity and environmental factors (i.e. temperature, humidity, air velocity, and clothing) were selected to ensure participants were either compensable or uncompensable, irrespective of acclimation status based on previous evidence of skin wettedness in unacclimated individuals (see Calculations section; (8)). The 45-min exercise bout in the compensable trial was followed by a 60-min humidity ramp protocol, during which

participants continued to exercise at the same intensity, and the results from this standardized protocol have been previously reported (40). Briefly, the humidity ramp protocol confirmed that the compensable and uncompensable heat stress trials were in fact compensable or uncompensable, respectively, irrespective of acclimation status. No supplemental air flow was provided, and any differences in self-generated air flow were minimised by maintaining a similar within-subject walking speed POST-TRN and POST-HA as PRE-TRN by increasing or decreasing grade to account for any alterations in walking efficiency. Body mass measurements were taken, with all instrumentation attached and wires affixed to an adjacent stationary cart in exactly the same manner each time, immediately before exercise and every 15 minutes of exercise using a platform scale accurate to the nearest ±2 g (Combics 2, Sartorius, Mississauga, ON, Canada). Body mass measurements took no more than 20 seconds to complete; the participant stepped laterally onto a platform scale from the treadmill, the measurement was taken, and they immediately resumed exercise.

Instrumentation

Rectal (T_{re}) and esophageal (T_{es}) temperatures were measured using general purpose pediatric grade thermistors (Mon-A-Therm General Purpose Temperature Probe 400TM; Covidien, Mansfield, MA, USA). Participants self-inserted the T_{re} thermistor ~20 cm beyond the anal sphincter. The T_{es} thermistor was inserted by trained personnel through the nasal cavity into the esophagus to a depth of ~40 cm; estimated to be at a region nearest the left ventricle. Skin temperature was measured at 4 sites with thermistor heat flux sensors (Concept Engineering, Old Saybrook, CT, USA), which were secured to the skin with surgical tape (Transpore®, 3M, London, ON). Core and skin temperatures were sampled every 5 s (NI cDAQ-91722 module, National Instruments, Austin, TX). Mean skin temperature (T_{sk}) was calculated using the weighted average

of the four regions measured (39); chest 30%, triceps 30%, thigh 20%, and calf 20%. Mean body temperature (T_b) was calculated as the weighted average between T_{es} (80%) and T_{sk} (20%) (19).

Two ventilated sweat capsules (4.1 cm^2) were secured to the skin using surgical tape to measure local sweat rates of the arm (LSR_{arm}) and back (LSR_{back}). Anhydrous air was supplied to each capsule and the flow of gas was maintained at a constant rate using two factory-calibrated flow meters (Omega FMA-A2307, Omega Engineering, Stamford, CT) at 1.0 $L \cdot min^{-1}$ and 1.2 $L \cdot min^{-1}$ for LSR_{back} and LSR_{arm}, respectively. The temperature and humidity of the air exiting each capsule was measured using independent calibrated capacitance hygrometers (HMT333, Vaisala, Vantaa, Finland) every 5 s. Local sweat rate was calculated as the product of absolute humidity and flow rate expressed relative to the surface area covered by the capsule and averaged every minute ($mg \cdot cm^{-2} \cdot min^{-1}$). The local sudomotor thermosensitivity was determined via linear regressions using the 1-minute averages of local sweat rates and the change in mean body temperature from baseline (51). The response time (in minutes) for increases in sweating of the arm and back following the onset of exercise was determined via linear segmental regression using 15-second averages of LSR. Whole-body sweat rate (WBSR) was determined as the difference in mass every 15 minutes of exercise corrected for respiratory water loss (29) and expressed in $g \cdot min^{-1}$, and the sum of these 15-min intervals were expressed as the cumulative whole-body sweat loss (WBSL), which includes periods of both non-steady-state and steady-state sweating.

Calculations

Heat production was calculated as the net difference between metabolic rate (M) and the external work done (W). M was estimated using the following equation (32):

$$M = VO_2 \cdot \frac{\left(\left(\frac{RER - 0.7}{0.3}\right)e_c\right) + \left(\left(\frac{1.0 - RER}{0.3}\right)e_f\right)}{60} \cdot 1000\ [W] \qquad (1)$$

Where: VO_2 is the rate of oxygen consumption ($L \cdot min^{-1}$), e_c is the caloric equivalent per liter of oxygen for the oxidation of carbohydrates (21.12 kJ per L of O_2 consumed), e_f is the caloric equivalent per liter of oxygen for the oxidation of lipids (19.62 kJ per L of O_2 consumed), and respiratory exchange ratio (RER) is the ratio of carbon dioxide production and oxygen consumption (VCO_2/VO_2).

External work to the treadmill was estimated using the following equation from Gibson et al. (15):

$$W = [10^3 (BW \cdot v \cdot gr)] / (36\ 720) \quad [W] \qquad (2)$$

Where: BW is mass in kg, v is the velocity of the belt (in $km \cdot h^{-1}$), and gr is the incline of the belt defined as the fraction of vertical displacement (in meters) for every 100 m of belt rotation.

To ensure that the selected combinations of climate and activity were compensable and uncompensable as required independent of acclimation status, the skin wettedness required (ω_{req}) for heat balance for each trial was estimated prior to study onset based on previously reported data (8). Assuming all heat produced must be liberated via evaporation (e.g. 450 W) due to the near-zero temperature gradient expected between the skin and air, the maximum evaporative potential (E_{max}) for each condition was calculated using the following equation:

$$E_{max} = A_D \cdot (P_{sk,s} - P_a) / (R_{e,cl} + [1/h_e]) \ [W] \qquad (3)$$

Where the body surface area (A_D) was estimated as 1.9 m^2, the vapour pressure gradient between fully saturated skin surface (e.g. 100%RH) and air ($P_{sk,s} - P_a$) to be 4.4 kPa and 2.5 kPa for compensable (30%RH) and uncompensable (60%RH) heat stress, respectively, the evaporative resistance for the clothing ($R_{e,cl}$) was 0.002 $kPa \cdot m^{-2} \cdot W^{-1}$, and the evaporative heat transfer

coefficient (h_e) was assumed to be 120.25 $W \cdot m^{-2} \cdot kPa^{-1}$ for treadmill walking at 5.6 $km \cdot h^{-1}$ (33). The E_{max} of the compensable and uncompensable conditions were estimated to be 750 W and 450 W, respectively. Following, exercise intensity was selected to obtain a desired ω_{req} - the ratio between the evaporative requirements for heat balance (E_{req}) and E_{max} - as ~0.60 and ~1.00 for the compensable and uncompensable conditions, respectively. These values for ω_{req} ensured heat balance was physiologically obtainable (e.g. compensable) or impossible (e.g. uncompensable) independent of acclimation status (Figure 1) as previously reported in the literature (8). The degree of uncompensability was not extended greater than ω_{req} = 1.00 *a priori* as pilot testing outlined an increased risk of hypethermia during 60 minutes of uncompensable heat stress when ω_{req} exceeded 1.00.

Statistical Analysis

All data are reported as the mean ± standard deviation. A two-way repeated measures analysis of variance (ANOVA) with the independent variables of acclimation status (three levels: PRE-TRN, POST-TRN, POST-HA) and exercise time (four levels: 0, 15, 30, 45 min) were used to analyze the dependent variables of T_{es}, T_{re}, T_{sk}, ΔT_{es}, ΔT_{re}, ΔT_{sk}, LSR_{arm}, LSR_{back}, and WBSR during the compensable heat stress trials. A two-way repeated measures ANOVA with the independent variables of acclimation status and time (five levels: 0, 15, 30, 45, 60 min) were used to analyze the same dependent variables during the uncompensable heat stress trials. Separate one-way ANOVAs with the independent variable of acclimation status were used to assess WBSL, sudomotor response time and thermosensitivity of the arm and back during compensable and uncompensable heat stress. A two-way repeated measures ANOVA with the independent variables of acclimation status and condition (compensable vs uncompensable) were used to compare LSR_{arm} at 45 minutes of exercise, LSR_{back} at 45 minutes of exercise, and WBSL between the 31st

and 45th minute of exercise. When a significant interaction was detected, post-hoc comparisons were made using paired-samples *t*-tests. The probability of making a Type I error in all tests was maintained at 5% using a Holm-Bonferroni correction. All statistical analyses were conducted using GraphPad Prism Version 6.0 for Windows (Graphpad Software, La Jolla, CA).

RESULTS

Core and skin temperatures

Compensable Heat Stress: Resting T_{es} was progressively lower POST-HA (36.60±0.27°C) compared to POST-TRN (36.74±0.27°C, P=0.05) and PRE-TRN (36.99±0.19°C; P=0.01); and lower POST-TRN compared to PRE-TRN (P=0.03) As reported previously (40). Further, end-exercise T_{es} was lower POST-HA (37.03±0.32°C) compared to and POST-TRN (37.17±0.27°C, P=0.05) and PRE-TRN (37.39±0.20°C; P=0.01); and lower POST-TRN compared to PRE-TRN (P=0.03). However, the ΔT_{es} (Figure 2A) was similar (P=0.97) PRE-TRN (0.40±0.23°C), POST-TRN (ΔT_{es}: 0.42±0.20°C), and POST-HA (ΔT_{es}: 0.43±0.12°C) despite the observed reduction in absolute core temperature with progressive acclimation.

As reported previously (40), resting T_{re} was progressively lower POST-HA (36.72±0.14°C), compared to POST-TRN (36.89±0.23°C, P=0.03) and PRE-TRN (37.15±0.17°C; P=0.001), and POST-TRN compared to PRE-TRN (P=0.05). Moreover, end-exercise T_{re} was lower POST-HA (37.38±0.16°C) compared to POST-TRN (37.63±0.24°C, P=0.03) and PRE-TRN (37.88±0.17°C, P<0.001), and POST-TRN was lower than PRE-TRN (P=0.05). Although the absolute T_{re} was progressively lower with acclimation throughout exercise, the ΔT_{re} (Figure 2B) following compensable heat stress remained similar (P=0.63) PRE-TRN (ΔT_{re}: 0.73±0.11°C), POST-TRN (ΔT_{re}: 0.74±0.14°C), and POST-HA (ΔT_{re}: 0.70±0.08°C).

Heat acclimation and compensable heat stress

Mean skin temperature prior to exercise demonstrated a similar pattern to core temperature with progressively lower values PRE-TRN (37.07±0.34°C) compared to POST-TRN (36.69±0.38°C, P=0.001) and POST-HA (36.56±0.42°C, P=0.006) as reported previously (40). Similarly, T_{sk} from 30 to 45 minutes of exercise was lower POST-HA (36.84±0.34°C) compared to POST-TRN (37.20±0.32°C, P<0.001) and PRE-TRN (37.69±0.31°C, P<0.001), with POST-TRN also lower than PRE-TRN (P<0.001). However, ΔT_{sk} at the end of the compensable heat stress trial was significantly lower POST-HA (0.29±0.39°C) compared to POST-TRN (0.55±0.36°C, P=0.004) and PRE-TRN (0.67±0.30°C, P=0.001; Figure 2C).

Uncompensable Heat Stress: As during the compensable heat stress trials, resting T_{es} was lower POST-HA (36.62±0.15°C) compared to POST-TRN (36.77±0.22°C, P=0.03) and PRE-TRN (36.86±0.24°C P=0.03), and POST-TRN was lower than PRE-TRN (P=0.05). Also, end-exercise T_{es} was lower POST-HA (37.26±0.18°C) compared to POST-TRN (37.54±0.17°C, P=0.001) and PRE-TRN (37.74±0.25°C P=0.001), and POST-TRN was lower than PRE-TRN (P=0.02). However, in contrast to compensable heat stress, even when accounting for the reduction in resting T_{es} with progressive acclimation, ΔT_{es} during uncompensable heat stress was lower POST-TRN (0.77±0.19°C; P=0.05) and POST-HA (0.75±0.15°C; P=0.04) compared to PRE-TRN (1.10±0.32°C) after 60 min of exercise, however no difference between POST-TRN and POST-HA was observed (P=0.92, Figure 2D).

Again, similarly to compensable heat stress, resting T_{re} was lower POST-HA (36.79±0.16°C) compared to POST-TRN (36.93±0.20°C, P=0.04) and PRE-TRN (37.07±0.2°C, P=0.03), and POST-TRN was lower than PRE-TRN (P=0.05). Further, end-exercise T_{re} was lower POST-HA (37.60±0.19°C) compared to POST-TRN (37.89±0.25°C, P<0.001) and PRE-TRN (37.99±0.12°C, P<0.001), with POST-TRN lower than PRE-TRN (P=0.04). However, in addition

to the progressive decline in resting T_{re} with acclimation, ΔT_{re} during uncompensable heat stress was lower POST-TRN (0.96±0.14°C; P<0.001) and POST-HA (0.96±0.23°C; P=0.003) compared to PRE-TRN (1.13±0.16°C), with no difference observed between POST-TRN and POST-HA (P=0.81, Figure 2E).

Baseline T_{sk} was not different between PRE-TRN (36.91±0.27°C) and POST-TRN (36.72±0.47°C, P=0.80) or POST-HA (36.71±0.34°C, P=0.80). However, T_{sk} was lower following 60 minutes of uncompensable heat stress POST-HA (37.14±0.48°C) in comparison to POST-TRN (37.47±0.41°C; P=0.01) and PRE-TRN (38.04±0.41°C; P<0.001). As such, ΔT_{sk} after 60-min of exercise was lower POST-HA (0.43±0.45°C) compared to POST-TRN (0.75±0.25°C, P<0.001) and PRE-TRN (1.13±0.39°C, P<0.001), and was lower POST-TRN compared to PRE-TRN (P<0.001, Figure 2F).

Sweating

Compensable Heat Stress: WBSL (Fig. 3A) over the course of the 45-min exercise bout was not different between PRE-TRN (494±59 g) and POST-TRN (528±39 g, P=0.17), nor between POST-TRN to POST-HA (557±40 g, P=0.28). However, WBSL was greater POST-HA compared to PRE-TRN (P=0.01). Non-steady-state WBSR (Fig. 2B) during the first 15 minutes of exercise was greater POST-HA (11.8±0.9 g/min, P<0.001) and POST-TRN (11.2±1.2 g/min, P=0.01) compared to PRE-TRN (9.9±2.1 g/min), and POST-HA was greater than POST-TRN (P=0.03). However, when steady-state was achieved (i.e. 31 to 45 minutes of exercise), WBSR (Figure 3B) was not different between POST-TRN (12.7±1.0 g/min) and POST-HA (12.9±0.8 g/min, P=0.80), although WBSR was slightly, but significantly, greater POST-TRN (P=0.02) and POST-HA (P=0.004) in comparison to PRE-TRN (11.7±0.9 g/min).

LSR_{back} (Figure 4B) was similar throughout exercise in a compensable heat stress environment irrespective of acclimation status (P=0.94). However, LSR_{arm} (Figure 4A) was higher after 45 minutes of exercise POST-HA (0.75±0.16 mg/cm^2/min) compared to POST-TRN (0.70±0.14 mg/cm^2/min, P=0.05) and PRE-TRN (0.61±0.15 mg/cm^2/min, P<0.001), and POST-TRN was higher than PRE-TRN (P<0.001).

Uncompensable Heat Stress: WBSL (Figure 3C) was greatest POST-HA (913±126 g) compared to POST-TRN (794±78 g, P=0.002) and PRE-TRN (671±83 g, P<0.001), and POST-TRN greater than PRE-TRN (P=0.002). Additionally, WBSR (Figure 3D) was consistently greater throughout exercise in an uncompensable heat stress environment POST-HA compared to POST-TRN (P=0.02) and PRE-TRN (P<0.001), and greater POST-TRN compared to PRE-TRN (P=0.02).

After 60 minutes of exercise in an uncompensable heat stress environment, LSR_{back} (Figure 4D) was greater POST-HA (1.48±0.28 mg/cm^2/min) compared to POST-TRN (1.39±0.24 mg/cm^2/min, P=0.02) and PRE-TRN (1.21±0.26 mg/cm^2/min, P<0.001), and POST-TRN was greater than PRE-TRN (P<0.001). Similarly, end-exercise LSR_{arm} (Figure 4C) was greater POST-HA (1.20±0.33 mg/cm^2/min) compared to POST-TRN (1.09±0.25 mg/cm^2/min, P=0.007) and PRE-TRN (0.91±0.26 mg/cm^2/min, P<0.001, Fig. 2).

Effect of environment: As illustrated in Fig. 5, time-matched comparisons demonstrate an interaction between heat acclimation status (PRE-TRN, POST-TRN, and POST-HA) compared to environment conditions (compensable vs uncompensable) for LSR_{back} (P=0.03) and WBSL (P=0.02), however not significant with LSR_{arm} (P=0.10).

Sweating response time and Thermosensitivity

Compensable Heat Stress: The response time for increases in sweating of the arm from baseline values was earlier POST-HA (3.0±0.4 mins) compared to POST-TRN (3.7±0.8 mins, P=0.03) and PRE-TRN (4.6±0.7 min, P<0.001), and earlier POST-TRN compared to PRE-TRN (P=0.004). Similarly, the response time for increases in sweating of the back was earlier POST-HA (2.7±0.6 mins) compared to POST-TRN (3.7±0.9 mins, P=0.009) and PRE-TRN (4.5±1.2 mins, P=0.01) with a trend for an earlier sweating response time of the back POST-TRN compared to PRE-TRN (P=0.10). The thermosensitivity of the arm was greater POST-HA compared to PRE- and POST-TRN (P<0.001, Fig. 6). Conversely, the thermosensitivity of the back was not different between PRE-TRN, POST-TRN, and POST-HA (P=0.56, Figure 6).

Uncompensable Heat Stress: An earlier response time for sweating of the arm from baseline values was observed POST-HA (1.9±0.4 mins) in comparison to POST-TRN (3.2±0.7 mins, P=0.02) and PRE-TRN (4.2±1.0 mins, P<0.001), and POST-TRN was earlier than PRE-TRN (P=0.03). Again, the response time for increased sweating of the back was earlier POST-HA (1.8±0.5 mins) compared to POST-TRN (2.9±0.7 mins, P=0.03) and PRE-TRN (3.9±1.0 mins, P<0.001), with POST-TRN earlier than PRE-TRN (P=0.03). The thermosensitivity of the arm was greater POST-HA (P=0.02) and POST-TRN (P=0.04) compared to PRE-TRN, and POST-HA was greater than POST-TRN (P=0.05, Fig. 4). Compared to PRE-TRN, the thermosensitivity of the back was greater POST-HA (P=0.004) and trending to be greater POST-TRN (P=0.08, Figure 5).

DISCUSSION

The present study demonstrates that the display of an altered change in core temperature and to an extent sweating during exercise with partial and complete heat acclimation is only evident during uncompensable heat stress, and not during compensable heat stress. Notwithstanding any cardiovascular adjustment, the principal thermal mechanism of heat

acclimation seems to be the elevation of the upper limit for heat dissipation. That is, when an exercise heat stress is below this upper limit (i.e. compensable heat stress), changes in core temperature are similar irrespective of heat acclimation status. Sweating is slightly augmented, apparently on the arms but not the back, but this does not have a measurable thermoregulatory benefit as any additional evaporation proved insufficient to reduce elevations in core temperature measured in the rectum or esophagus. On the other hand, when exercise is performed under conditions that require a rate of heat dissipation that is beyond the upper physiological limit (i.e. uncompensable heat stress), the thermoregulatory benefits of heat acclimation are evident within the conditions tested. The increase in the upper limit of heat dissipation with acclimation due to a greater maximum skin wettedness (40) supported by much greater sweat rates means that a given combination of exercise and climate is less uncompensable resulting in a slower rate of rise in core temperature with acclimation. This finding also has practical experimental relevance for researchers assessing signs of heat acclimation, as it is clear that uncompensable heat stress conditions must be employed.

Compensable heat stress is characterized by the attainment of heat balance, that is, thermoregulatory heat loss responses sufficiently counterbalance the combined endogenous and exogenous heat load resulting in core temperature reaching an equilibrium (i.e. steady-state). The prevailing theory to date seems to have been that heat acclimation increases the sweating response to heat stress irrespective of the compensability of the exercise heat stress condition (4, 20, 43, 47), resulting in a smaller rise in core temperature. The dependence of the display of the primary hallmarks of heat acclimation on the compensability of the exercise heat stress, to the best of our knowledge, has not been explicitly identified. Previous work has either compared pre- and post-acclimation responses in an uncompensable environment, or under conditions that actually

straddled compensability where the combination of environment and exercise intensity resulted in an uncompensable condition pre-acclimation, but the expected increase in maximum skin wettedness (40), and therefore maximum whole-body evaporative heat loss, transformed the identical conditions to a compensable heat stress condition post-heat acclimation. For example, Frye and Kamon (13) assessed the core temperature and sweating responses of males and females before and after heat acclimation using a standardized exercise heat stress test (30% VO_{2max} and 48°C/14% RH) that, according to standard biophysical calculations, required a skin wettedness of ~0.82 for heat balance. In a recent study (13), we reported a maximum possible skin wettedness pre- and post- heat acclimation were 0.74 and 0.95, respectively, thereby positioning the skin wettedness required for heat balance of the Frye and Kamon (13) conditions either side of the upper limit of heat dissipation depending on acclimation status. It follows that the majority of previous studies assessing the effects of heat acclimation in hot environments used either uncompensable conditions both pre- and post-acclimation (3, 9, 16, 28, 35, 36, 46, 52), or conditions that were uncompensable pre-acclimation but became compensable post-acclimation (1, 4, 10, 13, 20, 21, 31, 44) (Table 2).

Compensable heat stress condition

The present findings clearly demonstrate that when the required level of heat dissipation is attainable (e.g. compensable heat stress), the core temperature response to exercise is unaltered at a fixed rate of heat production irrespective of acclimation status (Figure 2A-B). While we did observe a lower absolute core temperature at the end of exercise during compensable heat stress, this is purely a result of a lower core temperature at baseline, a classic physiological characteristic associated with heat acclimation.

Heat acclimation and compensable heat stress

Previous studies have clearly demonstrated that steady-state whole-body (14) and local (12) sweat rates are determined by the prevailing evaporative requirement for heat balance (E_{req}). Since within each participant E_{req} was fixed, and by definition physiologically attainable in the compensable condition at all stages of our study, we hypothesized that while greater sweat rates would be observed post-acclimation during the early stages of exercise due to an earlier onset and thermosensitivity of sweating, steady-state sweat rates would be similar irrespective of acclimation status. As expected, the exercise time elapsed before an increase in sweating was observed was progressively shorter with acclimation at both the arm and back, and this earlier rise in sweating translated to a greater whole-body sweat loss during the early stages of sweating (i.e. 0-15 mins of exercise in Figure 3B) with heat acclimation. Unexpectedly however, whole-body sweat rates remained marginally greater (i.e. ~0.5 g/min) at steady-state (i.e. 31-45 mins of exercise in Figure 3B) following heat acclimation, apparently supported by greater local sweating on the arm (Figure 4A), but not the upper back (Figure 4B). Consequently, cumulative whole-body sweat loss over the 45-min exercise bout (which includes non-steady-state and steady-state sweating) was ~60 g greater with complete heat acclimation during compensable heat stress (Fig. 2A). In contrast to LSRback and WBSL at steady state (Fig. 6), the greater LSR_{arm} was proportional with progressive heat acclimation in both compensable and uncompensable. Importantly however, this greater sweating with complete heat acclimation seemed to have a relatively minimal biophysical impact in the present study. The additional sweat secreted during compensable heat stress following acclimation would have carried an extra ~50 W of evaporative potential. However, changes in both rectal temperature and esophageal temperature remained similar irrespective of acclimation status throughout (Figure 2A-B). Nevertheless, a smaller rise in skin temperature did occur with acclimation (Figure 2C) indicating any additional cooling effect was restricted to the skin.

Uncompensable heat stress condition

Similar to many previous studies (3, 16, 28, 35, 46) the rise in esophageal temperature and rectal temperature was lower following heat acclimation in comparison to an unacclimated state during uncompensable heat stress (Fig. 2D-E). During uncompensable heat stress, the sweat rate required to achieve the rate of evaporation necessary to maintain heat balance is by definition unobtainable resulting in a continually rising core temperature throughout exercise. Partial and complete heat acclimation are known to increase maximum skin wettedness and thus increase the capacity for evaporative heat loss (40), thereby expanding the upper limit for heat dissipation. This greater skin wettedness is physiologically supported by a clear progressive rise in both whole-body (Figure 3C, D) and local sweat rates (Figure 4C, D) following partial and complete heat acclimation. Further, and as corroborated by others (13, 25, 30, 35, 43), a greater thermosensitivity of the arm and back (Figure 5) were reported confirming the acquisition of sudomotor adaptations associated with heat acclimation during uncompensable heat stress. However, core temperature responses were similar between partial and complete heat acclimation despite more than 110 g of additional sweat lost with complete acclimation (Figure 3C). Similarly, others have reported no difference in the change in core temperature despite greater whole-body sweating following training (48) or heat acclimation (36) following 60 minutes of uncompensable heat stress. On the other hand, the rise in skin temperature was lowest with complete heat acclimation following 60 minutes of uncompensable heat stress (Figure 2F) suggesting any additional evaporation facilitated by greater sweating following complete compared to partial acclimation only permitted more superficial cooling.

Perspectives

The thermal benefits of heat acclimation are predominantly defined by raising the upper limit for heat dissipation, that is an increased maximum skin wettedness and therefore a greater maximum evaporative potential. However, if the evaporative heat loss requirements of a given environmental condition are below the maximum evaporative heat loss potential then acclimation provides a marginal (if any) benefit during exercise. Heat acclimation results in a lower absolute core temperature during exercise, however this is simply a result of a lower core temperature prior to exercise. Apart from minor differences in sweating and a smaller rise in mean skin temperature the majority of the thermoregulatory responses to exercise heat stress when the upper limit of evaporative heat dissipation is not challenged appear similar irrespective of acclimation status. When the upper limit for heat dissipation is challenged (i.e. exceeded), the greater sudomotor adaptation associated with heat acclimation is clearly evident through higher local and whole-body sweat rates, which are sufficient to profoundly blunt the rise in core temperature.

Considerations

Prior to the baseline period, participants were instrumented within the conditions tested to ensure they fully equilibrated with the environment prior to the onset of exercise. While sudomotor priming may have occurred during the baseline period (5, 26), the local sweat rate of the arm and back at the onset of exercise was similar irrespective of acclimation status during compensable and uncompressible heat stress. Further, the onset for rises in local sweating following the initiation of exercise was expressed relative to absolute time and not a physiological parameter such as core temperature due to the small time elapsed until sweating was observed (~3 -5 mins) as previous evidence has demonstrated that even changes in T_{es} may take ~ 3 minutes to be observed (42). Lastly, no control group was utilized in the present study to control for the

independent effect of our heat acclimation protocol (i.e. no training), however it stands to reason based on the past (40) and present findings that the heat acclimation protocol employed was sufficient to increase sudomotor responses for a given uncompensable heat stress. Thus, further evaluation is warranted.

CONCLUSION

Despite the lower absolute core temperature at rest and throughout exercise during compensable heat stress, the change in core temperature remained unaltered with heat acclimation. An earlier rise in sweating following the onset of exercise was observed with partial and complete heat acclimation in comparison to an unacclimated state, resulting in a greater cumulative whole-body sweat loss during compensable heat stress in addition to a greater local sweat rate on the arm. While steady-state whole-body sweat rate was unexpectedly higher following heat acclimation during compensable heat stress any extra evaporative cooling proved insufficient to alter core temperature but did reduce the rise in skin temperature. In comparison to an unacclimated state, partial and complete heat acclimation greatly blunted the rise in core temperature during uncompensable heat stress due to large parallel increases in whole-body and local sweat rates of the arm and back.

Author contributions. N.R., P.I., and O.J. were involved in conception and design of the experimental protocol. N.R. and G.C. were responsible for data collection. Data analysis and interpretation was performed by N.R. and O.J. N.R. drafted the manuscript. O.J. critically revised the manuscript.

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Table 1 The participant characteristics prior to and following the training intervention.

	Pre-Training	**Post-Training**
VO_{2peak} (ml/kg/min)	45.8±11.6	52.0±11.1*
VO_{2peak} (L/min)	3.6±0.8	4.0±0.8*
Weight (kg)	80.2±16.7	78.9±15.5
BSA (m^2)	2.0±0.2	1.9±0.2
Body Fat (%)	26.0±12.0	24.2±11.6†

VO_{2peak} peak oxygen consumption; **BSA** body surface area. *Significantly greater Post-Training ($P < 0.001$). †Significantly lower Post-Training ($P<0.05$).

Table 2. Subjects reported fitness levels, intervention details estimated heat production, and the calculated skin wettedness requirements (ω_{req}) during the heat tolerance tests (HTT) utilized in previous studies investigating the effects of heat acclimation (HA) on thermoregulatory responses.

Study	Intervention (Duration)	Training Status	Ambient Conditions	Heat Production	Estimated HTT ω_{req}	Main Findings (Pre vs Post)
Robinson et al. (1943)	HA (7 - 23 d)	**Physically active**	**40°C, 23%RH**	**560 W**	**0.90**	↓ End-exercise T_{core} ↓ Δ T_{core} = Sweating
Hertig (1963)	AT (2 - 3 wk)	**Physically active**	**45°C, 19%RH**	**240 W**	**0.85**	↓ End-exercise T_{core} ↓ Δ T_{core} ↑ Sweating
Allan (1965)	HA (14 d)	**Physically active**	**40°C, 50%RH**	**430 W**	**0.92**	↓ End-exercise T_{core} ↓ Δ T_{core} ↑ Sweating
Gisolfi and Robinson (1969)	AT (6 wk)	**Healthy and physically fit**	**50°C, 16%RH**	**420 W**	**1.02**	↓ End-exercise T_{core} ↓ Δ T_{core} = Sweating
Mitchel (1976)	HA (10 - d)	**N/A**	**45°C, 40%RH**	**370 W**	**1.40**	↓ End-exercise T_{core} ↓ Δ T_{core} ↑ Sweating
Shvartz (1979)	HA (8 d)	**Untrained**	**40°C, 49%RH**	**480 W**	**1.07**	↓ End-exercise T_{core} ↓ Δ T_{core} ↑ Sweating
Avellini et al. (1979)	HA (10 d)	**Physically active**	**36°C, 64%RH**	**400 W**	**1.82**	↓ End-exercise T_{core} ↓ Δ T_{core} ↑ Sweating
Frye and Kamon (1981)	HA (8 - 9 d)	**Physically active**	**48°C, 14%RH**	**390 W**	♂ **0.82** ♀ **0.83**	= End-exercise T_{core} = Δ T_{core} ↑ Sweating
Cohen and Gisolfi (1982)	AT (11 - wk) + HA (8 - d)	**Untrained**	**45°C, 24%RH**	**300 W**	**0.79**	↓ End-exercise T_{core} ↓ Δ T_{core} = Sweating
Horstman & Christensen (1982)	HA (14 d)	**Physically active**	**45°C, 13%RH**	**440 W**	♂ **0.81** ♀ **0.75**	↓ End-exercise T_{core} ↓ Δ T_{core} ↑ Sweating
Avellini (1982)	AT (4 wk)	**Untrained**	**49°C, 20%RH**	**370 W**	**0.92**	↓ End-exercise T_{core} ↑ Sweating
Pandolf (1988)	HA (10 d)	**Aerobically fit**	**49°C, 20%RH**	**495 W**	**1.09**	↓ End-exercise T_{core} ↑ Sweating
Nielsen (1993)	HA (9 - 12 d)	**Aerobically fit**	**40°C, 15%RH**	**710 W**	**1.77**	↓ End-exercise T_{core} ↓ Δ T_{core} ↑ Sweating
Cheung & McLellan (1998)	HA (14 d)	**Aerobically fit**	**40°C, 30%RH**	**350 W**	***NPC**	↓ End-exercise T_{core} ↑ Sweating
Patterson et al. (2004)	HA (22 d)	**Physically active**	**40°C, 59%RH**	**550 W**	**1.16**	↓ End-exercise T_{core} ↑ Sweating
Weller et al. (2007)	HA (10 d)	**Physically active**	**46°C, 18% RH**	**620 W**	**1.22**	↓ End-exercise T_{core} ↑ Sweating

T_{core}: core temperature, AT: aerobic training
*non-permeable clothing

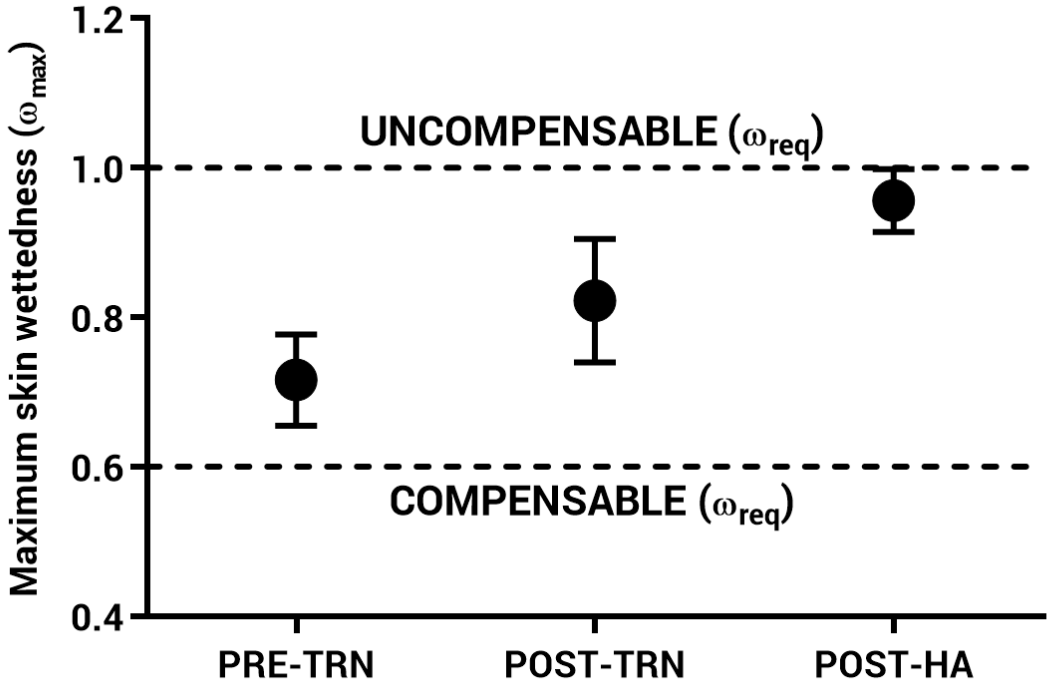

Figure 1. The calculated skin wettedness required (ω_{req}; dashed line) for the compensable (~0.60) and uncompensable (~1.00) heat stress trials contrasted against the previously identified maximum skin wettedness (ω_{max}) for the participants tested **(40).**

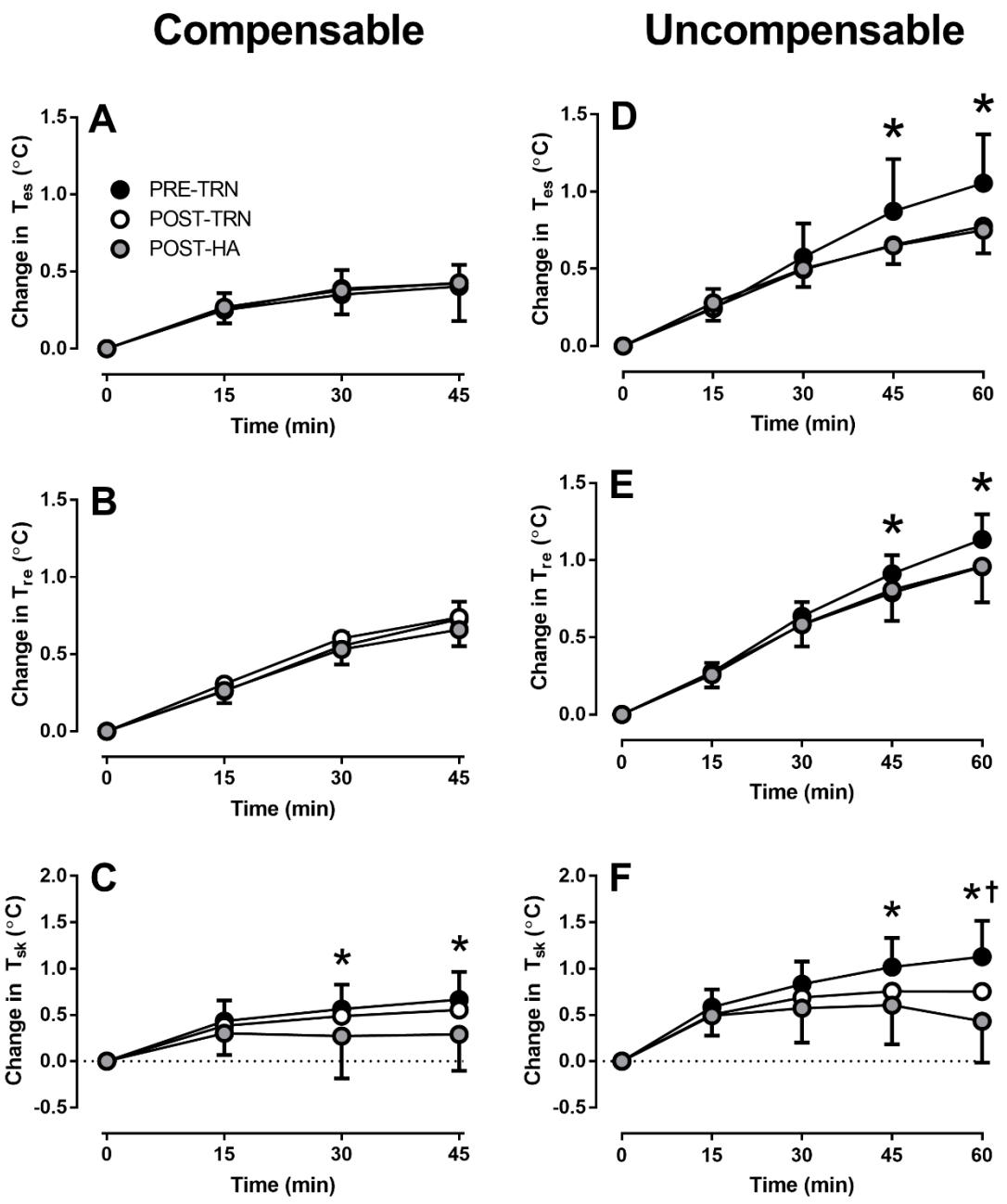

Figure 2. The change in esophageal (T_{es}), rectal (T_{re}), and mean skin temperature (T_{sk}) during compensable (A, B, and C, respectively) and uncompensable (D, E, and F, respectively) heat stress prior to the aerobic training intervention (PRE-TRN), following (POST-TRN), and following training and heat acclimation (POST-HA; n=8). *Significantly greater than PRE-TRN ($P<0.05$). † POST-TRN greater than PRE-TRN ($P<0.05$).

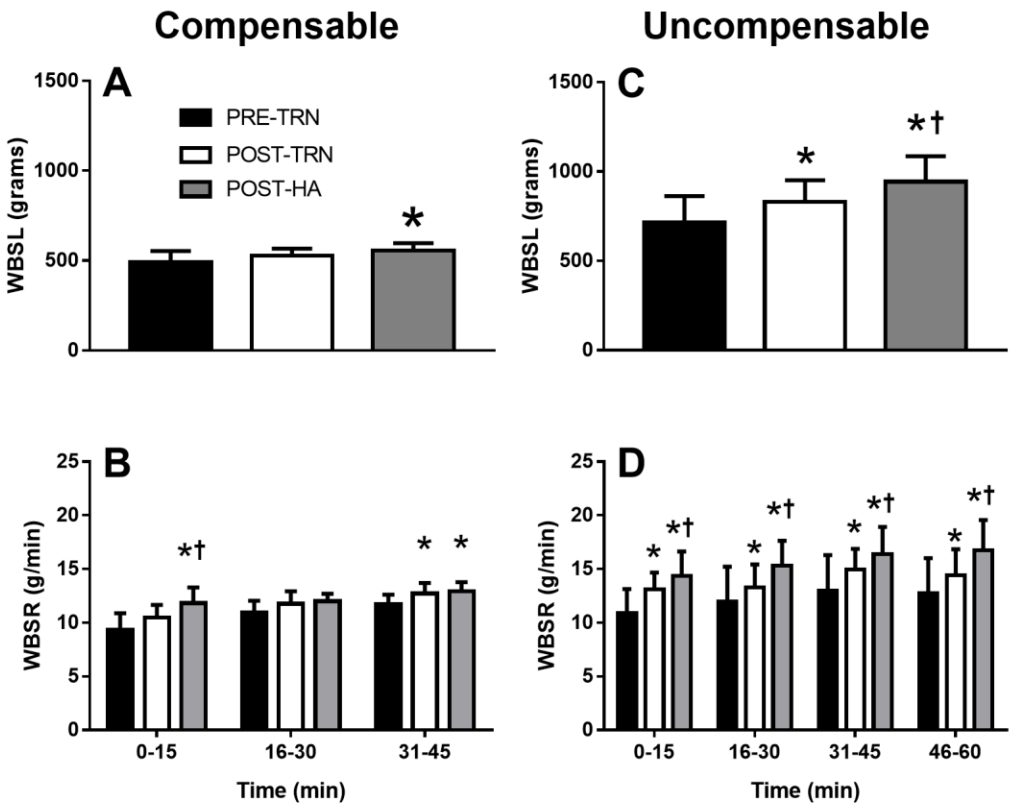

Figure 3. The cumulative whole-body sweat loss (WBSL; A, C) and whole-body sweat rate (WBSR; B, D) prior to the aerobic training intervention (PRE-TRN), following (POST-TRN), and following training and heat acclimation (POST-HA) during compensable and uncompensable heat stress (n=8). *POST-HA greater than PRE-TRN (P<0.05). † POST-TRN greater than PRE-TRN (P<0.05).

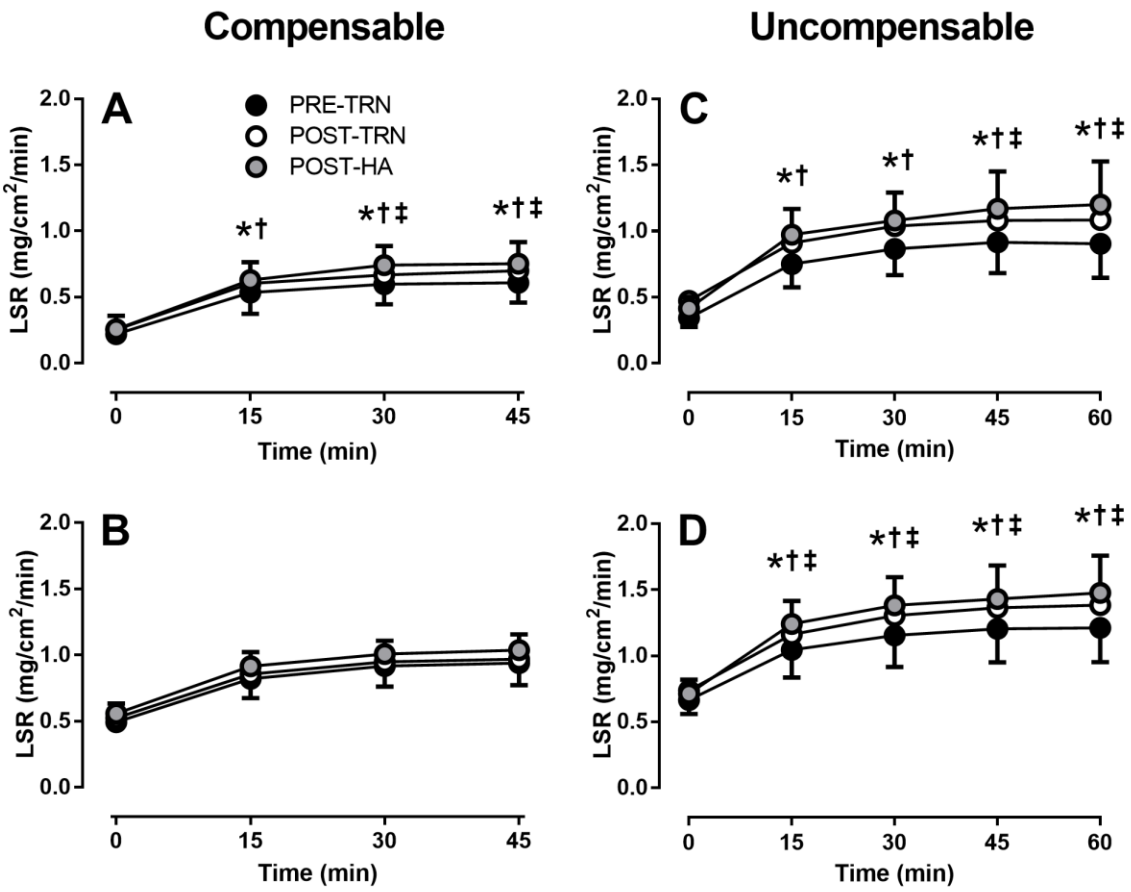

Figure 4. Local sweat rates (LSR) of the arm and back during compensable (A, B) and uncompensable (C, D) heat stress prior to the aerobic training intervention (PRE-TRN), following (POST-TRN), and following training and heat acclimation (POST-HA; n=8). *POST-HA greater than PRE-TRN ($P<0.05$). † POST-TRN greater than PRE-TRN ($P<0.05$). ‡POST-HA greater than POST-TRN ($P<0.05$).

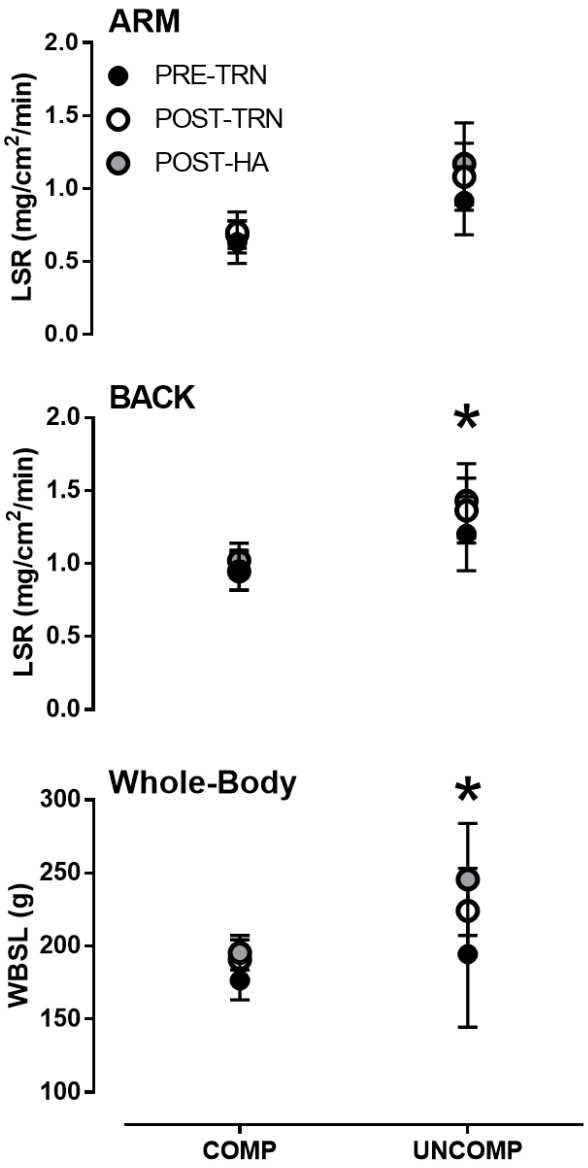

Figure 5. Local sweat rate of the arm (top) and back (middle) at the 45th minute of exercise and whole body sweat rate (WBSL) between the 30th and 45th minute during compensable (COMP) and uncompensable (UNCOMP) heat stress prior to the aerobic training intervention (PRE-TRN), following (POST-TRN), and following training and heat acclimation (POST-HA; n=8). *Significantly interaction between environment (COMP vs UNCOMP) and heat acclimation status (PRE-TRN, POST-TRN, and POST-HA) ($P<0.05$).

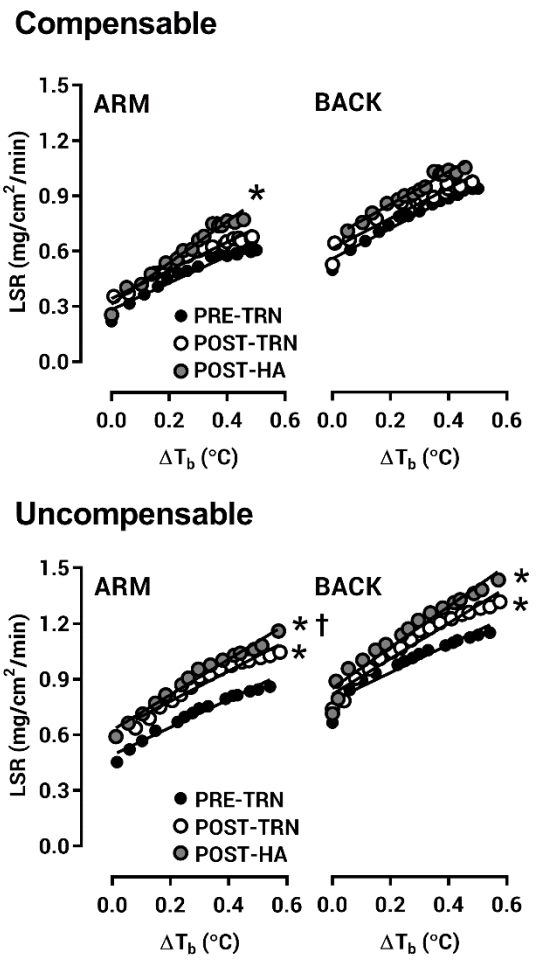

Figure 6. The thermosensitivity of the arm and back sweat rate response to increasing mean body temperature during compensable (top) and uncompensable (bottom) heat stress prior to the aerobic training intervention (PRE-TRN), following (POST-TRN), and following training and heat acclimation (POST-HA; n=8). *Significantly greater than PRE-TRN (P<0.05). †Significantly greater than POST-TRN (P=0.05).

3.3 Thesis Study #3

This article was accepted for publication to *Medicine & Science in Sports & Exercise* in September 2017 and has been formatted accordingly. The final published version can be found in Appendix B.

Maximum skin wettedness following aerobic training with and without heat acclimation

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Running Title: *Training, acclimation, and skin wettedness*

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ABSTRACT

PURPOSE: To quantify how maximum skin wettedness (ω_{max}), i.e. the determinant of the boundary between compensable and uncompensable heat stress, is i) altered by aerobic training in previously unfit individuals, and ii) further augmented by heat acclimation. **METHODS:** Eight untrained individuals completed an 8-week aerobic training program immediately followed by 8 days of hot/humid (38°C, 65%RH) heat acclimation. Participants completed a humidity ramp protocol pre-training (PRE-TRN), post-training (POST-TRN), and post-heat acclimation (POST-HA), involving treadmill marching at a heat production of 450 W for 105 mins in 37.5°C, 2.0 kPa (35%RH). After attaining a steady-state esophageal temperature (T_{es}), humidity increased 0.04 $kPa \cdot min^{-1}$. An upward inflection in T_{es} indicated the upper limit of physiological compensability (P_{crit}), which was then used to quantify ω_{max}. Local sweat rate (LSR), activated sweat gland density (ASGD) and sweat gland output (SGO) on the back and arm were simultaneously measured throughout. **RESULTS:** Peak aerobic capacity increased POST-TRN by ~14% (PRE-TRN:45.8±11.8 $ml \cdot kg^{-1} \cdot min^{-1}$; POST-TRN:52.0±11.1 $ml \cdot kg^{-1} \cdot min^{-1}$, $P<0.001$). ω_{max} values became progressively greater from PRE-TRN (0.72±0.06) to POST-TRN (0.84±0.08; P=0.02), to POST-HA (0.95±0.05; P=0.03). These shifts in ω_{max} were facilitated by a progressively greater LSR and ASGD from PRE-TRN (0.84±0.21 $mg \cdot cm^{-2} \cdot min^{-1}$; 67±20 $glands \cdot cm^{-2}$) to POST-TRN (0.96±0.21 $mg \cdot cm^{-2} \cdot min^{-1}$, P=0.03; 86±27 $glands \cdot cm^{-2}$; P=0.009), to POST-HA (1.15±0.21 $mg \cdot cm^{-2} \cdot min^{-1}$; $P<0.001$; 98±35 $glands \cdot cm^{-2}$; $P<0.001$). No differences in SGO were observed. **CONCLUSION:** A greater ω_{max} occurred after 8 weeks of aerobic training, but ω_{max} was further augmented with heat acclimation, indicating only a partially increased heat loss capacity with training. These ω_{max} values may assist future predictions of heat stress risk in untrained/trained unacclimated individuals, as well as trained heat-acclimated individuals.

Introduction

The evaporation of sweat from the skin surface is the largest modifiable heat loss pathway for maintaining thermal equilibrium during heat stress. Understanding the factors that define the maximum capacity for evaporative heat loss (E_{max}), and thus the metabolic heat production that can be physiologically compensated before unchecked elevations in core temperature occur (i.e. uncompensability), is therefore essential for predicting heat stress risk in physically active people in hot environments (e.g. occupational workers, athletes, military).

In a given environment, E_{max} is determined by the proportion of total skin area that can be saturated in sweat (i.e. maximum skin wettedness (ω_{max})). A ω_{max} of 1.00 (i.e. 100% body surface coverage) is the highest value possible, and is widely considered to be attained following complete heat acclimation. On the other hand, unacclimated individuals are considered to be only capable of attaining a ω_{max} of 0.85 (1). Many existing computational models defining the environmental and/or duration limits for heat stressed occupational workers employ these assumed ω_{max} values of 0.85 for unacclimated and 1.00 for heat acclimated workers (ISO7933:2004 (2); Thermal Work Limit (3)). Yet, no ω_{max} value exists for a trained vs. untrained, unacclimated worker, except the suggestion that the ω_{max} changes that occur with training are analogous to heat acclimation (4). Even the widely accepted ω_{max} values for unacclimated and acclimated individuals are derived from a small sample size (n=4), in a supine posture, with passive heat acclimation, and unknown training status.

While steady-state core temperature and sweating responses do not seem to be altered by maximum aerobic capacity (5,6), it remains plausible that a partial heat acclimation associated with physical training may raise the upper limit of evaporative heat dissipation (i.e. ω_{max}). Indeed, aerobically trained individuals exhibit greater maximal sweat rates compared to untrained

individuals when exercising in hot and humid conditions (7) or via pharmacologically induced stimulation (8). The ability to attain greater sweat rates may also support why aerobically fit individuals achieve a heat acclimated state in fewer days compared to less fit individuals (9). However, a greater sweat rate may not directly translate to a greater ω_{max} and therefore E_{max} if the additional sweat secreted ultimately drips off the body providing no cooling. In fact, a greater ω_{max} and therefore E_{max} requires a more uniform and complete distribution of sweat across the body surface. While activated sweat gland density (ASGD) increases as a function of aerobic fitness (10,11), it remains unclear whether this enables a greater maximum sweat coverage (i.e. ω_{max}) in previously untrained people (e.g. individuals who do not engage in regular physical activity).

The purpose of the present study was to assess whether aerobic training increases ω_{max} and identify how this increase, if any, is further augmented by heat acclimation. We compared the evaporative capacity and sudomotor responses of young, untrained participants using a humidity ramp protocol (12) before and following an 8-week aerobic training program in a cool environment (22°C, 30%RH), and then after 8 days of heat acclimation in a hot and humid (38°C, 65%RH) environment that immediately followed. It was hypothesized that training increases ω_{max}, but this increase is augmented further with heat acclimation. It was also hypothesized that the progressively greater ω_{max} with training and then heat acclimation is facilitated by an increased ASGD.

Methods

Participants

Ethical approval was obtained from the University of Ottawa Health Sciences Research Ethics Board (H12-11-05) conforming to the principles set forth in the Declaration of Helsinki 2013. All volunteers gave both verbal and written consent prior to participation. To ensure

participants were sufficiently healthy to conduct the study protocols, they were required to fill out a Physical Activity Readiness Questionnaire and an American Heart Association Pre-participation Screening Questionnaire. All participants had no prior cardiovascular, neuromuscular, and/or respiratory medical condition that could be exacerbated with exercise, and were non-smokers or at least 12 months without smoking. Lastly, all participants reported no involvement in structured training programs and were failing to meet the weekly moderate physical activity recommendations set forth by the American College of Sports Medicine by more than 35% (13).

Based on previously reported data (14), a power calculation (G*Power 3.1.9.2) determined that a minimum of eight participants was required to demonstrate a significant difference. A Cohen's d effect size of 1.17 was determined using the previously reported critical ambient vapor pressure of heat acclimated (3.80 kPa) women (14) and a hypothesized trained but unacclimated (i.e. median of unacclimated and heat acclimated: 92.5%; 3.52 kPa) with a variance 2-fold greater than previously reported (0.24 kPa), and β- and α-values were equal to 0.80 and 0.05, respectively. All participants commenced during the winter months to eliminate any potentially seasonal partial acclimation (15). Initially, 10 people were recruited, however 2 participants voluntarily withdrew during the training intervention and therefore a total of 8 people (6 males, 2 females) completed in the study. Participant characteristics are given in Table 1.

Experimental Design

Participants completed an 8-week training intervention immediately followed by an 8-day heat acclimation protocol, whereby 2 aerobic capacity assessments (pre- and post-training) and 3 inflection trials (INF) at (i) pre-training, (ii) post-training, and (iii) post heat acclimation were performed within the study timeline (Figure 1). All VO_{2max} and INF trials were conducted at the same time of day to mitigate any influence of circadian rhythm (16). In order to account for the

potential influence of the menstrual cycle for female participants (17), the 8-week training intervention ensured pre- and post-training inflection trials occurred at a similar stage (e.g. week) of their respective menstrual cycle, which they verbally confirmed. Since both males and females respond similarly following heat acclimation, independent of the menstrual cycle (18), female participants readily completed the heat acclimation protocol immediately following the 2nd INF trial.

Fitness assessments: Participants were asked to refrain from food for 2 h prior to testing, however water ingestion was permitted *ad libitum*. First, the participant's body composition was assessed using a dual-energy x-ray absorptiometry scanner (GE-LUNAR Prodigy module, GE Medical Systems, Madison, WI). Next, the participant completed a Modified Bruce Treadmill Protocol (19) in accordance to the safe practice regulations outlined by the Canadian Society of Exercise Physiologists (CSEP (20)). Expired gases were measured via breath-by-breath indirect calorimetry using a metabolic cart (Vmax Encore, Care Fusion, Yorba Linda, CA) and averaged every minute and heart rate via a cardiotachometer (Polar RS 400CX, Polar Electro Oy, Kempele, Finland).

Inflection (INF) trial: Participants were instructed to eat a light meal ~2 h prior to arrival and to ensure adequate hydration. Upon arrival, participants provided a urine sample to confirm hydration status using urine specific gravity (USG) measured via a refractometer. Participants arrived with a similar hydration status (e.g. USG measure) prior to all trials (PRE-TRN: 1.012±0.007, POST-TRN: 1.011±0.006, POST-HA: 1.012±0.005). Participants were instructed to change into standardized clothing (males: shorts and shoes; females: shorts, shoes and sports bra), after which they self-inserted their rectal thermistor. The participant then entered the climatic chamber (37.5˚C and 2.0 kPa), was instrumented, and then rested for 30 minutes in a seated

position to equilibrate with the surrounding environment. Next, the participant began marching on a treadmill at an intensity that elicited a metabolic heat production (H_{prod}) of 450 W; monitored and maintained in real-time via indirect calorimetry. All participants achieved a steady state core temperature by the 38th minute of exercise; defined as a less than 0.05°C increase in esophageal temperature (T_{es}) during the preceding 10 minutes. After 45 minutes of exercise, ambient vapour pressure (P_a) of the room increased at a rate of ~0.04 kPa/min in a linear fashion until 4.60 kPa was reached (sixty additional minutes). The critical ambient vapour pressure (P_{crit}) was identified as the point at which an upward inflection in esophageal temperature (T_{es}) was observed signifying the transition from a compensable to uncompensable state ((12); Figure 2A). P_{crit} was verified using segmental linear regression (Graphpad Prism 7.0, La Jolla, CA; Figure 2B).

Training intervention: Each participant then underwent an 8-week training intervention where they were required to partake in 4 weekly sessions of supervised aerobic training in temperate conditions (~22°C, 30%RH) with the goal of increasing VO_{2peak} by at least 10%. All intensities prescribed during training were defined based on the heart rate associated for a given percentage of VO_{2peak}, therefore a cardiotachometer was worn for every session. The first week of training consisted of 4×60-minute sessions at 60% of VO_{2peak}. From the second week onwards, participants completed 3×60-minute sessions at 70% of VO_{2peak} and 1 high-intensity interval training (HIIT) session. The HIIT session consisted of a warm up at 50% of VO_{2peak}, followed by 10×3 minute intervals involving 1.5 minutes at 90% of VO_{2peak} followed by 1.5 minutes at 50% of VO_{2peak}, and a 10-minute self-paced cool-down. The absolute external work during the HIIT was increased by no more than 10% each week. The majority of aerobic training was performed on a treadmill, however due to safety concerns, HIIT was predominantly done on an upright cycle

ergometer. In sum, the training program increased in intensity every week thus minimizing the risk of observing non-responders to aerobic training (21).

Heat acclimation: Immediately following the second INF trial, participants completed 8 consecutive days of up to 90-minute exercise bouts in a hot and humid environment (38°C, 65% RH) where they walked on a treadmill with a slight grade (i.e. 3-5%) at 70% of maximum heart rate (HR_{max}). A clamped heart rate protocol permitted a progressive increase in workload throughout the 8-day intervention due to the rapid reductions in heart rate during heat acclimation (22), thus it was hypothesized a positive thermal impulse was sustained (23) as most recently observed by Garrett et al. (24) during a short-term heat acclimation protocol on elite male rowers. Body mass was taken immediately prior to and following each session using a platform scale (Combics 2; Sartorius, Mississauga, Ontario, Canada). Fluid was restricted during each session, however participants were given a volume of electrolyte replacement beverage (Gatorade G2®, Quaker Oats Company, Chicago, USA) equal to the total mass loss following each session.

Instrumentation

Thermometry: T_{es} was measured using a general purpose thermistor probe (Mon-A-Therm General Purpose Temperature Probe 400TM; Covidien, Mansfield, MA, USA) inserted through the nasal cavity into the esophagus. The end of the thermistor probe is estimated to be located at a region nearest the left ventricle (25). Rectal temperature (T_{re}) was measured using a general purpose thermistor probe inserted to a depth of 20 cm past the anal sphincter. Skin temperature was measured using 4 thermistor heat flux sensors (Concept Engineering, Old Saybrook, CT, USA) which were secured to the skin using surgical tape (Transpore®, 3M, London, ON). Temperature measurements were sampled every 5 s (NI cDAQ-91722 module, National Instruments, Austin, TX) and displayed in real-time on a desktop computer using customized

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LabView software (v7.0, National Instruments, Austin, TX). Mean skin temperature (T_{sk}) was calculated as the weighted average of four sites using the Ramanathan 1964 equation (26); chest 30%, triceps 30%, thigh 20%, and calf 20%.

Sweating: Ventilated sweat capsules secured to the skin using surgical tape were used to measure local sweat rates of the back (LSR_{back}) and forearm (LSR_{arm}). Anhydrous air was supplied through each 4.1-cm^2 capsule and flow was maintained at a constant rate of 1.0 $L \cdot min^{-1}$ and 1.2 $L \cdot min^{-1}$ for LSR_{back} and LSR_{arm}, respectively, using a factory calibrated flow meter (Omega FMA-A2307, Omega Engineering, Stamford, CT). The temperature and humidity of the capsules effluent air were sampled with region specific (i.e. arm and back) calibrated capacitance hygrometers (HMT333, Vaisala, Vantaa, Finland) every 5 s. The local sweat rate was calculated as the product of absolute humidity and flow rate, and expressed relative to the amount of skin surface covered by the capsule and averaged every minute ($mg \cdot cm^{-2} \cdot min^{-1}$). Activated sweat gland density of the arm ($ASGD_{arm}$) and back ($ASGD_{back}$) was measured within 2 cm of their respective ventilated capsule using the starch-iodine paper technique (27). Impressions were taken using a 9-cm^2 piece of 100% cotton paper (Moab Entrada, Legion Paper, New York, USA) every 15 minutes of exercise. Sweat gland output for the arm (SGO_{arm}) and back (SGO_{back}) was calculated by dividing the region-specific sweat rate by the respective activated sweat gland density (in $\mu g \cdot gland^{-1} \cdot min^{-1}$).

Calculations

Partitional Calorimetry: heat balance parameters were estimated via partitional calorimetry (28) and expressed relative to body surface area (BSA) estimated using the DuBois and DuBois equation (29).

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External work to the treadmill was estimated using the following equation (30):

$$W = \{[10^3 (BW \cdot v \cdot gr)] / (6.12 \times 60 \times 100)\}/A_D \ [W \cdot m^{-2}] \quad (1)$$

Where: BW is mass in kg, v is the velocity of the belt (in $km \cdot h^{-1}$), gr is the incline of the belt defined as the fraction of vertical displacement (in meters) for every 100 m of belt rotation, and A_D is body surface area (in m^2) estimated using the Dubois and DuBois equation (29).

The rate of metabolic heat production (H_{prod}) was calculated by subtracting the rate of external work (in W) from metabolic energy expenditure (M). M was estimated using the following equation:

$$M = \dot{V}O_2 \cdot \frac{\left(\left(\frac{RER - 0.7}{0.3}\right)e_c\right) + \left(\left(\frac{1.0 - RER}{0.3}\right)e_f\right)}{60 \cdot A_D} \cdot 1000 \ [W \cdot m^{-2}] \quad (2)$$

Where: $\dot{V}O_2$ is the rate of oxygen consumption (L/min), e_c is the caloric equivalent per liter of oxygen for the oxidation of carbohydrates (21.13 kJ per L of O_2 consumed), e_f is the caloric equivalent per liter of oxygen for the oxidation of lipids (19.62 kJ per L of O_2 consumed), and respiratory exchange ratio (RER) is the ratio of carbon dioxide production and oxygen consumption (VCO_2/VO_2).

Convective heat exchange from the skin, *C*, was calculated as (28):

$$C = h_c \cdot (T_{sk} - T_a) \ [W \cdot m^{-2}] \quad (3)$$

Where: h_c is the convective heat transfer coefficient for treadmill walking as derived by Nishi and Gagge (31):

$$h_c = 6.51 \cdot v^{0.391} \ [W \cdot m^{-2} \cdot K^{-1}] \quad (4)$$

Where: v is the walking speed (in $m \cdot s^{-1}$), A_D is body surface area (in m^2) estimated using the Dubois and DuBois equation (29). Within each participant, walking speed was consistent for each INF trial throughout the intervention and only grade was manipulated to maintain a fixed H_{prod}.

Radiant heat transfer (R) was estimated by:

$$R = h_r \cdot (T_{sk} - T_r) \ [W \cdot m^{-2}] \quad (5)$$

Where: h_r (radiant heat transfer coefficient) in $W \cdot m^{-2} \cdot K^{-1}$ is estimated using the following:

$$h_r = \varepsilon \cdot 4\sigma \cdot (A_r/A_D) \cdot ((T_{sk} + T_r)/2 + 273.15)^3 \ [W \cdot m^{-2} \cdot K^{-1}] \quad (6)$$

Where: ε is the area weighted emissivity of the body surface (0.95), σ is the Stefan-Boltzmann constant (5.67×10^{-8} $W/m^2/K^4$), A_r/A_D is the effective radiative surface area (ND) which can be estimated as 0.73 for a standing person (32), and $T_{sk} + T_r$ is the sum of the mean skin temperature and mean radiant temperature (°C), assumed to be equivalent to T_a (°C).

Respiratory heat loss was estimated using the following:

$$E_{res} + C_{res} = 0.0173 \cdot (H_{prod}) \cdot (5.87 - P_a) + 0.0014 \cdot (H_{prod}) \cdot (34 - T_a) \ [W \cdot m^{-2}] \quad (7)$$

The evaporative requirement to maintain heat balance (E_{req}) in W was estimated by rearranging the conceptual heat balance equation:

$$E_{req} = H_{prod} - (C + R + C_{res} + E_{res}) \ [W \cdot m^{-2}] \quad (8)$$

Estimating maximum skin wettedness (ω_{max}): The maximum rate of evaporative heat loss (E_{max}) for a given environment can be estimated as:

$$E_{max} = \omega_{max} \ (P_{sk,s} - P_a) \ / \ (R_{e,cl} + [1/h_e * f_{cl}]) \ [W \cdot m^{-2}] \quad (9)$$

Where: ω_{max} is the maximum skin wettedness (33); P_a is the absolute ambient vapour pressure at E_{max} (in kPa) which is equal to P_{crit} measured in the INF trial (Figure 1); $R_{e,cl}$ is the evaporative heat transfer resistance of the clothing ensemble (assumed to be 0.002 $kPa \cdot m^2 \cdot W^{-1}$); f_{cl} is the clothing area factor (surface area of the clothed body divided by the surface area of the nude body; assumed to be negligible); h_e is the evaporative heat transfer coefficient in $W \cdot m^{-2} \cdot kPa^{-1}$ which is the product of h_c (Eq. 4) and the Lewis Relationship (16.5 $K \cdot kPa^{-1}$); and $P_{sk,s}$ is the saturated water vapour pressure (in kPa) at skin temperature and was derived using Antoine's equation:

$$P_{sk,s} = (\exp (18.956 - [4030.18/(T_{sk} + 235)])/10 \text{ [kPa]} \quad (10)$$

At the breakpoint of compensability (i.e. the upward inflection in T_{es}; Figure 1), E_{req} must equal the individual's actual E_{max}. Thus, ω_{max} can be estimated by rearranging Eq. 9 and substituting E_{max} with E_{req}:

$$\omega_{max} = (E_{req} * [R_{e,cl} + (1/h_e)])/(P_{sk,s} - P_{crit}) \quad (11)$$

Statistical analysis

All data are reported as mean and standard deviation (mean±SD). Paired t-tests were used to compared participant characteristics (mass, BSA, BSA:mass, body fat %, and VO_{2peak}) before and after the training intervention. A one-way analysis of variance (ANOVA) employing the independent variable of condition (3 levels: pre-training, post-training, and post-heat acclimation) was used to assess ω_{max}, P_{crit}, $P_{sk,s}$-P_{crit} gradient, T_{es}, T_{re}, T_{sk}, HR, LSR_{arm}, LSR_{back}, $ASGD_{arm}$, $ASGD_{back}$, SGO_{arm}, and SGO_{back} at the break-point of compensability (i.e. P_{crit}), as well as resting T_{es}, T_{re}, and T_{sk}, and HR. If significance was observed, post-hoc comparisons were conducted using a Holm-Sidak multiple comparisons test. All statistical analyses were conducted using GraphPad Prism Version 7.0 for Windows (Graphpad Software, La Jolla, CA, USA).

Results

Training intervention: VO_{2peak} was ~14% greater following the training intervention (P<0.001, Table 1). The training intervention did not alter mass, BSA, and BSA:mass, however a reduction in body fat % (P<0.03) following training was observed (Table 1).

Indicators of a physiological adaptation to the heat: Resting T_{es} and T_{re} were lower post-training (P=0.03) and further reduced after heat acclimation (P<0.001) in comparison to pre-training (Table 2). Similarly, Resting T_{sk} was lower post-training (P=0.003) and post heat acclimation (P<0.001) compared to pre-training. Resting heart rate was lower post-training (P=0.03) and post-heat acclimation (P<0.001) in comparison to pre-training, and post-heat acclimation was lower than post training (P=0.03). At the upper limit of compensability (e.g. P_{crit}), T_{re} and T_{es} were lower post heat acclimation in comparison to pre-training (P<0.001). T_{sk} was lower post-training (P<0.001) and following heat acclimation (P<0.001) in comparison to pre-training. Lastly, the HR at P_{crit} was lower post heat acclimation (P<0.001) and post-training (P=0.003) compared to pre-training, and lower post heat acclimation compared to post-training (P=0.05).

Maximum skin wettedness (ω_{max}): Individual and mean ω_{max} values pre-training, post-training, and post heat acclimation are presented in Fig. 3. In comparison to pre-training, ω_{max} was progressively greater post-training (P=0.02) and post heat acclimation (P<0.001, Table 2, Fig. 3). Additionally, ω_{max} post-acclimation was greater than post-training (P=0.04). Supporting the estimated ω_{max} values, P_{crit} was greater post-training (P=0.009) and post heat acclimation (P<0.001) compared to pre-training, and P_{crit} was greater post heat acclimation compared to post-training (P=0.005). Furthermore, the $P_{sk,s} - P_a$ gradient at P_{crit} was lower post heat acclimation

compared to pre- (P<0.001) and post-training (P=0.01), and lower post-training compared to pre-training (P=0.02).

Sweating: Figure 4 demonstrates all sudomotor parameters at the upper limit of physiological compensability (i.e. when ω_{max} was reached). At ω_{max}, LSR_{arm} was higher post-training (0.80±0.18 mg·cm^{-2}·min, P=0.004) and post-heat acclimation (1.00±0.22 mg·cm^{-2}·min, P<0.001) compared to pre-training (0.67±0.24 mg·cm^{-2}·min), and higher at ω_{max} post-heat acclimation compared to post-training (P=0.03). Similarly, LSR_{back} was higher post-heat acclimation (1.30±0.20 mg·cm^{-2}·min, P<0.001) and post-training (1.12±0.23 mg·cm^{-2}·min, P=0.009) compared to pre-training (1.00±0.18 mg·cm^{-2}·min), and higher post-heat acclimation compared to post-training (P=0.001). $ASGD_{arm}$ was higher at ω_{max} post-training (102±30 glands·cm^{-2}, P=0.008) and post-heat acclimation (117±45 glands·cm^{-2}, P=0.001) compared to pre-training (73±22 glands·cm^{-2}). Likewise, $ASGD_{back}$ was higher at ω_{max} post-training (70±23 glands·cm^{-2}, P=0.03) and post-heat acclimation (78±25 glands·cm^{-2}, P<0.001) compared to pre-training (61±18 glands·cm^{-2}). Further, $ASGD_{back}$ at ω_{max} was higher post-heat acclimation compared to post-training (P=0.03). No differences in SGO_{arm} or SGO_{back} were observed at ω_{max} between pre-training (Arm: 10.4±5.0 µg·gland·min^{-1}, Back: 18.5±8.8 µg·gland·min^{-1}), post-training (Arm: 8.8±3.9 µg·gland·min^{-1}, Back: 18.2±8.2 µg·gland·min^{-1}), and post-heat acclimation (Arm: 9.9±4.4 µg·gland·min^{-1}, Back: 19.0±8.6 µg·gland·min^{-1}).

Discussion

The present study is the first to our knowledge to quantify the shift in maximum skin wettedness with aerobic training relative to an untrained non-heat acclimated state, and a trained fully heat acclimated state. Untrained non-heat acclimated individuals were able to physiologically

wet a maximum of ~72% of their skin surface, and this was increased to ~84% following 8 weeks of aerobic training (and a ~14% increase in VO_{2max}). However, following 8-days of heat acclimation ~95% of the skin surface could be saturated with sweat, indicating only a partial heat acclimation response with aerobic training. Physiologically, the ability to achieve a higher ω_{max} with an improved training/acclimation status was facilitated by a higher LSR on both the arm and back mediated by a greater number of simultaneously activated sweat glands, which potentially facilitated an enhanced distribution of sweat on the skin surface and the attainment of greater rates of maximal evaporative heat loss.

While we have clearly shown in the past that between-group differences in VO_{2max} do not independently alter submaximal thermoregulatory responses in a compensable environment (5,6), the different ω_{max} values pre-training, post-training, and post-heat acclimation clearly demonstrates that aerobic training within a given individual can increase the upper biophysical limit for evaporative heat loss and thus the boundary between compensability and uncompensability. The present data indicate that the ω_{max} of an untrained and unacclimated person is ~10% lower than currently assumed by ISO standards (e.g. 0.85) (2). This difference may be attributed to earlier studies quantifying ω_{max} of unacclimated individuals while i) not fully accounting for the training status of their participants, and ii) limiting their exposures to passive heat stress in the supine position on a netted bed (1), which may not directly translate to upright exercise. For example, reductions in sweating efficiency during upright exercise have been reported to occur at a lower skin wettedness required for heat balance in comparison to supine rest (34). While sweat may accumulate on the chest or run to the back during supine rest, with upright exercise sweat droplets may drip more readily especially from moving extremities.

Training, acclimation, and skin wettedness

Eight days of heat acclimation further increased ω_{max} above post-training values by an additional ~10-15% demonstrating only a partial heat acclimation occurred with 8 weeks of aerobic training. The classical adjustments in thermo-physiological parameters indicative of a partial acclimation following aerobic training were observed (i.e. lower resting core and skin temperature, and higher maximal sweat rates; (22)). However, these parameters were further altered following heat acclimation thus supporting the partial, and not complete (Table 2, Fig. 3), heat acclimation response associated with aerobic training in the previously untrained cohort.

In comparison to pre-training, the graded increase in LSR on the back and arm following aerobic training and heat acclimation at ω_{max} illustrate a peripheral modification to attain a greater ω_{max} and by definition a greater E_{max}. Others have reported greater maximum sweat rates as a function of fitness (8) and following heat acclimation (35) via subcutaneous administration of acetylcholine. However whether this additional sweating could contribute to a greater evaporative capacity or would simply all drip off the body was unclear. The findings of the present study support the former notion. The greater LSR on the back and arm at ω_{max} was attained via a greater ASGD but not a greater SGO following both training and acclimation (Fig. 4). A higher maximum ASGD has been previously shown with training during pharmacological stimulation (11) or exercise in temperate conditions (10), and following heat acclimation (36). On the other hand, a greater SGO without changes in ASGD with training and/or acclimation have been reported by others with iontophoresis (8). Biophysically, the present findings seem to stand to reason with respect to the attainment of a greater ω_{max} following training and acclimation. Increasing the number of sweat glands activated per surface area would theoretically permit a more complete saturation of the skin surface (and thus a greater ω_{max}), whereas increasing SGO would potentially just yield a lower evaporative efficiency without altering ω_{max}.

Training, acclimation, and skin wettedness

Cardiorespiratory fitness has been previously hypothesized to predict the level of heat acclimation (9), and has recently been used to define ω_{max} in trained and untrained males as 1.00 and 0.85, respectively (4). Indeed, the 8-week aerobic training program in the present study increased VO_{2max} of all participants by ~15%, however ω_{max} post-training was not similar to predicted values for heat acclimated males as previously assumed (1.00). Rather post-training ω_{max} was comparable to the previously assumed ω_{max} of an unacclimated person, and pre-training ω_{max} values were lower compared to post-training (0.72 vs 0.84). While difficult to confirm with the present observations, we propose that a higher ω_{max} was not a result of a higher cardiorespiratory fitness *per se*, rather the frequent and repetitive bouts of aerobic training imposed sufficient heat stress to elicit sudomotor activation more regularly compared to pre-training, albeit almost certainly not a maximal level. The regular exposures to an endogenous thermal impulse (i.e. exercise) permitted the physiological adaptation to achieve a higher ω_{max}, and the combination of both regular exercise and heat stress (i.e. heat acclimation) presented an even greater thermal impulse thereby resulting in a near maximal physiological augmentation of ω_{max} (~0.95). In further support of the alterations in ω_{max} occurring independently of VO_{2max} *per se*, 2 of 8 participants despite satisfying our "untrained" inclusion criteria, presented at the beginning of the study with relatively high VO_{2peak} values (mean: ~4.3 $L \cdot min^{-1}$), however their mean ω_{max} was 0.76 pre-training and increased to 0.83 post-training with a mean increase in VO_{2peak} of 9.3% (~4.8 $L \cdot min^{-1}$).

While the present cohort had a similar mass and body surface area following training in comparison to pre-training, a reduction in adiposity (<2%) was observed (Table 1). No study to date has assessed the influence of adiposity on ω_{max}, however mass matched groups with a more than 25% difference in adiposity demonstrated similar whole body and local sweating responses

when exercising at similar, albeit physiologically compensable, rates of heat production (37). Thus, the marginal reduction in adiposity in the present study seems unlikely to have independently influenced ω_{max}.

Perspectives

The present findings can potentially contribute to the improvement of existing heat stress management guidelines in occupational and athletic settings. For example, a principal component of the heat exposure duration limits for occupational settings estimated by the ISO 7933:2004 PHS model (2) is the predicted physiological capacity for heat dissipation. Currently, the PHS model accounts for acclimation status of an individual, using a ω_{max} of 0.85 and 1.00 for non-heat-acclimated and heat-acclimated, respectively, which are based primarily on data derived from studies of people resting supine (1,2). The present findings demonstrate the necessity to account for training status as the ω_{max} traditionally associated with non-heat acclimated individuals (0.85) is only observed presently post-training (without heat acclimation; 0.84±0.13), while ω_{max} in untrained and non-heat acclimated individuals was ~15% lower (0.72±0.06). Thus, the present PHS model may overestimate safe exposure durations for persons who are untrained and non-heat-acclimated.

The present findings also have utility for pre-season heat acclimatization protocols implemented in some sports (e.g. American football) across all levels of competition, in order to mitigate the risk of heat related illness in pre-season training camps (9). Briefly, athletes engage in a reduced training volume with recovery bouts, and minimal protective equipment (e.g. helmet) for the first 3 – 5 days of the heat acclimatization protocol (38). The present findings demonstrate the clear protective effect, from the perspective of increasing maximum heat loss capacity, of aerobic training even without heat acclimation prior to the start of training camp.

Considerations

Our estimations of ω_{max} are reliant on the assumptions of $R_{e,cl}$ and h_e. In order to mitigate any independent influence on ω_{max}, $R_{e,cl}$ was assumed similar for all participants as identical clothing was worn pre-training, post-training, and post heat acclimation, and walking speed was similar (1.34±0.11 $m \cdot s^{-1}$) between and within participants in order to minimize its effect on h_e (31). Moreover, our observed P_{crit} and the partial pressure gradient between the skin and air at ω_{max} (i.e. $P_{sk,s}$-P_{crit}) following training and heat acclimation were similar to those previously reported (12) thus affirming our estimated ω_{max} values. VO_{2max} was not re-assessed following heat acclimation as the primary aim of the study was to determine the independent effect of training, and subsequent heat acclimation, on ω_{max}. Therefore it remains unknown whether the present heat acclimation protocol further increased aerobic capacity, although prior evidence suggests VO_{2max} remains unchanged following a heat acclimation protocol if it is preceded by an endurance training regime (39). The present study did not include a non-trained, but heat acclimated group as the primary aim was to determine the relative effect of training with and without heat acclimation. From a practical perspective, within a sporting context it seems unlikely that untrained yet heat acclimated athletes would conduct vigorous exercise in uncompensable heat stress conditions. However, such scenarios may be encountered in occupational settings where untrained personnel are required to perform physical tasks in uncompensable environments (e.g. miners, power-line technicians, construction workers). Thus it remains unknown whether the observed increase in ω_{max} following heat acclimation would be equivocal in an untrained cohort. Nevertheless, it has been traditionally accepted that a complete augmentation of ω_{max} does occur with full heat acclimation independent of training status (22,28). In support, Shvartz et al. (40) observed similar adaptations in thermoregulatory responses to heat stress following an 8-day heat acclimation protocol between

unfit, untrained, and trained participants. Lastly, all participants conducted the training intervention in a moderate environment (~22°C, 30%RH) in an attempt to observe the influence of endogenous heat stress on physiological adaptations to the heat. This environment provides ecological validity in an athletic context as it is representing conditions typically observed in commercial training facilities. Nevertheless, while it is likely that alterations in ω_{max} will be greater if training occurred in warmer environments, these values need to be quantified in future studies.

Conclusion

Eight weeks of aerobic training independently increased ω_{max} however this increase was further augmented (approximately doubled) by 8 days of heat acclimation. The greater ω_{max} following both training and acclimation was facilitated by a greater LSR secondary to a greater ASGD and without any changes in SGO. This is the first study to our knowledge to directly determine how ω_{max}, which defines the boundary between physiologically compensable and uncompensable heat stress, is altered by aerobic training status with and without heat acclimation.

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Author contributions. N.R., P.I., and O.J. were involved in conception and design of the experimental protocol. N.R. and G.C. were responsible for data collection. Data analysis and interpretation was performed by N.R. and O.J. N.R. drafted the manuscript. O.J. critically revised the manuscript. All authors have approved the final version of the manuscript.

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CONFLICT OF INTERESTS

The authors have no competing interests. The results were not endorsed by American College of Sports Medicine (ACSM). The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

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Table 1. Participant characteristics prior to, and following, 8 weeks of aerobic training.

	Pre-Training	**Post-Training**
VO_{2peak} (ml/kg/min)	45.8±11.6	52.0±11.1*
VO_{2peak} (L/min)	3.6±0.8	4.0±0.8*
HR_{max} (BPM)	185±10	184±9
Weight (kg)	80.2±16.7	78.9±15.5
BSA (m^2)	1.96±0.22	1.94±0.21
BSA/mass (cm^2/kg)	249±28	251±27
Body Fat (%)	26.0±12.0	24.2±11.6†

VO_{2peak} peak oxygen consumption; HR_{max} maximum heart rate; BSA body surface area. *Significantly greater Post-Training ($P < 0.001$). †Significantly lower Post-Training ($P<0.05$).

Table 2. Indicators of physiological adaptation to the heat at rest and at the upper limit of compensability (i.e. the upward inflection in esophageal temperature; INF) with biophysical parameters at INF pre-training (PRE-TRN), post-training (POST-TRN), and post heat acclimation (POST-HA).

	PRE-TRN	POST-TRN	POST-HA
Rest			
T_{re} (°C)	37.2±0.2	36.9±0.3*	36.7±0.2*
T_{es} (°C)	37.0±0.2	36.7±0.3*	36.6±0.3*
T_{sk} (°C)	37.1±0.4	36.7±0.4*	36.5±0.4*
HR (beats·min^{-1})	89±6	84±8*	79±6*†
INF			
T_{re} (°C)	38.0±0.2	37.8±0.3	37.6±0.1*
T_{es} (°C)	37.5±0.2	37.3±0.2	37.2±0.2*
T_{sk} (°C)	37.9±0.3	37.4±0.3*	37.3±0.3*
HR (beats·min^{-1})	131±12	117±16*	107±11*†
ω_{max}	0.72±0.06	0.84±0.08*	0.95±0.05*†
P_{crit} (kPa)	2.98±0.35	3.42±0.45*	3.95±0.07*†
$P_{sk,s} - P_{crit}$ (kPa)	3.48±0.31	3.10±0.44*	2.60±0.14*†

T_{re} Rectal temperature; T_{es} Esophageal temperature; T_{sk} Skin temperature; HR Heart rate; $P_{sk,s}$ - P_{crit} The vapour pressure gradient between the ambient air and skin's surface; ω_{max} Maximum skin wettedness expressed relative to post heat acclimation.
*Significantly different to PRE-TRN (P<0.05).
†Significantly different to POST-TRN (P<0.05).

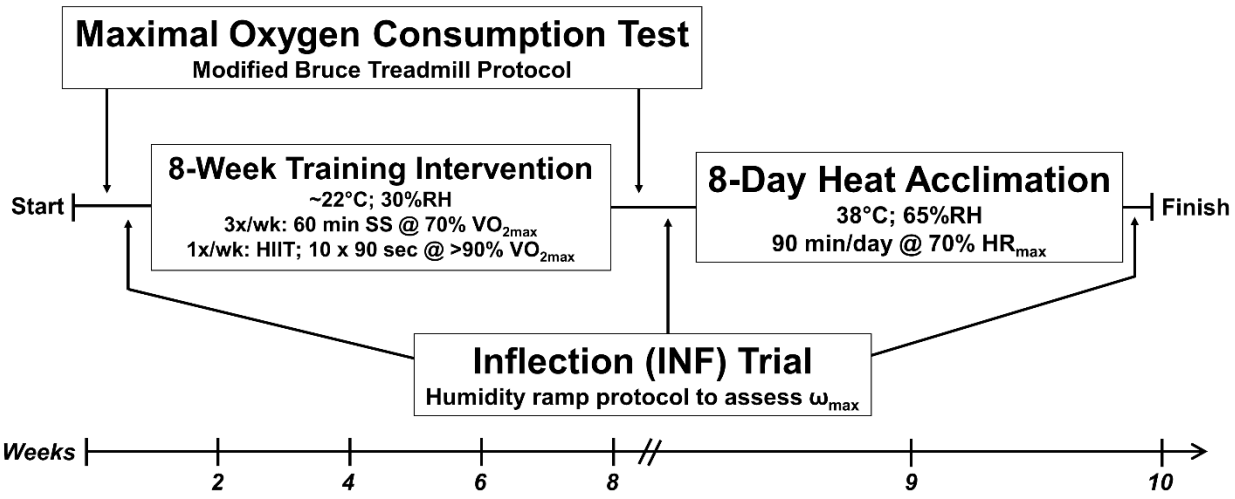

Figure 1. Illustration of the approximately 10-week study timeline for each participant. ω_{max} maximum skin wettedness; SS steady state exercise; VO_{2max} maximal oxygen consumption; HIIT high intensity interval training session; HR_{max} maximum heart rate.

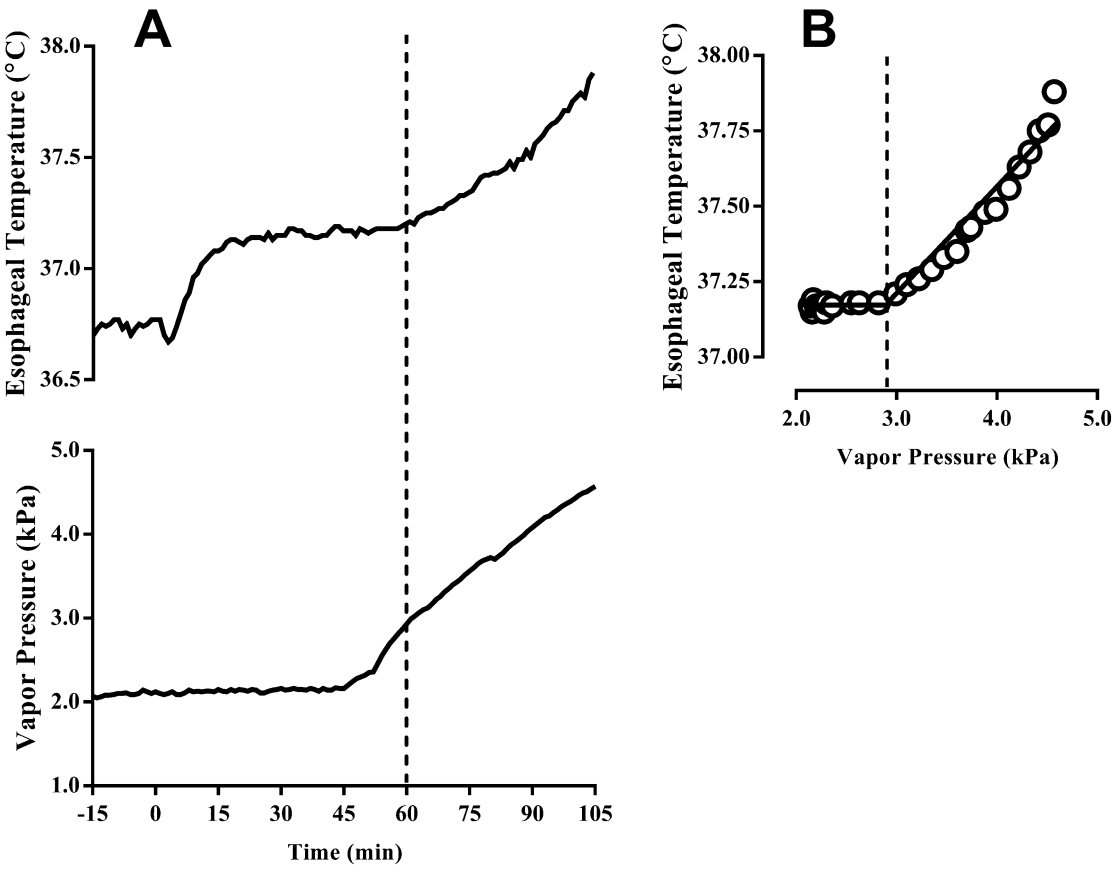

Figure 2. Example of esophageal temperature trace (A; top panel) and the humidity ramp protocol (A; bottom panel) during an inflection trial. After 45 minutes of steady-state exercise at a H_{prod} of 450 W, humidity was increased at a rate of 0.04 kPa·min^{-1}. Linear segmental regression was used in order to objectively identify the ambient vapour pressure coinciding with the upward inflection in esophageal temperature (B).

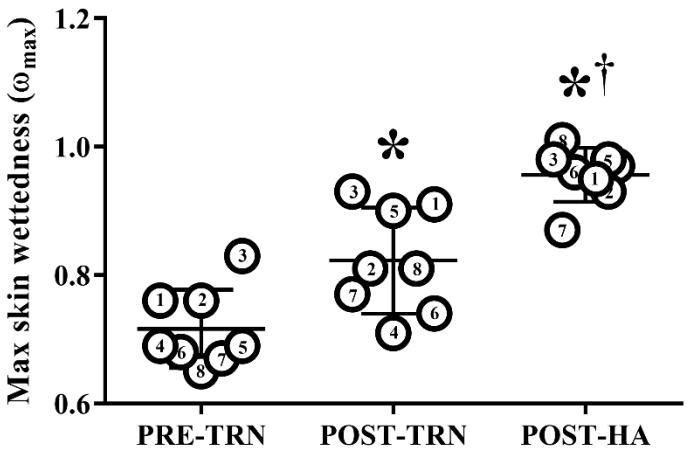

Figure 3. Individual and mean (with SD) values of maximum skin wettedness (ωmax) pre-training (PRE-TRN), post-training (POST-TRN), and following heat acclimation (POST-HA). Individual values are identified with a number in descending order of their preliminary maximum aerobic capacity (e.g. #1 had the highest preliminary aerobic capacity). *Significantly higher than PRE-TRN (P<0.05). †Significantly higher than POST-TRN (P=0.04).

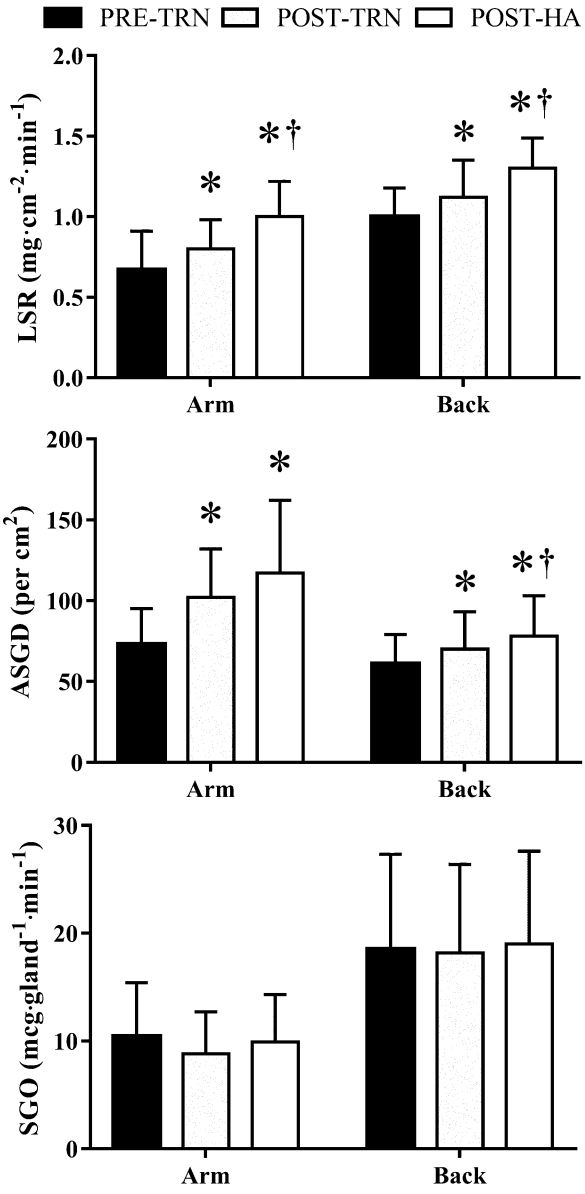

Figure 4. Local sweat rate (LSR), activated sweat gland density (ASGD), and sweat gland output (SGO) of the arm and back at the upper limit of compensability (i.e. ωmax) pre-training (PRE-TRN), post training (POST-TRN), and post heat acclimation (POST-HA). *Significantly greater than PRE-TRN (P<0.05). †Significantly greater than POST-TRN (P<0.05)

3.4 Thesis Study #4

Aerobic training and an associated partial acclimation, not fitness, independently alters the core temperature and sweating response to uncompensable heat stress

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ABSTRACT

A greater aerobic fitness, defined by the maximum rate of oxygen consumption (VO_{2max}), has been associated with a greater thermoregulatory capacity and a blunted rise in core temperature in uncompensable environments in comparison to less fit individuals. However, it remains unclear whether an improved thermoregulatory capacity is due to a greater VO_{2max} per se, or due to a partial heat acclimation associated with repeated bouts of exercise-induced heat stress with aerobic training. The present study sought to assess whether VO_{2max} interpedently influences thermoregulatory sweating, maximum skin wettedness (ω_{max}) and the change in rectal temperature (ΔT_{re}) during 60 mins of exercise in an uncompensable environment (37.0±0.8°C, 4.0±0.2 kPa, 64±3% RH) at a fixed rate of heat production per unit mass (6 $W \cdot kg^{-1}$). A total of 21 participants separated into 3 groups were assessed: an aerobically unfit (UF; n=7; VO_{2max}:41.7±9.4 ml/kg/min) and an aerobically fit (F; n=7; VO_{2max}:50.0±4.3 ml/kg/min; P=0.004) group both without aerobic training, and a group of aerobically unfit individuals (n=7) before (UT; VO_{2max}: 47.3±11.6 ml/kg/min) and after (T; VO_{2max}:53.6±10.9 ml/kg/min; P<0.001) an 8-week aerobic training intervention. ω_{max} was similar between UF (0.74±0.09) and F (0.78±0.08, P=0.22), however ω_{max} was greater with T (0.82±0.09) compared to UT (0.73±0.06, P=0.007). Mean local sweat rate (forearm and upper-back) was greater with T (1.22±0.19 $mg/cm^2/min$) compared to UT (0.99±0.16 $mg/cm^2/min$, P<0.001) but similar between UF (0.94±0.31 $mg/cm^2/min$, P=0.90) and F (1.02±0.30 $mg/cm^2/min$) following 60-min of uncompensable heat stress. The ΔT_{re} after 60-min of exercise was higher in UT (1.19±0.16°C, *P*<0.01) compared to T (0.97±0.14°C), but similar between UF (0.85±0.29°C, *P*=0.22) and F (0.95±0.22°C). Taken together, aerobic training, not VO_{2max} per se, confers an increased ω_{max}, higher sweat rate, and reduced rise in core temperature to mitigate heat strain during uncompensable heat stress.

Introduction

Aerobic fitness, as traditionally characterized by the maximum rate of oxygen consumption (VO_{2max}), has often been proposed to increase the with a greater thermoregulatory capacity and thus a blunted rise in core temperature during heat stress relative to less fit individuals (1, 21). It has long been suggested that aerobically fit individuals are partially heat acclimated (3, 8, 21, 22), characterized by a greater heat loss potential primarily via a higher sweat rate translating to a reduced rise in core temperature during exercise-induced heat stress (10, 22, 31). However, during exercise in a compensable heat stress environment, it has been demonstrated that VO_{2max} does not seem to alter the change in core temperature or steady-state sweat rates (11). To our knowledge, this longstanding association between VO_{2max} and partial heat acclimation is supported by limited evidence (21) and has potentially resulted in the assumption that VO_{2max} may be used as a proxy for heat acclimation status, lending to guidelines advocating a reduced protocol duration relative to aerobic fitness (28, 33). If the proposed partial heat acclimation associated with aerobic fitness were correct, then the upper limit for evaporative heat dissipation would be augmented via a greater maximum skin wettedness (ω_{max} (25)), which is the ratio of skin surface that can be saturated in sweat, and would thus mitigate the rise in core temperature during uncompensable heat stress.

During heat stress, sweating facilitates the predominant avenue of heat dissipation, i.e. skin surface evaporation, and is critical for preventing unchecked rises in internal body temperature. However, during uncompensable heat stress where the required rate of evaporative heat loss to maintain heat balance (E_{req}) exceeds the maximum evaporative capacity (E_{max}), even with maximum sweating the body is unable to attain a thermal steady-state. Thus, increasing E_{max} would be advantageous for mitigating the rate of rise in core temperature when exposed to periods of uncompensable heat stress by reducing the rate of heat storage accumulation. The only

physiologically modifiable characteristic that can be altered to increase E_{max} is ω_{max}. We've recently demonstrated that 8 weeks of aerobic training can increase ω_{max} by approximately 12% (25) and can reduce the change in core temperature of ~0.2°C during 60 minutes of uncompensable heat stress (Unpublished data, Chapter 3). However, VO_{2max} increased by ~15% secondary to training in the aforementioned study and thus the independent influence of VO_{2max} on thermoregulatory responses remains unclear. Alternatively, studies evaluating the relationship between aerobic fitness and end-exercise rectal temperature in the heat have reported that aerobic capacity accounts for 4% (14) to 46% (31) of the variability observed. Thus, it remains unclear if VO_{2max} per se alters the upper limit for evaporative heat dissipation and consequently reduces the rise in core temperature, or if it is a due to the partial heat acclimation associated with physical training as a result of frequent repeated bouts of exercise-induced heat stress.

Thus, the purpose of the present study was to assess whether VO_{2max} per se influences the thermoregulatory sweating, ω_{max} and the change in core temperature during exercise in an uncompensable environment. As such, two groups of untrained participants matched for body size, age and sex but with distinctly different VO_{2max} were recruited and their thermoregulatory responses were compared during an uncompensable heat stress exercise test. Furthermore, the thermoregulatory responses of a separate group of untrained participants were compared during the same uncompensable heat stress exercise test administered before and after their VO_{2max} was modified through an 8-week aerobic training program. It was hypothesized that VO_{2max} would not independently alter the change in core temperature, ω_{max}, or the thermoregulatory sweating response to uncompensable heat stress, whereas aerobic training would mitigate the change in core temperature via greater sweat rates and a higher ω_{max}.

Methods

The data presented in this manuscript are part of two larger studies examining the influence of body size (26) and aerobic training ((25), Chapter 3.2, 3.3) on thermoregulatory responses to uncompensable heat stress. Only 7 of 8 participants' data from the aerobic training study have been presented in the following manuscript to match the two groups of 7 from the body size study (26), and thus reported mean values will differ slightly from previous reports. Ethical approvals were obtained from the University of Ottawa Health Sciences Research Ethics Board (H12-11-05, H12-14-06) conforming to the principles set forth in the Declaration of Helsinki 2013. All volunteers gave consent (verbal and written) prior to any preliminary and experimental trials and were required to fill out a Physical Activity Readiness Questionnaire and an American Heart Association Pre-participation Screening Questionnaire.

A power calculation with G*Power (3.1.9.2) using α- and β- values set to 0.05 and 0.80, respectively, determined that a sample size of 14 subjects (7 per group) was required to report a significant difference between ΔT_{re} in two independent groups using previously reported data (26). A total of 21 participants were recruited and separated in to 3 groups; two independent groups of aerobically unfit (UF; n=7) and fit (F; n=7) participants without any structured aerobic training, and one group of aerobically unfit individuals who were tested prior to (UT) and following (T) an 8-week aerobic training intervention (Table 1). All participants completed a i) preliminary trial, followed by ii) an assessment of maximum skin wettedness, and iii) an uncompensable heat stress trial.

Preliminary Session

Height and weight were measured using a wall-mounted stadiometer (HR-200, Tanita, Arlington Heights, IL) and digital scale (BWB-800, Tanita, Arlington Heights, IL), respectively. Body composition was measured by dual-energy x-ray absorptiometry (GE-LUNAR Prodigy module, GE Medical Systems, Madison, WI). The VO_{2max} of the UF and F groups were assessed using an incremental exercise test to exhaustion on an upright cycle ergometer (Kettler ErgoRace, Virginia Beach, VA) in accordance with guidelines from the Canadian Society of Exercise Physiology (7). Following a self-paced warmup and at least 10-minute rest period, the protocol commenced with an external workload of 80 W that increased at a rate of 20 $W \cdot min^{-1}$ until physical or volitional exhaustion. The VO_{2max} of the group receiving an aerobic training intervention was assessed pre- and post-training (e.g. UT and T, respectively) using a Modified Bruce Treadmill Protocol. Expired gases were measured via breath-by-breath indirect calorimetry using a metabolic cart (Vmax Encore, Care Fusion, Yorba Linda, CA).

Maximum skin wettedness assessment

Maximum skin wettedness was determined using a humidity ramp protocol as previously described (13, 25, 26). Briefly, participants arrived at the facility and changed into standardized clothing (males: shorts and shoes; females: shorts, shoes and sports bra). The participant then entered the climatic chamber (37.5˚C and 2.0 kPa), were instrumented with an esophageal thermistor and skin temperature sensors, and then rested for 30 minutes in a seated position. Next, the participant began to either cycle (F and UF) or march (T and UT) on a treadmill at an intensity that elicited a metabolic heat production (H_{prod}) of ~450 W. Following a steady-state period, after 30- and 45-min for cycling (26) and treadmill (25) exercise, respectively, ambient vapour pressure (P_a) of the room increased until 4.60 kPa was reached. The critical ambient vapour pressure (P_{crit})

was identified as the point at which an upward inflection in esophageal temperature (T_{es}) was observed signifying the transition from a compensable to an uncompensable state.

Uncompensable heat stress trial

Participants were asked to abstain from caffeine and alcohol and avoid strenuous exercise for 12 h prior to arrival to the laboratory. Participants changed in to standardized clothing (i.e. cotton shorts for males, shorts and sports bra for females) and were instructed to insert a rectal thermistor. Participants then entered the climatic chamber set to 37.0±0.8°C and an absolute humidity of 4.0±0.2 kPa for the remaining instrumentation. After a 30-minute baseline period, an initial body mass measurement was taken using a platform scale followed by the initiation of exercise for 60 minutes at a fixed rate of heat production of 6 W per kilogram of total body mass. The rate of heat production was monitored in real-time to account for the influence of any differences in mechanical efficiency on metabolic heat production. Groups UF and F conducted exercise on an upright cycle ergometer, and groups UT and T utilized a motorized treadmill. Recent work from our laboratory have demonstrated similar changes in rectal temperature over time, independent of exercise modality, when exercise is prescribed as the rate of heat production per kilogram (6, 32). Upon the completion of exercise, a final body mass measurement was taken using the adjacent platform scale.

Instrumentation

Thermometry: Rectal (T_{re}) and esophageal (T_{es}) temperature were measured using a pediatric grade thermistor (Mon-a-therm, Mallinckrodt Medical, St. Louis, MO). T_{re} was measured at a depth of 10 cm past the anal sphincter. Esophageal temperature was measured by inserting the thermistor probe through the nasal cavity to a depth not exceeding 40 cm, to a region proximal to the right ventricle of the heart (15) and was only recorded for the first 15 minutes to determine

sudomotor thermosensitivity. Skin temperature was measured at four sites using thermistor heat flux sensors (Concept Engineering, Old Saybrook, CT) and affixed using double sided adhesive sticks (3M Health care, Neuss, Germany) and surgical tape (Transpore, 3M, London, ON, Canada). Mean skin temperature was derived as the weight average of each site (24): chest, 30%; shoulder, 30%; thigh, 20%; calf, 20%. Thermometric measurements were recorded at 5 second intervals using a data acquisition system (NI cDAQ-9172, National Instruments, Austin, TX) and LabView software (Version 7.0, National Instruments, Austin, TX) and then averaged every minute. Mean body temperature (T_b) was derived as the weighted average of T_{es} (80%) and T_{sk} (20%).

Sweating: Local sweat rate of the left arm and back were measured using ventilated sweat capsules (4.1 cm^2) placed on the anterior region of the forearm and immediately below the scapular spine, respectively. The ventilated sweat capsules were secured to the skin using double sided adhesive sticks and surgical tape. Each capsule was supplied with anhydrous air which was regulated at 1.0 L/min and 1.2 L/min for arm and back, respectively (FMA-A2307, Omega Engineering, Stamford, CT). The effluent air water vapor content was sampled every 5 seconds using factory calibrated capacitance hygrometers (HMT333, Viasala, Vantaa, Finland). Local sweat rate was derived as the product of water vapor content and flow rate normalized to the skin surface area covered by the capsule for the arm and back, and expressed as an average of both regions (LSR_{mean}). Steady state sweat rate was reported as average in LSR_{mean} from the 31^{st} to 60^{th} min of exercise where a plateau in LSR was observed. Sudomotor thermosensitivity was determined via linear regression using 1-min averages of LSR_{mean} and ΔT_b (12, 34). Whole body sweat loss (WBSL) was calculated as the net difference in pre- and post-exercise nude body mass measurements expressed relative to body surface area (g/m^2), and corrected for metabolic mass loss, and respiratory vapor loss (17).

Heat production: The target heat production (H_{prod}; in $W \cdot kg^{-1}$) was calculated prior to experimental sessions as the difference between the rate of metabolic energy expenditure (M) and the rate of external work performed (W), and normalized to the participants total body mass. M was estimated as:

$$M = VO_2 \cdot \frac{\left(\left(\frac{RER - 0.7}{0.3}\right)e_c\right) + \left(\left(\frac{1.0 - RER}{0.3}\right)e_f\right)}{60 \cdot kg} \cdot 1000 \; [W \cdot kg^{-1}] \qquad [1]$$

Where: VO_2 is the rate of oxygen consumption (L/min), e_c is the caloric equivalent per liter of oxygen for the oxidation of carbohydrates (21.13 kJ per L of O_2 consumed), e_f is the caloric equivalent per liter of oxygen for the oxidation of lipids (19.62 kJ per L of O_2 consumed), respiratory exchange ratio (RER) is the ratio of carbon dioxide production and oxygen consumption (VCO_2/VO_2).

The rate of external work (W) was either measured by the upright ergometer, or estimated for treadmill work using the follow equation (9):

$$W = [10^3 \; (v \cdot gr)] \; / \; (6.12 \cdot 60 \cdot 100) \; [W \cdot kg^{-1}] \qquad [2]$$

Where: v is the velocity of the belt (in $km \cdot h^{-1}$), and gr is the incline of the belt defined as the fraction of vertical displacement (in meters) for every 100 m of belt rotation.

The following heat balance parameters were calculated relative to surface area (e.g. $W \cdot m^{-2}$) for the determination of $\omega_{max.}$ The evaporative requirement for heat balance (E_{req}) was calculated by rearranging the conceptual heat balance equation;

$$E_{req} = H_{prod} - [\pm C \pm R \pm K + (E_{res} \pm C_{res})] \quad [W \cdot m^{-2}] \qquad [3]$$

Where: C is the net convective heat transfer, R is the net radiative heat transfer, K is the conductive heat transfer, and ($E_{res} \pm C_{res}$) is the net heat loss via respiration. The values of each component to the conceptual heat balance equation (Equation 3) were calculated using standardized equations previously described in the literature (6, 26).

Lastly, ω_{max} for each participant was determined using the P_{crit} value obtained from the humidity ramp protocol (see maximum skin wettedness assessment). While the details of this process have been explained previously (13, 25, 26) and in Chapter 3.2, briefly, the equation for E_{max} was rearranged to solve for ω_{max} with E_{max} substituted for E_{req};

$$\omega_{max} = E_{req} (R_{e,cl} + [1/h_e]) / (P_{s,sk} - P_{crit}) \qquad [W \cdot m^{-2}] \qquad [4]$$

Where: $R_{e,cl}$ is the evaporative heat transfer resistance of the standardized clothing (assumed to be 0.002 $kPa \cdot m^{-2} \cdot W^{-1}$); h_e is the evaporative heat transfer coefficient in $W \cdot m^{-2} \cdot kPa^{-1}$ which is the product of the convective heat transfer coefficient (h_c) and the Lewis Relationship (16.5 $K \cdot kPa^{-1}$), and ($P_{s,sk} - P_{crit}$) is the humidity gradient between the skin and air at the inflection point in esophageal temperature. For cycling exercise, h_c was calculated as;

$$h_c = 11.6\ v^{0.5}\ [W \cdot m^{-2} \cdot K^{-1}] \qquad [5]$$

Where: v was the mean air velocity from forced convection (~1.2 m/s). For treadmill exercise, forced convection was absent and thus h_c was determined using the Nishi and Gagge (20) equation for treadmill walking;

$$h_c = 6.51 \cdot v^{0.391}\ [W \cdot m^{-2} \cdot K^{-1}] \qquad [6]$$

Lastly, the saturated vapour pressure on the skin ($P_{sk,s}$, in kPa) was derived using Antoine's equation:

$P_{sk,s} = (\exp (18.956 – [4030.18/(T_{sk} + 235)])/10$ [kPa] [7]

Where T_{sk} is mean skin temperature (°C).

Statistical analysis

All data are expressed as means±SD. Independent sample or paired t-tests were used to compare participant characteristics for the UT groups and T groups, respectively. A two-way mixed model ANOVA was performed to compare $\Delta T_{re,}$ ΔT_{sk} and LSR_{mean} between the non-repeated factors of fitness (two levels: UF vs F) with the repeated factor of time (five levels: baseline, 15, 30, 45, and 60 min). A two-way ANOVA was performed to compare $\Delta T_{re,}$ ΔT_{sk} and LSR_{mean} between the repeated factor of training (two levels: UT vs T) and time (five levels: baseline, 15, 30, 45, and 60 min). Independent sample or paired t-tests with a Bonferroni correction for multiple comparisons (e.g. at each time point) were used to compare UF vs F and UT vs T, respectively, if a significant interaction was observed. WBSL, sudomotor thermosensitivity, and ω_{max} were compared using independent sample or paired t-tests for UF vs F and UT vs T, respectively. A P-value less than 0.05 was considered as statistically significant. All statistical analyses were performed with GraphPad Prism (version 7.0, Graphpad Software, La Jolla, CA).

Results

Thermometry: Absolute T_{re} at baseline was trending to be lower in F (36.59±0.17°C) compared to UF (37.00±0.35°C, *P*=0.07; Fig. 1) prior to the uncompensable heat stress trial. A main effect of fitness (*P*=0.05) was observed for absolute T_{re} during the uncompensable heat stress trial (F vs UF). The change in T_{re} was not different between the independent groups of F (0.95±0.22°C) and UF (0.85±0.29°C, *P*=0.22; Fig.1). Following 60 minutes of uncompensable heat stress, absolute T_{sk} was similar between UF (37.42±0.29°C) and F (37.15±0.31°C, P=0.10).

The change in mean skin temperature was similar between UF (1.35±0.21°C) and F (1.07±0.45°C, P=0.18) during uncompensable heat stress.

The absolute T_{re} at baseline was trending to be lower with T (36.60±0.17°C) compared to UT (37.00±0.35, *P*=0.07; Fig. 1). However, both a main effect (*P*=0.002) and interaction (*P*<0.001) was observed for absolute T_{re} with training (UT vs T). In contrast to UF vs F, following an aerobic training intervention, the end-exercise change in T_{re} was reduced in T (0.97±0.14°C) compared to UT (1.19±0.16°C, *P*<0.01, Fig. 1). Absolute T_{sk} following 60 minutes of uncompensable heat stress was higher in UT (38.05±0.44°C) compared to T (37.53±0.43°C, P<0.001). From 45 minutes onwards, the change in T_{sk} was lower with T (0.79±0.35°C) compared to UT (1.03±0.35°C, *P*=0.01).

Maximum Skin Wettedness (ω_{max}): The ω_{max} was similar between UF (0.74±0.09) and F (0.78±0.08, P=0.22), however the ω_{max} was significantly greater with T (0.82±0.09) in comparison to UT (0.73±0.06, P=0.007; Fig. 2).

Sweating: No difference in mean local sweat rate was observed prior to (*P*>0.90) and after 60 minutes of exercise between UF (0.94±0.31 $mg \cdot cm^{-2} \cdot min^{-1}$) and F (1.02±0.30 $mg \cdot cm^{-2} \cdot min^{-1}$, P=0.90; Fig. 3A). As expected, whole body sweat losses were similar between UF (343±56 $g \cdot m^{-2}$) and F (359±32 $g \cdot m^{-2}$, *P*=0.54; Fig. 4). However, the mean local sweat rate was greater from 15 minutes onwards during uncompensable heat stress following T in comparison to the UT state (Fig. 3B). Moreover, whole body sweat losses were ~20% greater with T (403±47 $g \cdot m^{-2}$) compared to UT (337±30 $g \cdot m^{-2}$, *P*=0.03; Fig. 4).

Thermosensitivity: The sudomotor thermosensitivity (LSR:T_b) was similar between UF (1.2±0.4 $mg \cdot cm^{-2} \cdot min^{-1} \cdot °C$) and F (1.1±0.5 $mg \cdot cm^{-2} \cdot min^{-1} \cdot °C$, P=0.72). However, training

increased sudomotor thermosensitivity (1.1±0.2 $mg \cdot cm^{-2} \cdot min^{-1} \cdot °C$) compared to pre-training (0.9±0.2 $mg \cdot cm^{-2} \cdot min^{-1} \cdot °C$, P=0.02) during uncompensable heat stress.

Discussion

The present study clearly demonstrates that aerobic training, and not fitness (i.e. VO_{2max}) per se, independently alters the core temperature and sweating response during uncompensable heat stress. Aerobic training in thermoneutral conditions (22°C, 30% RH) induced what was apparently a partially heat acclimated state, evidenced by a greater local and whole body sweat rate enabling a greater ω_{max} thereby resulting in a smaller rise in core temperature after 60 minutes of uncompensable heat stress. However, the ω_{max} was similar between groups with different VO_{2max} levels but unaccompanied by regular aerobic training, and no differences in the sweating or core temperature responses to uncompensable heat stress were observed. Nevertheless, a lower absolute resting core temperature was observed in the fit group, confirming that VO_{2max} does not independently induce the greater evaporative heat loss capacity associated with a partially heat acclimated state.

For a given uncompensable heat stress, heat acclimation has been demonstrated to increase local and whole body sweat rates, reduce resting core temperature, and reduce heart rate for a given workload (2, 16, 19, 22, 31). The prevailing notion to date has been that aerobically fit individuals possess the same, or similar, physiological adaptations as their heat acclimated counterparts. Indeed, a higher VO_{2max} as a result of aerobic training has been observed to confer a greater tolerance to uncompensable heat stress, as indicated by longer exercise durations (4) or the ability to tolerate a higher core temperature (29) in comparison to individuals with a lower VO_{2max} in encapsulated environments (i.e. participants wearing vapour impermeable clothing). However, whether a greater VO_{2max} alone confers a partial or complete heat acclimation remains unclear. It

has been proposed that frequent bouts of heat stress experienced during aerobic training, which simultaneously increase VO_{2max}, elicit the thermoregulatory adaptations associated with heat acclimation (22). During uncompensable heat stress, the most important avenue of skin surface heat dissipation is the evaporation of sweat. As evident in the present findings, aerobic training which resulted in a >10% increase in aerobic fitness also enabled the attainment of a greater ω_{max} thereby improving the maximum rate of evaporative heat loss and reducing the rise in core temperature during 60 minutes of uncompensable heat stress. In addition to the greater E_{max} secondary to the physiological modification of ω_{max}, aerobic training enhanced the thermosensitivity of sweating to changes in mean body temperature and reduced the rise in core temperature during uncompensable heat stress; all traditional characteristics indicative of heat acclimation (1, 18, 23, 27). In stark comparison, the higher VO_{2max} group that did not participate in structured physical training (e.g. F) demonstrated a similar change in core temperature, ω_{max}, and sweating responses to the UF group during uncompensable heat stress despite a greater difference in VO_{2max} to the T group relative to their UT status. These observations provide empirical support to Corbett et al. (5) who reported that aerobic fitness did not correlate with thermo-physiological responses (e.g. sweat rates and change in core temperature) following exercise in the heat. The present findings confirm that VO_{2max} per se provides little to the characterization of heat acclimation status and must be accompanied by frequent aerobic training to induce partial heat acclimation. As such, a person's VO_{2max} per se should not be considered a proxy indicator of their heat acclimation status and thus their heat stress risk, but rather the frequent bouts of exercise-induced heat stress with aerobic training may prove as a greater determinant of the rise in core temperature during uncompensable heat stress.

Of note, the resting absolute core temperature observed was higher in the UF and UT groups compared to the F and T groups, respectively (Figure 1A,C). A lower resting core temperature has been a well documented physiological adaptation following heat acclimation (2, 16, 19, 22, 31) and in individuals with a high VO_{2max} (29, 31, 32), however the exact physiological benefit remains unclear. Nevertheless, as evident in the present study, the lower resting core temperature was not associated with an enhanced heat dissipation capacity between UF and F groups, respectively, suggesting that the alterations in resting core temperature may occur independently of augmented heat loss responses.

The aerobic training regimen in the present study was apparently a sufficient heat stress stimulus, despite being carried out in a relatively cool environment, to elicit the induction of partial, but not complete, heat acclimation (25). Alternative training programs may provide varying degrees of heat acclimation while simultaneously increasing aerobic fitness. For example, Avellini et al. (2) observed little difference in sweating and core temperature responses to a standardized heat stress test before and after a 4-week aerobic underwater (20°C) training program, which would eliminate the necessity to sweat, despite a 13% increase in aerobic capacity. In contrast, a comparison group who conducted the same aerobic underwater training program in warmer water (32°C) with a similar increase in aerobic capacity (~15%) demonstrated a greater sweat rate and reduced end-exercise core temperature to the same heat stress test. Futhermore, Henane et al. (10) observed between VO_{2max} matched swimmers and cross-country skiers (~66 ml/kg/min) that swimmers presented with a lower whole body sweat loss and greater rectal temperature following 100 minutes of uncompensable heat stress. Taken together with the present findings, perhaps aerobic training does not independently induce the adaptations associated heat acclimation, rather a net heat load arising from a combination of environmental factors and exercise intensity

ultimately provide the impulse for thermal adaptation, and physiological heat loss modifications only occur once an adaptive threshold is exceeded. As such, in addition to training status, the thermal environment in which training takes place must also be considered when determining an individual's heat acclimation status and the associated risk of a given physiological heat strain during uncompensable heat stress.

Limitations

It must be noted that two different exercise modalities were employed in the present study. While VO_{2max} was assessed using trial-specific modalities, the UF and F groups presented with a higher VO_{2max} compared to the UT and T groups, respectively, despite being assessed with an upright cycle ergometer which is known to provide VO_{2max} estimates ~10% lower than a treadmill-based maximal exertion tests (30). The duration of steady-state exercise prior to the inflection protocol for evaluating ω_{max} was shorter for the UF and F groups (30 mins) compared to the UT and T (45 mins). Despite the additional 15 minutes of steady-state exercise, a similar ω_{max} was measured for UF (0.74±0.09), F (0.78±0.08), and UT (0.73±0.06), suggesting that the shorter steady-state period did not alter the estimated ω_{max} between groups with a similar unacclimated state. In addition, although statistically similar, a net mean difference in body mass of ~10 kg was observed between the fit and unfit group. In order to mitigate the potential introduction of bias associated with the effects of varying modalities and body morphology, exercise intensity was fixed to sustain the same heat production per unit mass ($W \cdot kg^{-1}$) between all trials (26). This exercise prescription model (e.g. $W \cdot kg^{-1}$) has been shown to permit unbiased comparisons between core temperature and sweating responses during uncompensable heat stress in groups varying by as much as 30 kg in body mass (26). Moreover, all comparisons made in the present study were modality-specific thereby isolating the independent effects of either aerobic fitness or training.

Conclusion

Aerobic training status, not aerobic fitness, (i.e. VO_{2max}) confers some of the physiological adaptations associated with heat acclimation such as an increased ω_{max}, higher sweat rate, and reduced rise in core temperature during uncompensable heat stress.

Author contributions. N.R., P.I., and O.J. were involved in conception and design of the retrospective analysis. Data analysis and interpretation was performed by N.R. and O.J. N.R. drafted the manuscript. O.J. and P.I. critically revised the manuscript.

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Table 1 Mean participant characteristics.

Group (n)	Age (y)	Mass (kg)	BSA (m^2)	BSA/mass ($cm \cdot m^{-2}$)	VO_{2max} ($ml \cdot kg^{-1} \cdot min^{-1}$)
Unfit (7)	26.3±4.3	84.2±16.3	2.04±0.26	245±17	41.7±9.4
Fit (7)	23.3±4.2	71.4±13.1	1.86±0.17	234±26	50.0±4.3*
Untrained (7)	26.5±5.6	78.8±17.6	1.94±0.23	252±29	47.3±11.6
Trained (7)	26.5±5.7	77.7±16.4	1.93±0.22	254±28	53.6±10.9†

BSA Body surface area, **VO_{2max}** maximum rate of oxygen consumption

*Significantly greater than Unfit (P=0.004)

†Significantly greater than Untrained (P<0.001)

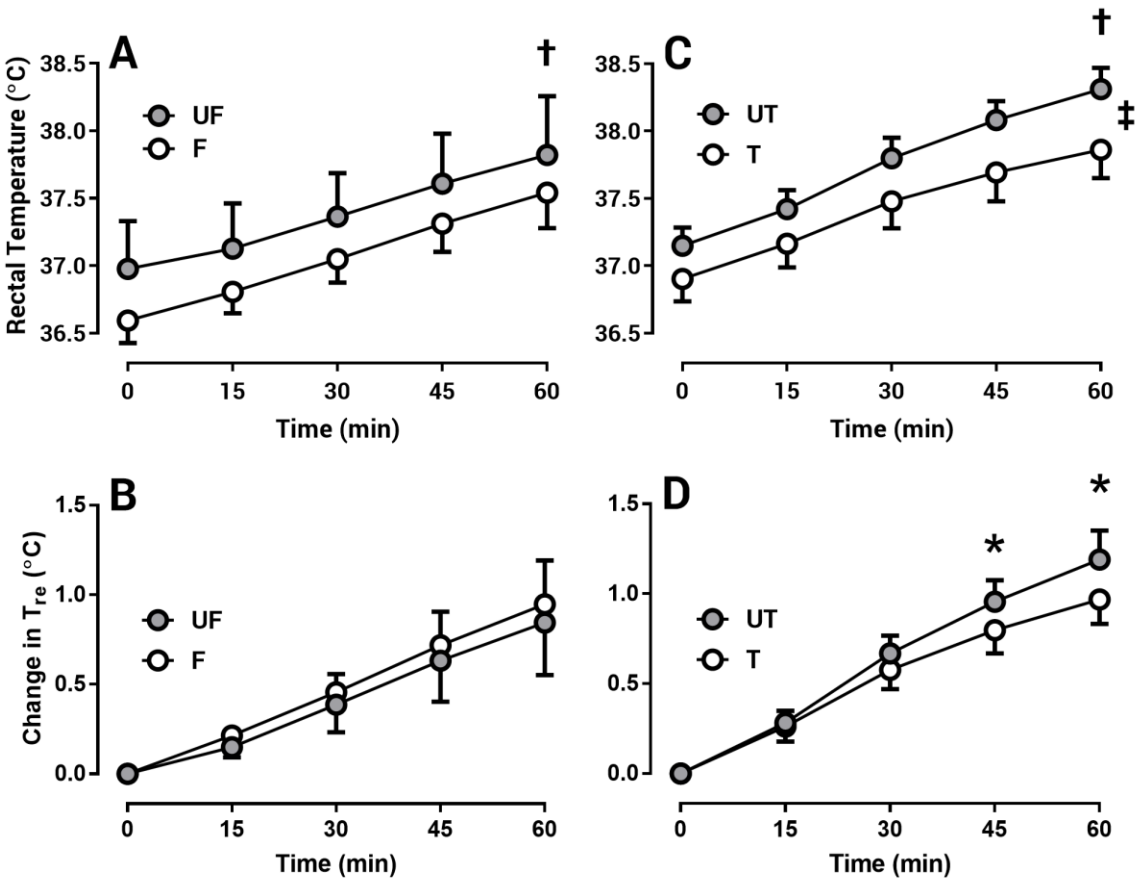

Figure 1 The mean absolute (A, C) and change (B, D) in rectal temperature (T_{re}) during uncompensable heat stress for unfit (UF), fit (F), untrained (UT), and trained (T) participants. *Significantly greater than trained ($P<0.05$). †Main effect between groups ($P<0.05$). ‡Interaction between groups ($P<0.001$).

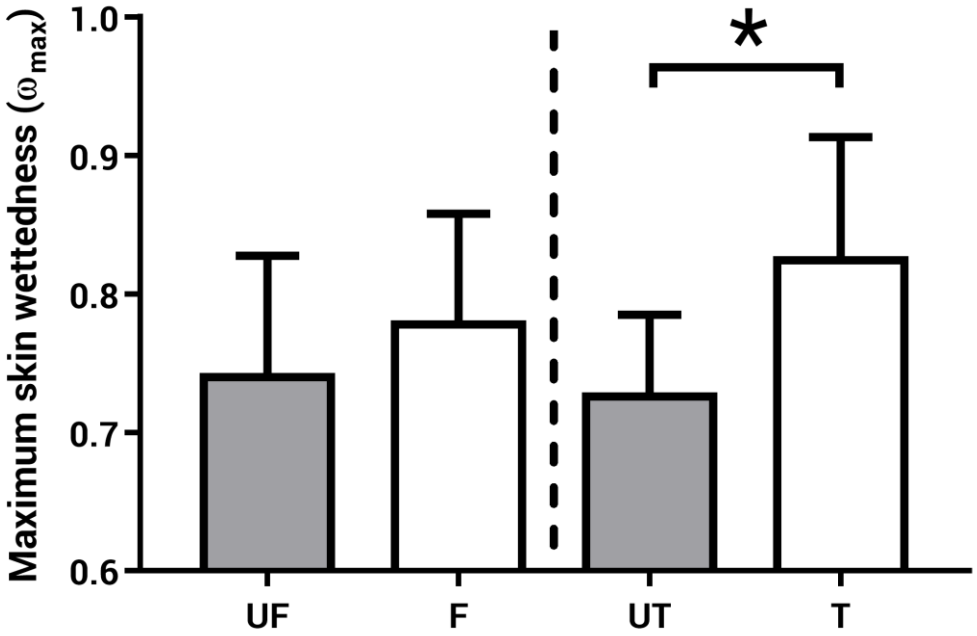

Figure 2 The mean maximum skin wettedness (ω_{max}) for the unfit (UF), fit (F), untrained (UT), and trained (T) participants determined during the humidity ramp protocol. *Significantly greater in trained compared to untrained (P=0.007).

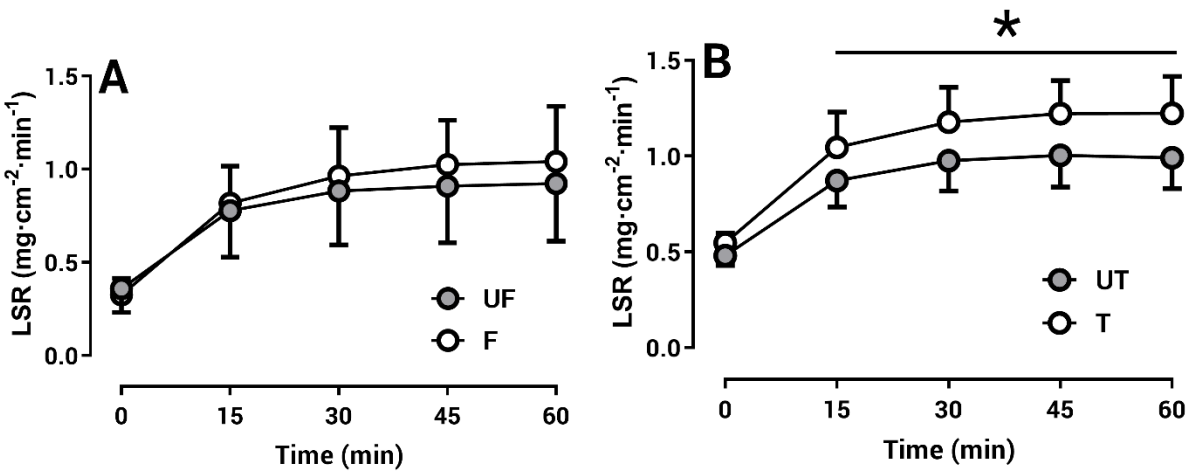

Figure 3 The mean local sweat rate (LSR) during uncompensable heat stress for the unfit (UF) and fit (F), and untrained (UT) and trained (T)**,** in panel A and B, respectively. *Significantly greater in trained compared to untrained (P<0.05).

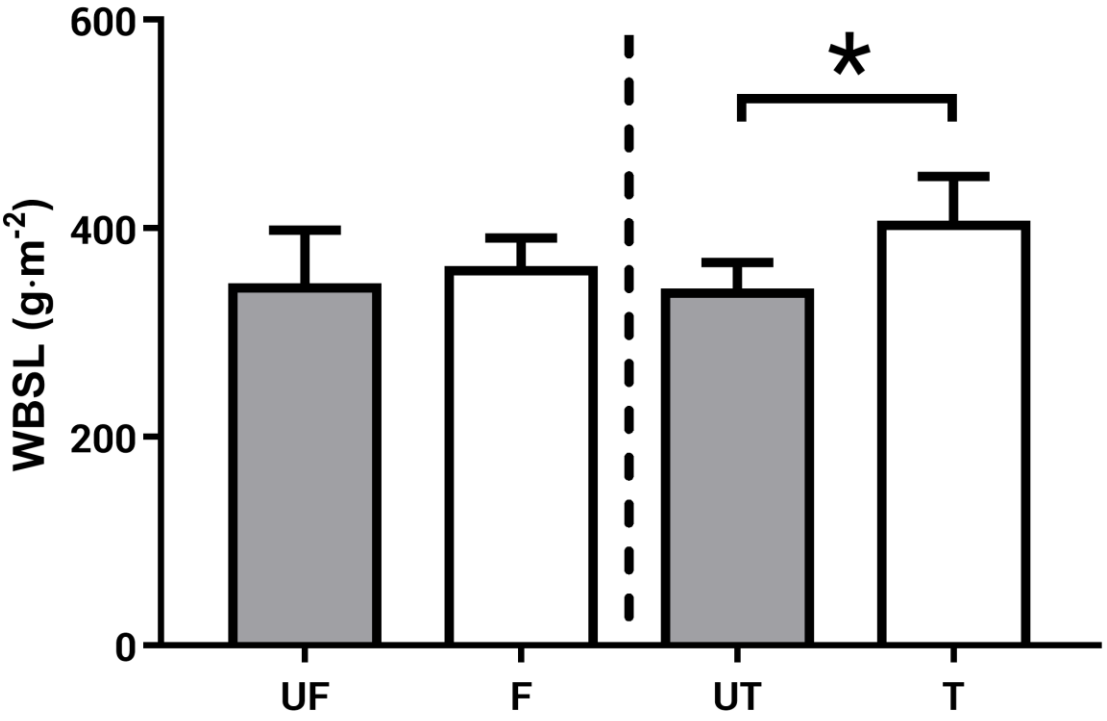

Figure 4 The whole body sweat loss (WBSL) following uncompensable heat stress for the unfit (UF), fit (F), untrained (UT), and trained (T). *Significantly greater in trained compared to untrained (P=0.03).

CHAPTER 4: THESIS DISCUSSION

4.1 Summary

A common understanding of thermoregulatory control for some time has been that the absolute core temperature attained during exercise-induced heat stress determines the steady-state sudomotor response (20, 130, 131, 136, 180). However fundamental heat balance theory indicates that the rate of evaporation required for heat balance (E_{req}) should determine the steady-state sweat rate during compensable heat stress (51, 66). Some previous studies (59, 76, 83, 142, 167) have assumed that aerobic training induces similar thermoregulatory adaptations (i.e. higher sweat rates, increased maximum skin wettedness (ω_{max})) as observed following complete heat acclimation (7, 34, 40, 109, 124, 154) due to the frequent and repetitive exercise-induced heat stress associated with aerobic training (9, 69). It would seem unlikely that the greater maximum sweat rate following partial or complete heat acclimation would affect the steady-state sweat rate observed during compensable heat stress, whereas the greater maximum sweat rate would serve to mitigate heat strain during conditions that exceed the limits of heat balance (i.e. uncompensable heat stress). Further, the maximum skin wettedness for an unacclimated and acclimated individual is suggested to be 0.85 and 1.00 (40), respectively, however it has not yet been determined whether the alterations in ω_{max} precipitated presumably by the greater maximum sweat rate following aerobic training, if any, are equivocal to complete heat acclimation. Lastly, studies (43, 167) exploring the influence of aerobic fitness during uncompensable heat stress have performed cross-sectional study designs characterizing independent groups by their aerobic fitness (i.e. VO_{2max}) without accounting whether the person actively engages in frequent aerobic training which may independently alter the sudomotor responses if aerobic training indeed induces partial heat

acclimation (9, 121, 142). In sum, the present thesis was designed to answer four primary questions:

1. Do systematic differences in absolute core temperature (induced by circadian rhythm) during exercise at a fixed E_{req} alter steady-state sweat rates during exercise in compensable conditions?
2. Does partial and complete heat acclimation alter the change in core temperature and the local and whole-body sweating responses during exercise in compensable conditions or only when the upper limit for heat dissipation is challenged (e.g. uncompensable)?
3. Does the partial heat acclimation associated with aerobic training alter ω_{max} (i.e. the boundary between compensable and uncompensable heat stress) similarly to complete heat acclimation?
4. Does having a high VO_{2max} without aerobic training alter the core temperature and sweating responses to uncompensable heat stress, or does a person need to engage in frequent aerobic training and thus be exposed to repeated bouts of exercise-induced heat stress to elicit such an adaptation?

Table 1 summarizing the findings from the four studies performed to address the research questions proposed.

Study 1	1. Steady-state sweat rate was not different at a fixed E_{req} despite a difference in absolute core temperature in the AM compared to PM 2. Steady-state sweat rate was not different when exercise was performed at a different heat production to elicit a fixed E_{req} at different air temperatures despite a difference in absolute skin and core temperature

	3. Steady-state sweat rates were only different when exercise intensity was altered to elicit different levels of E_{req}.
Study 2	1. Neither partial or complete heat acclimation altered the core temperature response to compensable heat stress, despite marginally greater steady-state whole-body sweat rates and greater forearm sweat rates with complete heat acclimation compared to unacclimated. 2. The physiological adaptations associated with heat acclimation were most apparent during uncompensable heat stress where the upper limit for heat dissipation was challenged. 3. The greater maximum sweat rates following complete heat acclimation compared to partial heat acclimation (induced by aerobic training) did not further mitigate the rise in core temperature during 60 minutes of uncompensable heat stress.
Study 3	1. The partial heat acclimation associated with frequent aerobic training increased ω_{max} relative to an unacclimated state. 2. The ω_{max} observed following complete heat acclimation was greater than following partial heat acclimation.
Study 4	1. VO_{2max} per se does not independently increase the sudomotor response or the rise in core temperature to uncompensable heat stress. 2. The repetitive bouts of exercise-induced heat stress with aerobic training precipitated the higher sweat rates associated with partial heat acclimation mitigating the rise in core temperature during uncompensable heat stress.

4.2 Discussion of findings and future directions

The results of Study #1 demonstrate that using circadian rhythm to modulate absolute core temperature within participants, when the evaporative requirements for heat balance are the same, there is no difference in steady state sweat rate even when absolute core temperature is different by ~0.2°C, a finding somewhat contradictory to the traditional viewpoint that absolute core temperature attained determines the sweat rate achieved (11, 81, 82, 86, 114). These findings

promote an alternative hypothesis on the determinants of steady-state sweat rates, which seems to be independent of both absolute core temperature and, as a consequence of the model used to alter core temperature, circadian rhythm. That is, the evaporative heat balance requirements determine the steady-state sweat rate whereas the onset and thermosensitivity of heat loss responses following the integration of core and skin thermoreceptors determines the cumulative heat gain, and thus the change in core temperature, prior to achieving thermal equilibrium. For example, when comparing E_{req} matched AM and PM trials in Study 1, the absolute core temperature attained at steady-state was greater in the afternoon while local and whole-body steady-state sweat rate remained similar. Moreover, the greater steady-state absolute core temperature in the afternoon compared to morning paralleled the increased baseline absolute core temperature. When exercise was fixed to elicit a different E_{req} (200 vs 250 W/m^2) under the same environmental conditions (33°C), a greater steady-state local and whole-body sweat rate, and steady-state absolute core temperature was observed with a higher E_{req}. However, when comparing the E_{req}-matched trials with different air temperatures (23°C vs 33°C) within Study 1, the onset time for sweating was shorter at 33°C compared to 23°C as supported by the traditional model of thermoregulatory control (131, 154), yet a similar steady-state sweat rate was ultimately attained (Fig. 4.1). Moreover, the change in core temperature (a proxy of heat storage) was ~0.5°C greater in the 23°C trial compared to 33°C. Taken together, despite the earlier onset which is often used to characterize the responsivity of the thermoregulatory system in conjunction with thermosensitivity (48, 86, 111, 131, 154), it did not translate to a higher steady-state sweat rate during compensable heat stress. Indeed, an earlier onset for sweating would incur a higher cumulative sweat loss over time, however this difference will become diluted with a longer fixed intensity exercise or rather a greater ratio of steady-state to non-steady-state sweating periods. Thus, when designing experiments to compare steady-state or

time-dependent sweat rates it is crucial that exercise intensity be fixed to elicit a given E_{req} and not a change in, or absolute, core temperature. These findings corroborate recent evidence for protocols which eliminate systematic bias for comparing singular physiological variables in people with varying morphological characteristics, disease, or thermoregulatory dysfunction (51, 66).

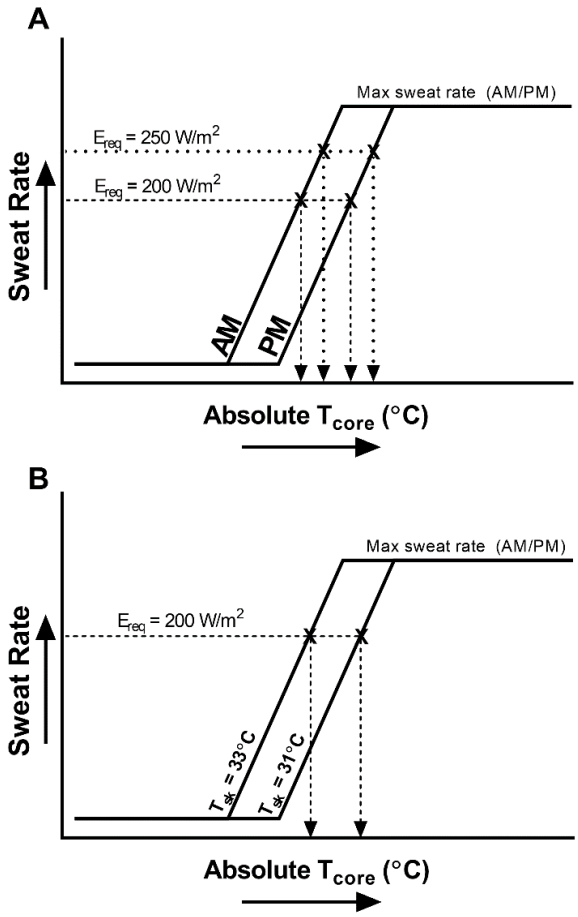

Figure 1 Graphical depiction of the change in sweat rate as a function of absolute core temperature (T_{core}) between trials fixed to elicit 2 different levels of evaporative requirements for heat balance (E_{req}, 200 W/m^2 and 250 W/m^2) in the morning (AM) and afternoon (PM) (A), and between two different skin temperatures (T_{sk}) due to differences in air temperature (23°C vs 33°C) matched for time of day (B). The dotted lines denote the attainment of steady-state sweating and T_{core} during each condition. During compensable heat stress, steady-state sweat rates were similar irrespective of absolute T_{core}, suggesting that E_{req} is what determines steady-state sudomotor activity. The absolute T_{core} attained at steady state is due to the controller's sensitivity to heat stress, that is, the onset and thermosensitivity of sweating to changes in T_{core}.

Traditional thermoregulatory control has generally been described as efferent responses which are up- or down- regulated following the deviation of absolute core temperature from a reference or set-point as defined by the hypothalamus (23, 25, 28, 61, 79, 81). However, this classical negative feedback loop is further complicated by conditions where absolute core temperature is manipulated by thermal (e.g. exercise or passive heat stress, (136, 160, 177)) or by non-thermal manipulations of core temperature (e.g. circadian rhythm as in thesis study #1 or the menstrual cycle in women (60, 188)). Moreover, thermal stimulation of the skin (131), gastro-intestinal tract (129), or abdominal region (151) can indeed modulate the thermoregulatory responses observed. Nadel et al. (131) proposed that the regulation of sudomotor output was driven by absolute core temperature and modified by skin temperature and others have suggested that extra-hypothalamic signals may modify the set point or sensitivity of the thermoregulatory responses (79, 125). Collectively, absolute core temperature has remained the primary controlling variable whereby additional thermal or non-thermal factors may integrate to modify the efferent thermoregulatory response. Alternatively, Houdas (90, 91) and Werner (191–193) have contested that absolute core temperature is not the primary regulator of thermoregulatory control, but that absolute core temperature is simply the result (or output) of the passive system during external or internal heat load (Figure 2). Rather, it is the input to the passive system (i.e. heat balance) which determines the controller output. The combination of effectors can be viewed in terms of heat balance parameters to simplify the analogy (see Figure 2). During exercise prior to the attainment of heat balance (i.e. non-steady-state), the rate of heat loss does not match the rate of heat production and therefore the input to the passive system results in a rise in core temperature. The rise in core temperature will be determined by the speed of onset and thermosensitivity by the controller which may be modified by physiological characteristics (i.e. heat acclimation status, see

Figure 3). When the rate of heat production is matched by an equal rate of heat loss, the passive system will reach a steady-state, as defined by the absence in the rate of change of temperature, thereby signalling that the present thermoregulatory response is sufficient to maintain heat balance. This hypothesis of thermoregulatory control eliminates the requirement for a pre-defined set-point, and suggests that heat transfer is what determines the steady-state thermoregulatory response. In support as depicted in Study 1, when exercise was fixed for a given E_{req}, the steady-state sweat rate was the same, regardless of the absolute core (Figure 1A) and skin (Figure 1B) temperature.

While it can be challenged that absolute core temperature does not alter the steady-state sweating response during compensable heat stress at a fixed E_{req}, the change in core temperature was similar between matched conditions in the AM and PM (unreported data) due to the within subject comparison study design. In order to eliminate the potential influence of a change in core temperature as the load error which determines the thermoregulatory responses (37, 79), a fixed E_{req} between a thermoneutral (23ºC) and warm (33ºC) condition was employed which would require different rates of heat production to counterbalance the dry heat loss and thereby result in different changes in core temperature. Despite observing a similar steady-state sweat rate with differences in the change in (and absolute) core temperature when exercise was fixed to elicit a given E_{req} between different ambient temperatures (Figure 1), skin temperature at steady state was greater at 33ºC compared to 23ºC. These findings can be seen to directly support the work of Nadel et al. (130, 131) who proposed that a combination of core and skin temperature can independently modify the sudomotor output. However, Dervis et al. (54) observed the same steady-state sweat rate response with similar skin temperatures when exercise was fixed to elicit a similar E_{req} between individuals matched for mass and surface area, but presenting with different levels of adiposity which resulted in differences in the mean specific heat capacity of the body. For the same

heat production, and by design E_{req}, between individuals dissimilar in adiposity, the group with a lower mean specific heat capacity had a greater change in core temperature. The greater change in core temperature observed in the higher fatness group did not precipitate any alterations in the steady-state sweat rate observed for a fixed E_{req} (54). Collectively, the findings from thesis study #1 in conjunction with the findings from Dervis et al. (54) provide evidence that neither absolute core temperature, or change, determine the sudomotor response, but rather the input to the passive system (i.e. heat balance) determines steady-state sweating responses during compensable heat stress. The absolute core temperature, or change in core temperature, attained at steady state is simply a result of the output of the passive system.

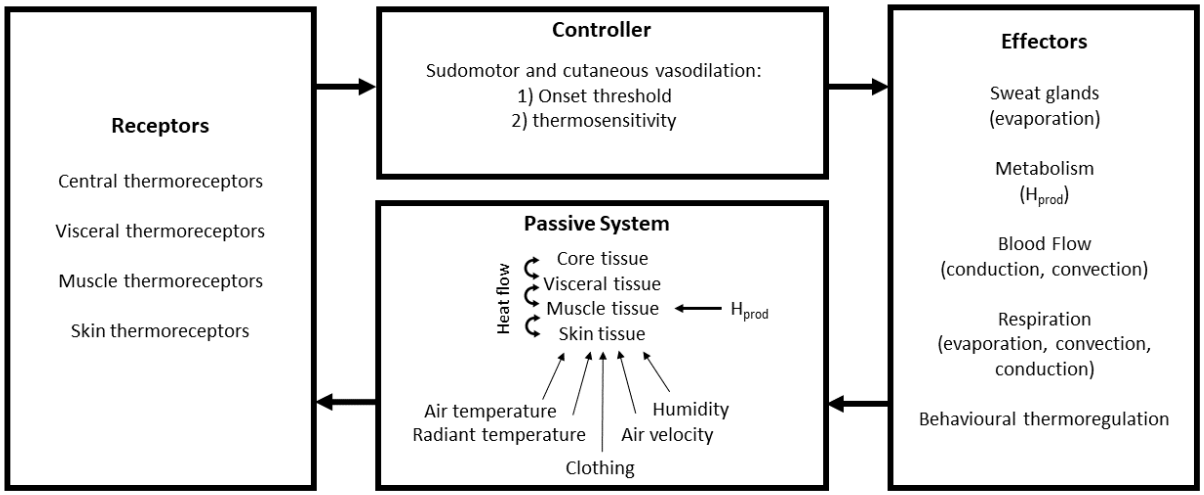

Figure 2. Schematic diagram outlining the thermoregulatory system in the absence of a set-point (adapted from Werner (191)). The effectors act upon the passive system directly via heat transfer. The receptors which measure temperature within the passive system transmit the information to the controllers which activate effector responses. In this model, the notion of an arbitrary set-point core temperature is eliminated, rather it is the influence of the effectors on the passive system which determines the thermoregulatory response.

A further implication of Study 1 is that previous investigators interested in thermoregulatory responses have repeatedly controlled for circadian variation as limited evidence in the past has suggested that sweat rates are higher in the afternoon in comparison to the morning

(102) and that the onset for sweating occurs at a higher core temperature (179, 190), although the rightward shift in the absolute core temperature sweating onset parallels the diurnal variation in resting core temperature. As such, if absolute core temperature is not a primary outcome variable, results of Study 1 confirm that the change in core temperature and steady-state sweat rates remain unaltered despite a difference in absolute core temperature of ~0.2°C between identical exercise sessions conducted in the morning (0800h) or the afternoon (1600h). The liberty to test participants at different times of days without alterations in thermoregulatory responses is paramount for researchers who investigate individuals with illnesses or thermoregulatory dysfunction where unforeseen issues or idiopathic symptoms may postpone their scheduled experimental session (e.g. multiple sclerosis, spinal cord injuries, etc). Further, due to the previous literature, it has been proposed that dehydration is hastened later in the day due to the greater observed sweat rates (184, 185) independently of metabolic heat production and E_{req}. However, the present findings do not support this point of view.

By definition, compensable heat stress is characterized by the ability to physiologically compensate heat production via heat dissipation from the skin surface to the surrounding environment. To date, the literature indicates that the partial heat acclimation associated with regular aerobic training (and consequently a higher aerobic capacity) improves heat dissipation via greater evaporation from the skin surface (9, 12, 70, 135). However, it has been previously demonstrated that in groups differing greatly in aerobic capacity (~20 ml/kg/min) but matched for morphological characteristics, the change in core temperature remains the same when exercise is prescribed as a fixed rate of heat production with similar steady-state whole body and local sweat rates between groups in a compensable environment (99). Thus, the thermal benefits of a higher heat dissipation mechanism (e.g. greater sweat rates) perhaps is most evident during

uncompensable heat stress where the upper limit for heat dissipation is challenged. As such, thesis study #3 was designed to examine whether partial or complete heat acclimation, as induced by aerobic training and a conventional heat acclimation protocol, respectively, alters the core temperature and sweating responses in both a compensable and uncompensable environment. Despite the marginally greater sweat rate observed with partial and complete heat acclimation in thesis study #3, the change in core temperature remained similar when the same compensable heat stress was applied. Physiologically, heat balance is attained by an integration of core and peripheral thermoreceptors signalling perturbations in temperature (25, 71, 131, 177). With respect to Figure 2, the resultant output of the passive system (tissue temperature measured by thermoreceptors) will be determined by the net difference in heat production and heat loss (the input to the passive system). Prior to the attainment of heat balance in a compensable environment, heat storage occurs which triggers the onset of thermoregulatory heat dissipation mechanisms to minimize the rate of heat storage as exercise continues. Following ~30 minutes of steady state exercise, heat balance should be achieved, that is the rate of heat production is matched with an equal rate of heat dissipation (Figure 2, 3). As often proposed, aerobically fit individuals have enhanced heat dissipation mechanisms primarily via a greater evaporative heat loss (9, 12, 70, 135), even during compensable heat stress (39). However, if this were true, from a biophysical perspective, heat dissipation would exceed heat loss and consequently heat storage would be negative (e.g. more heat being dissipated than produces). It would thus be expected that core temperature would drop with prolonged exercise due to the greater heat loss relative to heat production. This was not observed in Study 2 during compensable heat stress where the change in core temperature remained the same independent of heat acclimation status. In contrast, the influence of partial and complete heat acclimation on the associated physiological adaptations (e.g. sweating) was most

evident during uncompensable heat stress where the upper limit for heat dissipation was challenged (Figure 3). Expectedly, the greater sweat rates achieved following partial and complete heat acclimation (Figure 3) mitigated the change in core temperature relative to unacclimated. In support, the greater evaporation from the skin surface can be hypothesized by the progressively lower change in mean skin temperature with heat acclimation during uncompensable heat stress. However, whilst there may be evidence for greater evaporative heat loss following complete compared to partial heat acclimation, the additional heat loss was insufficient to mitigate the change in core temperature during 60 minutes of uncompensable heat stress. Nevertheless, it can be concluded that the hallmark physiological adaptations associated with direct heat dissipation mechanisms (i.e. increased sweat rates, (5, 12, 69, 124, 171)) following heat acclimation are most evident during uncompensable heat stress and therefore such environmental conditions are considered most appropriate for identifying the heat acclimation status of an individual.

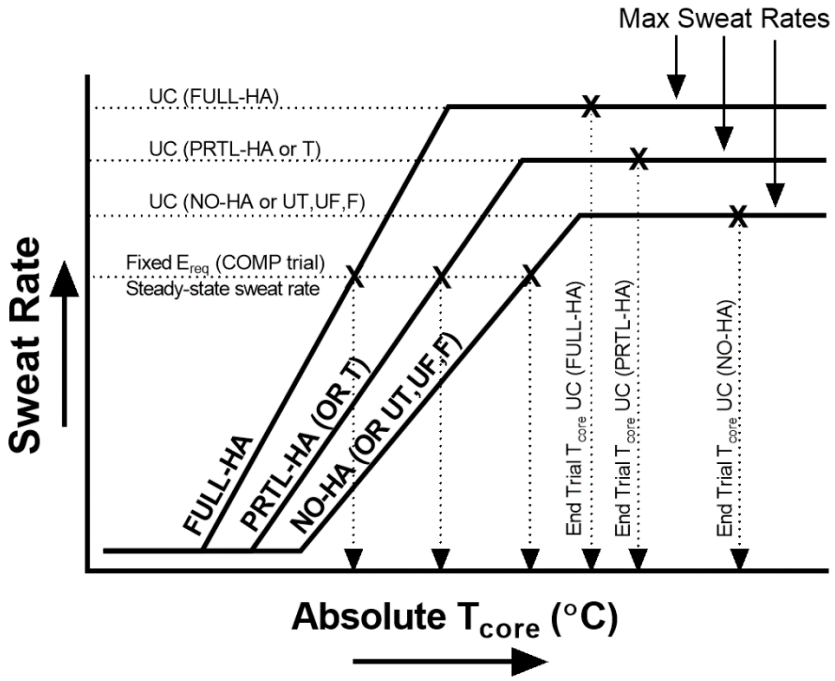

Figure 4 The influence of acclimation (unacclimated: **NO-HA**, partial acclimation: **PRTL-HA**, and complete acclimation: **FULL-HA**), fitness (unfit: **UF**, fit: **F**), and training (untrained: **UT**, and trained: **T**) on sweat rate during compensable (**COMP**, Study 3) heat stress matched for a fixed evaporative requirement for heat balance (**E_{req}**), and when E_{req} exceeded the maximum evaporative capacity (uncompensable: **UC**). When steady-state sweat rates were achieved during compensable heat stress in Study 2 where exercise was fixed to elicit a given E_{req}, the steady-state absolute core temperature observed was progressively lower with PRTL-HA and FULL-HA compared to NO-HA. During UC heat stress (Study 1, 2 and 4), progressive heat acclimation permitted a greater maximum sweat rate in addition to an earlier onset and greater thermosensitivity, which reduced the absolute core temperature observed following 60 minutes of exercise.

Previous evidence had identified that ω_{max} is higher following heat acclimation in comparison to unacclimated individuals during passive heat stress (40). However, the potential for aerobic training to provide comparable increases in maximum skin wettedness as heat acclimation remained unclear. As demonstrated in Study 3, aerobic training provided physiological adaptations that were suggestive of partial heat acclimation, that is, the ω_{max} following 8 weeks of aerobic training (0.84±0.08) resided above what was possible prior to training (0.72±0.06) but less than what was observed following complete heat acclimation (0.95±0.05). The ability to attain a greater

skin wettedness provides individuals the potential to extend their range of compensable conditions by permitting a greater maximum evaporative heat loss (Figure 4). This evidence is critical for creating evidence-based heat stress guidelines for occupational settings or sporting events where periods of prolonged heat exposure may be endured. More specifically, it potentially enables more specific values to be applied in current standardized heat stress modelling equations (e.g. ISO:7933) which presently permit a binary input to account for ω_{max} of an individual (unacclimated or acclimated). In order to maintain ecological validity, training protocol employed in Study 3 was conducted in environmental conditions comparable to a commercial training facility (~22°C and 30% RH) and thus it remains unclear whether similar alterations in maximum skin wettedness would be observed in unfit individuals who engaged in an 8-week aerobic training regime in cooler, or warmer, environmental conditions. Additionally, it remains unclear whether varying exercise intensity and training session durations during the training protocol may alter the thermoregulatory adaptations observed in healthy populations. For example, more recent evidence indicates that frequent but acute (< 30 min) high intensity exercise training can improve aerobic capacity (14, 36, 58, 68, 84) similarly to training protocols incorporating moderate and high intensity training similarly to Study 3. Thus, future investigation is required to examine whether the short duration high intensity exercise training protocols may provide similar adaptations as characterized in Study 3 for partial heat acclimation.

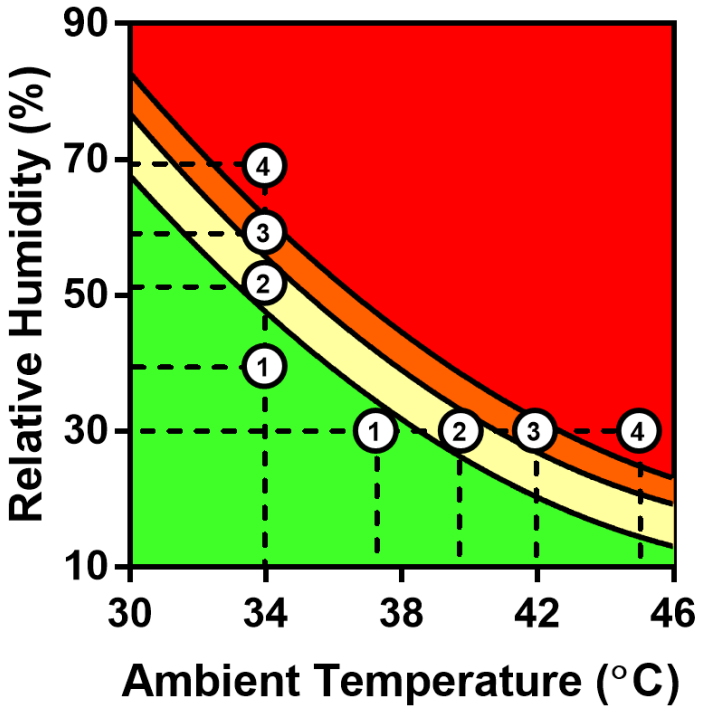

Figure 4. The potential increase in the range of physiologically compensable conditions for an individual who is unacclimated (green), partially heat acclimated (cream), fully heat acclimated (orange), and uncompensable regardless of heat acclimation status (red) for exercise at a fixed heat production of 600 W. (1) all individuals can attain heat balance. (2) Individuals who are partially acclimated or trained can attain heat balance. (3) Only fully heat acclimated individuals can attain heat balance. (4) No individual can attain heat balance.

From a biological perspective, an adaptation will occur following repeated stimulation to re-establishing homeostasis for a given stressor. Simply, the degree of heat strain is a difference between heat production and heat loss, and heat loss is the sum of radiation, conduction, convection, and evaporation from the skin surface in addition to respiratory heat transfer. Conceptually, if one exercises in environments that do not require evaporation to maintain heat balance, then the effector organ (i.e. sweat glands) will not receive an adequate stimulus for functional or morphological adaptations. For example, elite swimmers may present themselves with a high maximal aerobic capacity thereby enabling them to work at high rates of heat

production which must be dissipated to maintain thermal equilibrium. However, the high thermal conductance of water compared to air would equate to a reduced sweating requirement to maintain heat balance for a given rate of heat production. Thus, the stimulus for sweating throughout training would be lower despite having the capacity to attain high heat loads, which may translate to a reduced maximal capacity to dissipate heat through evaporation in comparison to athletes of equal fitness who train and compete in land-based sports. In fact, Henane (85) observed that swimmers had a lower sweat rate compared to runners and a greater change in core temperature during exercise heat stress; findings corroborated by Piwonka (146) and McMurray (122). Even under temperate or cool conditions, elite marathon or distance runners would rely heavily on evaporation to maintain heat balance since relatively little heat would be liberated through conduction, radiation, and convection (1, 44). The repetitive drive for sweating may independently alter the maximum sweating capacity of runners and may enable a greater ω_{max} compared to VO_{2max}-matched swimmers. Thus, perhaps it is not simply the act of physical training which augments sudomotor adaptation, but possibly an integration of both heat production and the environment for heat exchange that precipitate adaptation. Future research should attempt to identify the safest and most efficient combination of heat production and environmental conditions which will result in physiological adaptations comparable to traditional 7 to 14-day heat acclimation protocols (5, 19, 43, 135, 156, 187, 200). In addition, the ability to increase the evaporative heat loss potential via increasing maximum skin wettedness may serve as a viable alternative for mitigating the risk of hyperthermia during heat stress in vulnerable populations such as the elderly, spinal cord injured patients, burn victims, and other people who present with thermoregulatory dysfunction. More research is required to investigate whether frequent bouts of

aerobic training may offer similar increases in sudomotor adaptation as presented in Study 2 and 3 with healthy young adults.

The most important benefits from the ability to attain a greater ω_{max} are i) to extend the range of compensable conditions and ii) mitigate the level of heat strain experienced during uncompensable heat stress. For example, if for a given exercise intensity and environmental condition the skin wettedness required for heat balance is 0.80, a person who is untrained and unacclimated would possibly be unable to attain heat balance due to findings in Study 3, but the same environmental conditions would become compensable after 8 weeks of aerobic training (Figure 4). Furthermore, a greater ω_{max} would reduce the net heat storage, ultimately blunting the rate of change in core temperature during uncompensable heat stress. However, since the seminal work of Saltin and Hermansen (161), it has been often assumed that aerobic fitness independently alters the thermoregulatory responses to heat stress. Traditionally, aerobic fitness is characterized by the maximum rate of oxygen consumption, a physiological trait that may have minimal direct influence on thermoregulatory function. Rather, as outlined in Studies 2, 3, and 4, regular physical training determines the alterations to thermoregulatory capacity possibly due to the repetitive and frequent bouts of heat stress provided the heat stress induced requires evaporative means of heat dissipation. In fact, the observed sweating responses of the fit and unfit groups paralleled the responses observed in the unacclimated group in (Figure 3). Thus, when examining thermoregulatory function during uncompensable heat stress, VO_{2max} per se cannot be used as a proxy for heat acclimation status.

4.3 Thesis conclusions

The present thesis demonstrates the following: Using circadian rhythm and different ambient temperatures (coupled with differences in metabolic rate) to modulate absolute core and skin temperature respectively, the steady-state sweat rate response was not altered during compensable heat stress at a fixed E_{req}. While partial and complete heat acclimation marginally increased the forearm steady-state sweat rate and whole-body sweat rate for a fixed E_{req}, the change in core temperature was unaltered suggesting the additional sweat secreted provided no additional heat loss. However, the effects of partial and complete heat acclimation on heat loss were very pronounced when exercise was conducted in an uncompensable environment where the upper limits for heat dissipation were challenged. The progressively greater evaporative heat loss via a greater ω_{max} with partial and complete heat acclimation mitigated the rise in core temperature during uncompensable heat stress relative to an unacclimated state. While partial heat acclimation increased ω_{max} to 0.84±0.08 from an unacclimated state (0.72±0.06), the maximum skin wettedness observed following complete heat acclimation (0.95±0.05) was greater. Finally, VO_{2max} per se does not alter thermoregulatory responses to exercise in an uncompensable environment, rather the partial heat acclimation associated with frequent and repetitive bouts of exercise-induced heat stress with aerobic training are needed to augment the sudomotor responses.

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APPENDIX

APPENDIX A: Ethics approval for thesis studies

File Number: H12-14-06 **Date (mm/dd/yyyy):** 02/29/2016

Université d'Ottawa University of Ottawa
Bureau d'éthique et d'intégrité de la recherche 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	Supervisor
Ollie	Jay	Health Sciences / Human Kinetics	Co-Supervisor
Nicholas	Ravanelli	Health Sciences / Human Kinetics	Student Researcher
Geoff	Coombs	Health Sciences / Human Kinetics	Research Assistant

File Number: H12-14-06

Type of Project: Master's Thesis

Title: Does maximal aerobic capacity influence skin wettedness and sweating efficiency during uncompensable heat stress?

Renewal Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
02/24/2016	02/23/2017	Ia

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

Special Conditions / Comments:
N/A

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Ethics Approval Notice

Health Sciences and Science REB

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

First Name	Last Name	Affiliation	Role
Ollie	Jay	Health Sciences / Human Kinetics	Principal Investigator
Matthew	Cramer	Health Sciences / Human Kinetics	Co-investigator
Geoff	Coombs	Health Sciences / Human Kinetics	Research Assistant
Nicholas	Ravanelli	Health Sciences / Human Kinetics	Research Assistant

File Number: H12-12-04

Type of Project: Professor

Title: The influence of body surface area on the thermoregulatory sweating during exercise

Renewal Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
01/17/2017	01/16/2018	Renewal

Special Conditions / Comments:
N/A

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Bureau d'éthique et d'intégrité de la recherche 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
Nicholas	Ravanelli	Health Sciences / Human Kinetics	Co-investigator

File Number: H04-17-20

Type of Project: Professor

Title: The influence of circadian rhythm on heat loss responses and appetite regulation to exercise in thermoneutral and hot environments

Approval Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
05/03/2018	05/02/2019	Renewal

Special Conditions / Comments:
N/A

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APPENDIX B: Final published version of thesis study #3

Maximum Skin Wettedness after Aerobic Training with and without Heat Acclimation

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ABSTRACT

RAVANELLI, N., G. B. COOMBS, P. IMBEAULT, and O. JAY. Maximum Skin Wettedness after Aerobic Training with and without Heat Acclimation. *Med. Sci. Sports Exerc.*, Vol. 50, No. 2, pp. 299–307, 2018. **Purpose**: To quantify how maximum skin wettedness (ω_{max}); that is, the determinant of the boundary between compensable and uncompensable heat stress, is altered by aerobic training in previously unfit individuals and further augmented by heat acclimation. **Methods**: Eight untrained individuals completed an 8-wk aerobic training program immediately followed by 8 d of hot/humid (38°C, 65%RH) heat acclimation. Participants completed a humidity ramp protocol pretraining (PRE-TRN), posttraining (POST-TRN), and after heat acclimation (POST-HA), involving treadmill marching at a heat production of 450 W for 105 min in 37.5°C, 2.0 kPa (35%RH). After attaining a steady-state esophageal temperature (T_{es}), humidity increased 0.04 kPa·min^{-1}. An upward inflection in T_{es} indicated the upper limit of physiological compensability (P_{crit}), which was then used to quantify ω_{max}. Local sweat rate, activated sweat gland density, and sweat gland output on the back and arm were simultaneously measured throughout. **Results**: Peak aerobic capacity increased POST-TRN by approximately 14% (PRE-TRN: 45.8 ± 11.8 mL·kg^{-1}·min^{-1}; POST-TRN: 52.0 ± 11.1 mL·kg^{-1}·min^{-1}, $P < 0.001$). ω_{max} values became progressively greater from PRE-TRN (0.72 ± 0.06) to POST-TRN (0.84 ± 0.08; $P = 0.02$), to POST-HA (0.95 ± 0.05; $P = 0.03$). These shifts in ω_{max} were facilitated by a progressively greater local sweat rate and activated sweat gland density from PRE-TRN (0.84 ± 0.21 mg·cm^{-2}·min^{-1}; 67 ± 20 glands per square centimeter) to POST-TRN (0.96 ± 0.21 mg·cm^{-2}·min^{-1}, $P = 0.03$; 86 ± 27 glands per square centimeter; $P = 0.009$), to POST-HA (1.15 ± 0.21 mg·cm^{-2}·min^{-1}; $P < 0.001$; 98 ± 35 glands per square centimeter; $P < 0.001$). No differences in sweat gland output were observed. **Conclusions**: A greater ω_{max} occurred after 8 wk of aerobic training, but ω_{max} was further augmented with heat acclimation, indicating only a partially increased heat loss capacity with training. These ω_{max} values may assist future predictions of heat stress risk in untrained/trained unacclimated individuals and trained heat-acclimated individuals. **Key Words:** SWEATING, THERMOREGULATION, HEAT STRESS, SWEAT GLANDS

The evaporation of sweat from the skin surface is the largest modifiable heat loss pathway for maintaining thermal equilibrium during heat stress. Understanding the factors that define the maximum capacity for evaporative heat loss (E_{max}), and thus the metabolic heat production that can be physiologically compensated before unchecked elevations in core temperature occur (i.e., uncompensability), is therefore essential for predicting heat stress risk in physically active people in hot environments (e.g., occupational workers, athletes, military).

In a given environment, E_{max} is determined by the proportion of total skin area that can be saturated in sweat (i.e., maximum skin wettedness [ω_{max}]). A ω_{max} of 1.00 (i.e., 100% body surface coverage) is the highest value possible and is widely considered to be attained after complete heat acclimation. On the other hand, unacclimated individuals are considered to be only capable of attaining a ω_{max} of 0.85 (1). Many existing computational models defining the environmental and/or duration limits for heat stressed occupational workers use these assumed ω_{max} values of 0.85 for unacclimated and 1.00 for heat acclimated workers (ISO7933:2004 (2); thermal work limit (3)). Yet, no ω_{max} value exists for a trained versus untrained, unacclimated worker, except the suggestion that the ω_{max} changes that occur with training are analogous to heat acclimation (4). Even the widely accepted ω_{max} values for unacclimated and acclimated individuals are derived from a small sample size ($n = 4$), in a supine posture, with passive heat acclimation and unknown training status.

Although steady-state core temperature and sweating responses do not seem to be altered by maximum aerobic capacity (5,6), it remains plausible that a partial heat acclimation associated with physical training may raise the upper limit of evaporative heat dissipation (i.e., ω_{max}). Indeed, aerobically trained individuals exhibit greater maximal sweat rates compared with untrained individuals when exercising in hot and humid conditions (7) or via pharmacologically induced stimulation (8).

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The ability to attain greater sweat rates may also support why aerobically fit individuals achieve a heat-acclimated state in fewer days compared with less fit individuals (9). However, a greater sweat rate may not directly translate to a greater ω_{max} and, therefore, E_{max} if the additional sweat secreted ultimately drips off the body, providing no cooling. In fact, a greater ω_{max} and, therefore, E_{max} requires a more uniform and complete distribution of sweat across the body surface. Although activated sweat gland density (ASGD) increases as a function of aerobic fitness (10,11), it remains unclear whether this enables a greater maximum sweat coverage (i.e., ω_{max}) in previously untrained people (e.g., individuals who do not engage in regular physical activity).

The purpose of the present study was to assess whether aerobic training increases ω_{max} and identify how this increase, if any, is further augmented by heat acclimation. We compared the evaporative capacity and sudomotor responses of young, untrained participants using a humidity ramp protocol (12) before and after an 8-wk aerobic training program in a cool environment (22°C, 30%RH) and then after 8 d of heat acclimation in a hot and humid (38°C, 65%RH) environment that immediately followed. It was hypothesized that training increases ω_{max}, but this increase is augmented further with heat acclimation. It was also hypothesized that the progressively greater ω_{max} with training and then heat acclimation is facilitated by an increased ASGD.

METHODS

Participants

Ethical approval was obtained from the University of Ottawa Health Sciences Research Ethics Board (H12-11-05) conforming to the principles set forth in the Declaration of Helsinki 2013. All volunteers gave both verbal and written consent before participation. To ensure participants were sufficiently healthy to conduct the study protocols, they were required to fill out a Physical Activity Readiness Questionnaire and an American Heart Association Pre-participation Screening Questionnaire. All participants had no previous cardiovascular, neuromuscular, and/or respiratory medical condition that could be exacerbated with exercise and were nonsmokers or at least 12 months without smoking. Lastly, all participants reported no involvement in structured training programs and were failing to meet the weekly moderate physical activity recommendations set forth by the American College of Sports Medicine by more than 35% (13).

Based on previously reported data (14), a power calculation (G*Power 3.1.9.2) determined that a minimum of 8 participants was required to demonstrate a significant difference. A Cohen *d* effect size of 1.17 was determined using the previously reported critical ambient vapor pressure of heat acclimated (3.80 kPa) women (14) and a hypothesized trained but unacclimated (i.e., median of unacclimated and heat acclimated, 92.5%; 3.52 kPa) with a variance twofold greater than previously reported (0.24 kPa), and β and α values were equal to 0.80 and 0.05, respectively. All participants commenced during the winter months to eliminate any potentially seasonal partial acclimation (15). Initially, 10 people were recruited; however, 2 participants voluntarily withdrew during the training intervention, and therefore, a total of 8 people (6 male and 2 female subjects) completed the study. Participant characteristics are given in Table 1.

Experimental Design

Participants completed an 8-wk training intervention immediately followed by an 8-d heat acclimation protocol, whereby two aerobic capacity assessments (pretraining and posttraining) and three inflection (INF) trials at (i) pretraining, (ii) posttraining, and (iii) after heat acclimation were performed within the study timeline (Fig. 1). All $\dot{V}O_{2max}$ and INF trials were conducted at the same time of day to mitigate any influence of circadian rhythm (16). To account for the potential influence of the menstrual cycle for female participants (17), the 8-wk training intervention ensured pretraining and posttraining INF trials occurred at a similar stage (i.e., week) of their respective menstrual cycle, which they verbally confirmed. Because female subjects respond similarly after heat acclimation, independent of the menstrual cycle (18), they readily completed the heat acclimation protocol immediately after the second INF trial.

Fitness assessments. Participants were asked to refrain from food for 2 h before testing; however, water ingestion was permitted *ad libitum*. First, the participant's body composition was assessed using a dual-energy x-ray absorptiometry scanner (GE-LUNAR Prodigy module; GE Medical Systems, Madison, WI). Next, the participant completed a Modified Bruce Treadmill Protocol (19) in accordance to the safe practice regulations outlined by the Canadian Society of Exercise Physiologists (20)). Expired gases were measured via breath-by-breath indirect calorimetry using a metabolic cart (Vmax Encore; Care Fusion, Yorba Linda, CA) and averaged every minute and heart rate via a cardiotachometer (Polar RS 400CX; Polar Electro Oy, Kempele, Finland).

INF trial. Participants were instructed to eat a light meal approximately 2 h before arrival and to ensure adequate hydration. Upon arrival, participants provided a urine sample to confirm hydration status using urine specific gravity measured with a refractometer. Participants arrived with similar urine specific gravity measure before all trials

TABLE 1. Participant characteristics before and after 8 wk of aerobic training.

	Pretraining	Posttraining
$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	45.8 ± 11.6	52.0 ± 11.1*
$\dot{V}O_{2peak}$ (L·min^{-1})	3.6 ± 0.8	4.0 ± 0.8*
HR_{max} (bpm)	185 ± 10	184 ± 9
Weight (kg)	80.2 ± 16.7	78.9 ± 15.5
BSA (m^2)	1.96 ± 0.22	1.94 ± 0.21
BSA/mass (cm^2·kg^{-1})	249 ± 28	251 ± 27
Body fat (%)	26.0 ± 12.0	24.2 ± 11.6†

*Significantly greater posttraining ($P < 0.001$).
†Significantly lower posttraining ($P < 0.05$).
$\dot{V}O_{2peak}$, peak oxygen consumption; HR_{max}, maximum heart rate.

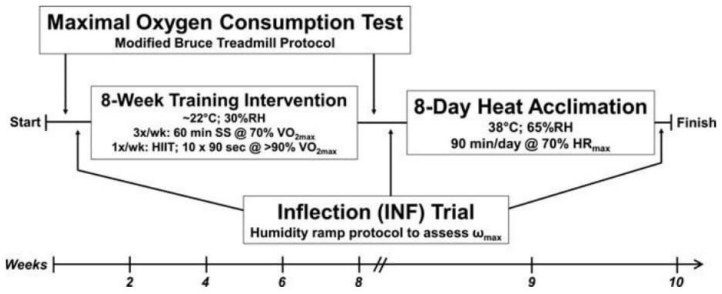

FIGURE 1—Illustration of the approximately 10-wk study timeline for each participant. ω_{max}, maximum skin wettedness; SS, steady state exercise; $\dot{V}O_{2max}$, maximal oxygen consumption; HIIT, high-intensity interval training session; HR_{max}, maximum heart rate.

(pretraining: 1.012 ± 0.007, posttraining: 1.011 ± 0.006, post heat acclimation: 1.012 ± 0.005). Participants were instructed to change into standardized clothing (male subjects: shorts and shoes; female subjects: shorts, shoes, and sports bra), after which, they self-inserted their rectal thermistor. The participant then entered the climatic chamber (37.5°C and 2.0 kPa), was instrumented, and then rested for 30 min in a seated position to equilibrate with the surrounding environment. Next, the participant began walking on a treadmill at an intensity that elicited a metabolic heat production (H_{prod}) of 450 W, monitored and maintained in real-time via indirect calorimetry. All participants achieved a steady-state core temperature by the 38th min of exercise, defined as a less than 0.05°C increase in esophageal temperature (T_{es}) during the preceding 10 min. After 45 min of exercise, ambient vapor pressure (P_a) of the room increased at a rate of approximately 0.04 kPa·min^{-1} in a linear fashion until 4.60 kPa was reached (additional 60 min). The critical ambient vapor pressure (P_{crit}) was identified as the point at which an upward inflection in esophageal temperature (T_{es}) was observed, signifying the transition from a compensable to uncompensable state ((12); Fig. 2A). P_{crit} was verified using segmental linear regression (GraphPad Prism 7.0; GraphPad, La Jolla, CA; Fig. 2B).

Training intervention. Each participant then underwent an 8-wk training intervention where they were required to partake in 4 weekly sessions of supervised aerobic training in temperate conditions (~22°C, 30%RH) with the goal of increasing $\dot{V}O_{2peak}$ by at least 10%. All intensities prescribed during training were defined based on the heart rate associated for a given percentage of $\dot{V}O_{2peak}$; therefore, a cardiotachometer

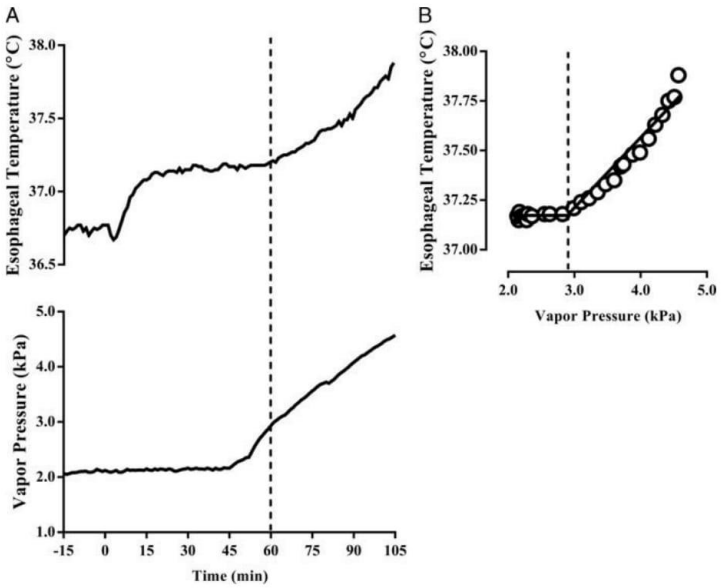

FIGURE 2—Example of esophageal temperature trace (A; top panel) and the humidity ramp protocol (A; bottom panel) during an INF trial. After 45 min of steady-state exercise at a H_{prod} of 450 W, humidity was increased at a rate of 0.04 kPa·min^{-1}. Linear segmental regression was used to objectively identify the ambient vapor pressure coinciding with the upward inflection in esophageal temperature (B).

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was worn for every session. The first week of training consisted of 4×60-min sessions at 60% of $\dot{V}O_{2peak}$. From the second week onward, participants completed 3×60-min sessions at 70% of $\dot{V}O_{2peak}$ and 1 high-intensity interval training (HIIT) session. The HIIT session consisted of a warm-up at 50% of $\dot{V}O_{2peak}$, followed by 10×3-min intervals involving 1.5 min at 90% of $\dot{V}O_{2peak}$ followed by 1.5 min at 50% of $\dot{V}O_{2peak}$, and a 10-min self-paced cooldown. The absolute external work during the HIIT was increased by no more than 10% each week. The majority of aerobic training was performed on a treadmill; however, because of safety concerns, HIIT was predominantly done on an upright cycle ergometer. In sum, the training program increased in intensity every week, thus minimizing the risk of observing "nonresponders" to aerobic training (21).

Heat acclimation. Immediately after the second INF trial, participants completed 8 consecutive days of up to 90-min exercise bouts in a hot and humid environment (38°C, 65% RH) where they walked on a treadmill with a slight grade (i.e., 3%–5%) at 70% of maximum heart rate (HR_{max}). A clamped heart rate protocol permitted a progressive increase in workload throughout the 8-d intervention because of the rapid reductions in heart rate during heat acclimation (22); thus, it was hypothesized a positive thermal impulse was sustained (23) as most recently observed by Garrett et al. (24) during a short-term heat acclimation protocol on elite male rowers. Body mass was taken immediately before and after each session using a platform scale (Combics 2; Sartorius, Mississauga, Ontario, Canada). Fluid was restricted during each session; however, participants were given a volume of electrolyte replacement beverage (Gatorade G2; Quaker Oats Company, Chicago, IL) equal to the total mass loss after each session.

Instrumentation

Thermometry. T_{es} was measured using a general purpose thermistor probe (Mon-a-therm General Purpose Temperature Probe 400TM; Covidien, Mansfield, MA) inserted through the nasal cavity into the esophagus. The end of the thermistor probe is estimated to be located at a region nearest the left ventricle (25). Rectal temperature (T_{re}) was measured using a general purpose thermistor probe inserted to a depth of 20 cm past the anal sphincter. Skin temperature was measured using four thermistor heat flux sensors (Concept Engineering, Old Saybrook, CT) which were secured to the skin using surgical tape (Transpore; 3M, London, Ontario, Canada). Temperature measurements were sampled every 5 s (NI cDAQ-91722 module; National Instruments, Austin, TX) and displayed in real-time on a desktop computer using customized LabVIEW software (v7.0; National Instruments). Mean skin temperature (T_{sk}) was calculated as the weighted average of four sites using the Ramanathan equation (26): chest 30%, triceps 30%, thigh 20%, and calf 20%.

Sweating. Ventilated sweat capsules secured to the skin using surgical tape were used to measure local sweat rates of the back (LSR_{back}) and forearm (LSR_{arm}). Anhydrous air was supplied through each 4.1-cm^2 capsule, and flow was maintained at a constant rate of 1.0 $L \cdot min^{-1}$ and 1.2 $L \cdot min^{-1}$ for LSR_{back} and LSR_{arm}, respectively, using a factory calibrated flow meter (Omega FMA-A2307; Omega Engineering, Stamford, CT). The temperature and humidity of the capsule effluent air were sampled with region-specific (i.e., arm and back) calibrated capacitance hygrometers (HMT333; Vaisala, Vantaa, Finland) every 5 s. The local sweat rate was calculated as the product of absolute humidity and flow rate and expressed relative to the amount of skin surface covered by the capsule and averaged every minute ($mg \cdot cm^{-2} \cdot min^{-1}$). Activated sweat gland density of the arm ($ASGD_{arm}$) and back ($ASGD_{back}$) was measured within 2 cm of their respective ventilated capsule using the starch-iodine paper technique (27). Impressions were taken using a 9-cm^2 piece of 100% cotton paper (Moab Entrada; Legion Paper, New York, NY) every 15 min of exercise. Sweat gland output for the arm (SGO_{arm}) and back (SGO_{back}) was calculated by dividing the region-specific sweat rate by the respective ASGD (in micrograms per gland per minute).

Calculations

Partitional calorimetry. Heat balance parameters were estimated via partitional calorimetry (28) and expressed relative to body surface area (BSA) estimated using the DuBois and DuBois equation (29).

External work to the treadmill was estimated using the following equation (30):

$$W = \{[10^3(\mathrm{BW} \times v \times \mathrm{gr})]/(6.12 \times 60 \times 100)\}/A_D \left[\mathrm{W \cdot m^{-2}}\right] \quad [1]$$

where BW is mass (kg), v is the velocity of the belt ($km \cdot h^{-1}$), gr is the incline of the belt defined as the fraction of vertical displacement (m) for every 100 m of belt rotation, and A_D is BSA (m^2) estimated using the Dubois and DuBois equation (29).

The rate of metabolic heat production (H_{prod}) was calculated by subtracting the rate of external work (W) from metabolic energy expenditure (M). M was estimated using the following equation:

$$M = \dot{V}O_2 \frac{\left(\left(\frac{\mathrm{RER}-0.7}{0.3}\right)e_c\right) + \left(\left(\frac{1.0-\mathrm{RER}}{0.3}\right)e_f\right)}{60 A_D} \times 1000 \left[\mathrm{W \cdot m^{-2}}\right] \quad [2]$$

where $\dot{V}O_2$ is the rate of oxygen consumption ($L \cdot min^{-1}$), e_c is the caloric equivalent per liter of oxygen for the oxidation of carbohydrates (21.13 $kJ \cdot L^{-1}$ of O_2 consumed), e_f is the caloric equivalent per liter of oxygen for the oxidation of lipids (19.62 $kJ \cdot L^{-1}$ of O_2 consumed), and respiratory exchange ratio is the ratio of carbon dioxide production and oxygen consumption ($\dot{V}CO_2/\dot{V}O_2$).

Convective heat exchange from the skin, C, was calculated as follows (28):

$$C = h_c(T_{sk} - T_a) \left[\mathrm{W \cdot m^{-2}}\right] \quad [3]$$

where h_c is the convective heat transfer coefficient for treadmill walking as derived by Nishi and Gagge (31):

$$h_c = 6.51 v^{0.391} \left[\mathrm{W \cdot m^{-2} \cdot K^{-1}}\right] \quad [4]$$

where v is the walking speed ($m \cdot s^{-1}$). Within each participant, walking speed was consistent for each INF trial and only grade was manipulated to maintain a fixed H_{prod}.

Radiant heat transfer (R) was estimated by the following:

$$R = h_r(T_{sk} - T_r)\ [W \cdot m^{-2}] \quad [5]$$

where h_r (radiant heat transfer coefficient, $W \cdot m^{-2} \cdot K^{-1}$) is estimated using the following:

$$h_r = \varepsilon 4\sigma(A_r/A_D)\left((T_{sk} + T_r)/2 + 273.15\right)^3\ [W \cdot m^{-2} \cdot K^{-1}] \quad [6]$$

where ε is the area weighted emissivity of the body surface (0.95), σ is the Stefan–Boltzmann constant (5.67×10^{-8} $W \cdot m^{-2} \cdot K^{-4}$), A_r/A_D is the effective radiative surface area (ND) which can be estimated as 0.73 for a standing person (32), and $T_{sk} + T_r$ is the sum of the mean skin temperature and mean radiant temperature (°C), assumed to be equivalent to T_a (°C).

Respiratory heat loss was estimated using the following:

$$E_{res} + C_{res} = 0.0173(H_{prod})(5.87 - P_a) + 0.0014(H_{prod})(34 - T_a)\ [W \cdot m^{-2}] \quad [7]$$

The evaporative requirement to maintain heat balance (E_{req}) in W was estimated by rearranging the conceptual heat balance equation:

$$E_{req} = H_{prod} - (C + R + C_{res} + E_{res})\ [W \cdot m^{-2}] \quad [8]$$

Estimating maximum skin wettedness (ω_{max}): The maximum rate of evaporative heat loss (E_{max}) for a given environment can be estimated as follows:

$$E_{max} = \omega_{max}(P_{sk,s} - P_a)/R_{e,cl} + [1/h_e f_{cl}])\ [W \cdot m^{-2}] \quad [9]$$

where ω_{max} is the maximum skin wettedness (33); P_a is the absolute ambient vapor pressure at E_{max} (kPa), which is equal to P_{crit} measured in the INF trial (Fig. 1); $R_{e,cl}$ is the evaporative heat transfer resistance of the clothing ensemble (assumed to be 0.002 $kPa \cdot m^{-2} \cdot W^{-1}$); f_{cl} is the clothing area factor (surface area of the clothed body divided by the surface area of the nude body; assumed to be negligible); h_e is the evaporative heat transfer coefficient ($W \cdot m^{-2} \cdot K^{-1}$), which is the product of h_c (equation 4) and the Lewis Relationship (16.5 $K \cdot kPa^{-1}$); and $P_{sk,s}$ is the saturated water vapor pressure (kPa) at skin temperature and was derived using Antoine equation:

$$P_{sk,s} = \exp(18.956 - [4030.18/(T_{sk} + 235)])/10[kPa] \quad [10]$$

At the breakpoint of compensability (i.e., the upward inflection in T_{es}; Fig. 1), E_{req} must equal the individual's actual E_{max}. Thus, ω_{max} can be estimated by rearranging equation 9 and substituting E_{max} with E_{req}:

$$\omega_{max} = (E_{req}[R_{e,cl} + (1/h_e)])/(P_{sk,s} - P_{crit}) \quad [11]$$

Statistical Analysis

All data are reported as mean and standard deviation (mean ± SD). Paired t tests were used to compare participant characteristics (mass, BSA, BSA-mass ratio, body fat percent, and $\dot{V}O_{2peak}$) before and after the training intervention. A one-way analysis of variance using the independent variable of condition (3 levels: pretraining, posttraining, and after heat acclimation) was used to assess ω_{max}, P_{crit}, $P_{sk,s} - P_{crit}$ gradient, T_{es}, T_{re}, T_{sk}, HR, LSR_{arm}, LSR_{back}, $ASGD_{arm}$, $ASGD_{back}$, SGO_{arm}, and SGO_{back} at the break point of compensability (i.e., P_{crit}), as well as resting T_{es}, T_{re}, and T_{sk} and HR. If significance was observed, *post hoc* comparisons were conducted using a Holm–Sidak multiple comparisons test. All statistical analyses were conducted using GraphPad Prism Version 7.0 for Windows.

RESULTS

Training Intervention

$\dot{V}O_{2peak}$ was approximately 14% greater after the training intervention ($P < 0.001$; Table 1). The training intervention did not alter mass, BSA, and BSA–mass ratio; however, a reduction in body fat % ($P < 0.03$) after training was observed (Table 1).

Indicators of a Physiological Adaptation to the Heat

Resting T_{es} and T_{re} were lower posttraining ($P = 0.03$) and further reduced after heat acclimation ($P < 0.001$) in comparison to pretraining (Table 2). Similarly, resting T_{sk} was lower posttraining ($P = 0.003$) and after heat acclimation ($P < 0.001$) compared with pretraining. Resting heart rate was lower posttraining ($P = 0.03$) and after heat acclimation ($P < 0.001$) in comparison to pretraining, and after heat acclimation was lower than posttraining ($P = 0.03$). At the upper limit of compensability (e.g., P_{crit}), T_{re} and T_{es} were lower after heat acclimation in comparison to pretraining ($P < 0.001$). T_{sk} was lower posttraining ($P < 0.001$) and after heat acclimation ($P < 0.001$) in comparison to pretraining. Lastly, the HR at P_{crit} was lower after heat acclimation ($P < 0.001$) and posttraining ($P = 0.003$) compared with pretraining and lower after heat acclimation compared with posttraining ($P = 0.05$).

Maximum Skin Wettedness (ω_{max})

Individual and mean ω_{max} values pretraining, posttraining, and after heat acclimation are presented in Figure 3. In comparison to pretraining, ω_{max} was progressively greater posttraining ($P = 0.02$) and after heat acclimation ($P < 0.001$; Table 2, Fig. 3). Additionally, ω_{max} after acclimation was greater than posttraining ($P = 0.04$). Supporting the estimated ω_{max} values, P_{crit} was greater posttraining ($P = 0.009$) and after heat acclimation ($P < 0.001$) compared with pretraining, and P_{crit} was greater after heat acclimation compared with posttraining ($P = 0.005$). Furthermore, the $P_{sk,s} - P_a$ gradient at P_{crit} was lower after heat acclimation compared with pretraining ($P < 0.001$) and posttraining ($P = 0.01$) and lower posttraining compared with pretraining ($P = 0.02$).

Sweating

Figure 4 demonstrates all sudomotor parameters at the upper limit of physiological compensability (i.e., when ω_{max}

TABLE 2. Indicators of physiological adaptation to the heat at rest and at the upper limit of compensability (i.e., the upward inflection in esophageal temperature; INF) with biophysical parameters at INF pretraining (PRE-TRN), posttraining (POST-TRN), and after heat acclimation (POST-HA).

	PRE-TRN	POST-TRN	POST-HA
Rest			
T_{re} (°C)	37.2 ± 0.2	36.9 ± 0.3*	36.7 ± 0.2*
T_{es} (°C)	37.0 ± 0.2	36.7 ± 0.3*	36.6 ± 0.3*
T_{sk} (°C)	37.1 ± 0.4	36.7 ± 0.4*	36.5 ± 0.4*
HR (bpm)	89 ± 6	84 ± 8*	79 ± 6*†
INF			
T_{re} (°C)	38.0 ± 0.2	37.8 ± 0.3	37.6 ± 0.1*
T_{es} (°C)	37.5 ± 0.2	37.3 ± 0.2	37.2 ± 0.2*
T_{sk} (°C)	37.9 ± 0.3	37.4 ± 0.3*	37.3 ± 0.3*
HR (bpm)	131 ± 12	117 ± 16*	107 ± 11*†
ω_{max}	0.72 ± 0.06	0.84 ± 0.08*	0.95 ± 0.05*†
P_{crit} (kPa)	2.98 ± 0.35	3.42 ± 0.45*	3.95 ± 0.07*†
$P_{sk,s} - P_{crit}$ (kPa)	3.48 ± 0.31	3.10 ± 0.44*	2.60 ± 0.14*†

*Significantly different to PRE-TRN ($P < 0.05$).
†Significantly different to POST-TRN ($P < 0.05$).
T_{re}, rectal temperature; T_{es}, esophageal temperature; T_{sk}, skin temperature; HR, heart rate; $P_{sk,s} - P_{crit}$, the vapor pressure gradient between the ambient air and skin surface; ω_{max}, maximum skin wettedness expressed.

was reached). At ω_{max}, LSR_{arm} was higher posttraining (0.80 ± 0.18 mg·cm^{-2}·min^{-1}, $P = 0.004$) and after heat acclimation (1.00 ± 0.22 mg·cm^{-2}·min^{-1}, $P < 0.001$) compared with pretraining (0.67 ± 0.24 mg·cm^{-2}·min^{-1}) and higher at ω_{max} after heat acclimation compared with posttraining ($P = 0.03$). Similarly, LSR_{back} was higher after heat acclimation (1.30 ± 0.20 mg·cm^{-2}·min^{-1}, $P < 0.001$) and posttraining (1.12 ± 0.23 mg·cm^{-2}·min^{-1}, $P = 0.009$) compared with pretraining (1.00 ± 0.18 mg·cm^{-2}·min^{-1}) and higher after heat acclimation compared with posttraining ($P = 0.001$). $ASGD_{arm}$ was higher at ω_{max} posttraining (102 ± 30 glands per square centimeter, $P = 0.008$) and after heat acclimation (117 ± 45 glands per square centimeter, $P = 0.001$) compared with pretraining (73 ± 22 glands per square centimeter). Likewise, $ASGD_{back}$ was higher at ω_{max} posttraining (70 ± 23 glands per square centimeter, $P = 0.03$) and after heat acclimation (78 ± 25 glands per square centimeter, $P < 0.001$) compared with pretraining (61 ± 18 glands per square centimeter). Furthermore, $ASGD_{back}$ at ω_{max}

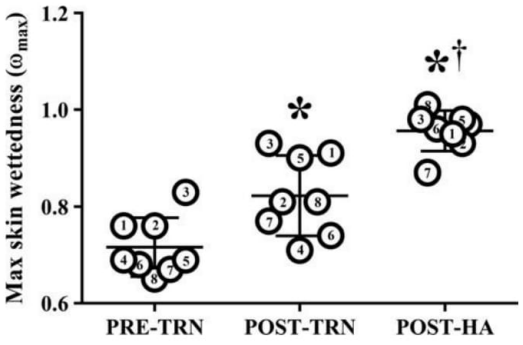

FIGURE 3—Individual and mean (with SD) values of maximum skin wettedness (ω_{max}) pretraining (PRE-TRN), posttraining (POST-TRN), and after heat acclimation (POST-HA). Individual values are identified with a number in descending order of their preliminary maximum aerobic capacity (e.g., no. 1 had the highest preliminary aerobic capacity). *Significantly higher than PRE-TRN ($P < 0.05$). †Significantly higher than POST-TRN ($P < 0.05$).

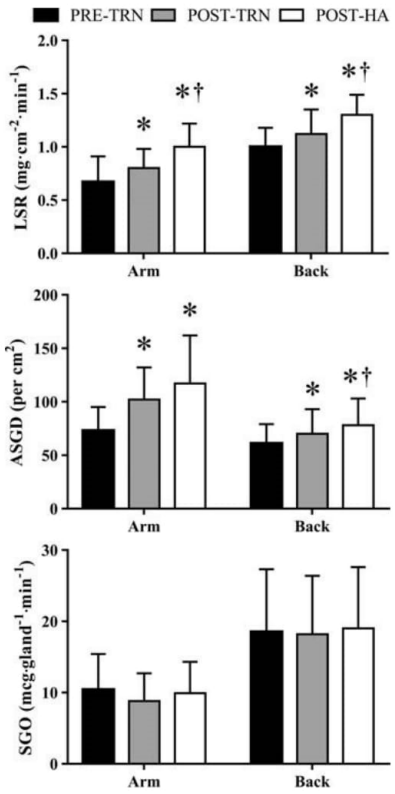

FIGURE 4—Local sweat rate (LSR), ASGD, and SGO of the arm and back at the upper limit of compensability (i.e., ω_{max}) pretraining (PRE-TRN), posttraining (POST-TRN), and after heat acclimation (POST-HA). *Significantly greater than PRE-TRN ($P < 0.05$). †Significantly greater than POST-TRN ($P < 0.05$).

was higher after heat acclimation compared with posttraining ($P = 0.03$). No differences in SGO_{arm} or SGO_{back} were observed at ω_{max} between pretraining (arm: 10.4 ± 5.0 μg per gland per minute, back: 18.5 ± 8.8 μg per gland per minute), posttraining (arm: 8.8 ± 3.9 μg per gland per minute, back: 18.2 ± 8.2 μg per gland per minute), and after heat acclimation (arm: 9.9 ± 4.4 μg per gland per minute, back: 19.0 ± 8.6 μg per gland per minute).

DISCUSSION

The present study is the first, to our knowledge, to quantify the shift in maximum skin wettedness with aerobic training relative to an untrained non–heat acclimated state and a trained fully heat acclimated state. Untrained non–heat acclimated individuals were able to physiologically wet a maximum of approximately 72% of their skin surface, and this was increased to approximately 84% after 8 wk of aerobic training (and a ~14% increase in $\dot{V}O_{2max}$). However, after 8 d of heat acclimation, approximately 95% of the skin surface could be saturated with sweat, indicating only a partial heat acclimation

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response with aerobic training. Physiologically, the ability to achieve a higher ω_{max} with an improved training/acclimation status was facilitated by a higher LSR on both the arm and back mediated by a greater number of simultaneously activated sweat glands, which potentially facilitated an enhanced distribution of sweat on the skin surface and the attainment of greater rates of maximal evaporative heat loss.

Although we have clearly shown in the past that between-group differences in $\dot{V}O_{2max}$ do not independently alter submaximal thermoregulatory responses in a compensable environment (5,6), the different ω_{max} values pretraining, posttraining, and after heat acclimation demonstrates that aerobic training within a given individual can increase the upper biophysical limit for evaporative heat loss and thus the boundary between compensability and uncompensability. The present data indicate that the ω_{max} of an untrained and unacclimated person is approximately 10% lower than currently assumed by ISO standards (e.g., 0.85) (2). This difference may be attributed to earlier studies quantifying ω_{max} of unacclimated individuals while not fully accounting for the training status of their participants and limiting their exposures to passive heat stress in the supine position on a netted bed (1), which may not directly translate to upright exercise. For example, reductions in sweating efficiency during upright exercise have been reported to occur at a lower skin wettedness required for heat balance in comparison to supine rest (34). Whereas sweat may accumulate on the chest or run to the back during supine rest, with upright exercise sweat droplets may drip more readily especially from moving extremities.

Eight days of heat acclimation further increased ω_{max} above posttraining values by an additional 10% to 15%, demonstrating only a partial heat acclimation occurred with 8 wk of aerobic training. The classical adjustments in thermophysiological parameters indicative of a partial acclimation after aerobic training were observed (i.e., lower resting core and skin temperature and higher maximal sweat rates; (22)). However, these parameters were further altered after heat acclimation, thus supporting the partial, and not complete (Table 2, Fig. 3), heat acclimation response associated with aerobic training in the previously untrained cohort.

In comparison to pretraining, the graded increase in LSR on the back and arm after aerobic training and heat acclimation at ω_{max} illustrate a peripheral modification to attain a greater ω_{max} and, by definition, a greater E_{max}. Others have reported greater maximum sweat rates as a function of fitness (8) and after heat acclimation (35) via subcutaneous administration of acetylcholine. However, whether this additional sweating could contribute to a greater evaporative capacity or would simply all drip off the body was unclear. The findings of the present study support the former notion. The greater LSR on the back and arm at ω_{max} was attained via a greater ASGD but not a greater SGO after both training and acclimation (Fig. 4). A higher maximum ASGD has been previously shown with training during pharmacological stimulation (11) or exercise in temperate conditions (10) and after heat acclimation (36). On the other hand, a greater SGO without changes in ASGD with training and/or acclimation have been reported by others with iontophoresis (8). Biophysically, the present findings seem to stand to reason with respect to the attainment of a greater ω_{max} after training and acclimation. Increasing the number of sweat glands activated per surface area would theoretically permit a more complete saturation of the skin surface (and thus a greater ω_{max}), whereas increasing SGO would potentially just yield a lower evaporative efficiency without altering ω_{max}.

Cardiorespiratory fitness has been previously hypothesized to predict the level of heat acclimation (9) and has recently been used to define ω_{max} in trained and untrained male subjects as 1.00 and 0.85, respectively (4). Indeed, the 8-wk aerobic training program in the present study increased $\dot{V}O_{2max}$ of all participants by approximately 15%; however, ω_{max} posttraining was not similar to predicted values for heat acclimated male subjects as previously assumed (1.00). Rather posttraining ω_{max} was comparable to the previously assumed ω_{max} of an unacclimated person, and pretraining ω_{max} values were lower compared with posttraining (0.72 vs 0.84). Although difficult to confirm with the present observations, we propose that a higher ω_{max} was not a result of a higher cardiorespiratory fitness *per se*, rather the frequent and repetitive bouts of aerobic training imposed sufficient heat stress to elicit sudomotor activation more regularly compared with pretraining, albeit almost certainly not a maximal level. The regular exposures to an endogenous thermal impulse (i.e., exercise) permitted the physiological adaptation to achieve a higher ω_{max}, and the combination of both regular exercise and heat stress (i.e., heat acclimation) presented an even greater thermal impulse, thereby resulting in a near maximal physiological augmentation of ω_{max} (~0.95). In further support of the alterations in ω_{max} occurring independently of $\dot{V}O_{2max}$ *per se*, 2 of 8 participants, despite satisfying our "untrained" inclusion criteria, presented at the beginning of the study with relatively high $\dot{V}O_{2peak}$ values (mean, ~4.3 $L \cdot min^{-1}$); however, their mean ω_{max} was 0.76 pretraining and increased to 0.83 posttraining with a mean increase in $\dot{V}O_{2peak}$ of 9.3% (~4.8 $L \cdot min^{-1}$).

Although the present cohort had a similar mass and BSA after training in comparison to pretraining, a reduction in adiposity (<2%) was observed (Table 1). No study to date has assessed the influence of adiposity on ω_{max}; however, mass matched groups with a more than 25% difference in adiposity demonstrated similar whole body and local sweating responses when exercising at similar, albeit physiologically compensable, rates of heat production (37). Thus, the marginal reduction in adiposity in the present study seems unlikely to have independently influenced ω_{max}.

Perspectives

The present findings can potentially contribute to the improvement of existing heat stress management guidelines in occupational and athletic settings. For example, a principal component of the heat exposure duration limits for occupational settings estimated by the ISO 7933:2004 PHS model (2) is the predicted physiological capacity for heat dissipation. Currently, the PHS model accounts for acclimation status of

an individual, using a ω_{max} of 0.85 and 1.00 for non–heat acclimated and heat acclimated, respectively, which are based primarily on data derived from studies of people resting supine (1,2). The present findings demonstrate the necessity to account for training status as the ω_{max} traditionally associated with non–heat acclimated individuals (0.85) is only observed presently posttraining (without heat acclimation; 0.84 ± 0.13), whereas ω_{max} in untrained and non–heat acclimated individuals was approximately 15% lower (0.72 ± 0.06). Thus, the present PHS model may overestimate safe exposure durations for persons who are untrained and non–heat acclimated.

The present findings also have utility for preseason heat acclimatization protocols implemented in some sports (e.g., American football) across all levels of competition, to mitigate the risk of heat-related illness in preseason training camps (9). Briefly, athletes engage in a reduced training volume with recovery bouts and minimal protective equipment (e.g., helmet) for the first 3 to 5 d of the heat acclimatization protocol (38). The present findings demonstrate the clear protective effect, from the perspective of increasing maximum heat loss capacity, of aerobic training even without heat acclimation before the start of training camp.

Considerations

Our estimations of ω_{max} are reliant on the assumptions of $R_{e,cl}$ and h_e. To mitigate any independent influence on ω_{max}, $R_{e,cl}$ was assumed similar for all participants as identical clothing was worn pretraining, posttraining, and after heat acclimation, and walking speed was similar (1.34 ± 0.11 $m \cdot s^{-1}$) between and within participants to minimize its effect on h_e (31). Moreover, our observed P_{crit} and the partial pressure gradient between the skin and air at ω_{max} (i.e., $P_{sk,s} - P_{crit}$) after training and heat acclimation were similar to those previously reported (12), thus affirming our estimated ω_{max} values. $\dot{V}O_{2max}$ was not reassessed after heat acclimation because the primary aim of the study was to determine the independent effect of training, and subsequent heat acclimation, on ω_{max}. Therefore, it remains unknown whether the present heat acclimation protocol further increased aerobic capacity, although previous evidence suggests $\dot{V}O_{2max}$ remains unchanged after a heat acclimation protocol if it is preceded by an endurance training program (39). The present study did not include a nontrained but heat acclimated group because the primary aim was to determine the relative effect of training with and without heat acclimation. From a practical perspective, within a sporting context, it seems unlikely that untrained yet heat acclimated athletes would conduct vigorous exercise in uncompensable heat stress conditions. However, such scenarios may be encountered in occupational settings where untrained personnel are required to perform physical tasks in uncompensable environments (e.g., miners, power line technicians, construction workers). Thus, it remains unknown whether the observed increase in ω_{max} after heat acclimation would be equivocal in an untrained cohort. Nevertheless, it has been traditionally accepted that a complete augmentation of ω_{max} does occur with full heat acclimation independent of training status (22,28). In support, Shvartz et al. (40) observed similar adaptations in thermoregulatory responses to heat stress after an 8-d heat acclimation protocol between unfit, untrained, and trained participants. Lastly, all participants conducted the training intervention in a moderate environment (~22°C, 30%RH) in an attempt to observe the influence of endogenous heat stress on physiological adaptations to the heat. This environment provided ecological validity in an athletic context because it represented conditions typically observed in commercial training facilities. Nevertheless, although it is likely that alterations in ω_{max} will be greater if training occurred in warmer environments, these values need to be quantified in future studies.

CONCLUSIONS

Eight weeks of aerobic training independently increased ω_{max}; however, this increase was further augmented (approximately doubled) by 8 d of heat acclimation. The greater ω_{max} after both training and acclimation was facilitated by a greater LSR secondary to a greater ASGD and without any changes in SGO. This is the first study, to our knowledge, to directly determine how ω_{max}, which defines the boundary between physiologically compensable and uncompensable heat stress, is altered by aerobic training status with and without heat acclimation.

The authors thank the participants for their efforts and unpaid commitment to the 3-month study and wish them the best in their future physical activity endeavors, and Samuel Duchesne-Belanger for the assistance with implementation and supervision of the training intervention.

The authors have no competing interests. The results were not endorsed by American College of Sports Medicine. The results of the study are presented clearly and honestly and without fabrication, falsification, or inappropriate data manipulation.

N. R., P. I., and O. J. were involved in conception and design of the experimental protocol. N. R. and G. C. were responsible for data collection. Data analysis and interpretation was performed by N. R., and O. J. and N. R. drafted the manuscript. O. J. critically revised the manuscript. All authors have approved the final version of the manuscript.

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APPENDIX C: Empirical evidence to support fan use during heat waves

Letters

RESEARCH LETTER

Heart Rate and Body Temperature Responses to Extreme Heat and Humidity With and Without Electric Fans

Patz et al[1] described the projected effects of more prolonged and severe heat waves on human health. A simple, low-cost cooling device is an electric fan. A Cochrane review[2] concluded "no evidence currently exists supporting or refuting the use of electric fans during heat waves" for mortality and morbidity. However, public health guidance typically warns against fan use in hot weather. Recommended upper limits range from 32.3°C (90°F) at 35% relative humidity (RH) to the high 90s (96-99°F; 35.6-37.2°C, no RH stated[2]).

The skin-to-air temperature gradient reverses with rising environmental temperature, causing dry heat transfer toward the body via convection rather than away from it. Fan use would increase this dry heat transfer, potentially accelerating body heating[3,4]; however, the efficiency of sweat evaporation from the skin would be simultaneously increased. Thus, fans could still improve net heat loss.

Sweat evaporation declines with increasing humidity, so in more humid environments fans may not prevent heat-induced elevations in cardiovascular (heart rate, HR) and thermal (core temperature) strain. This study examined the influence of fan use on the critical humidities at which hot environments can no longer be physiologically tolerated without rapid increases in HR and core temperature.

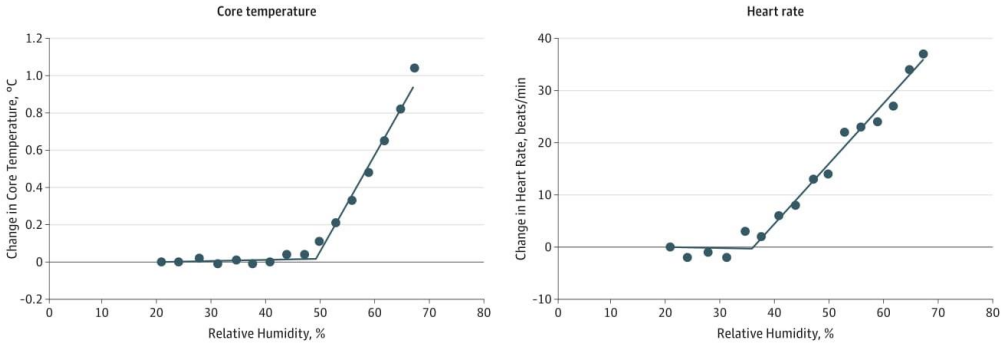
Methods | After University of Ottawa ethics approval, written informed consent was obtained from student volunteers. Each participant completed four 135-minute trials presented in randomized order and separated by more than 48 hours. Euhydration was confirmed prior to each trial (urine-specific gravity <1.025). Wearing shorts and t-shirts, participants sat in a chamber maintained at temperatures equal to (36°C; 97°F) or exceeding (42°C; 108°F) the limits currently recommended for fan use.

Each temperature was tested with and without an 18-in fan (Whirlpool) facing the participant from 1 m (air speed: 4.0 m/s). After a 20-minute baseline period, RH was increased in 15 equal steps (7.5 minutes each) from 25% to 95% at 36°C and from 20% to 70% at 42°C.[5] Heart rate (Polar) and core (esophageal) temperature (Covidien) were measured throughout. Whole-body sweat rate was determined using the 135-minute pre-to-post trial change in body mass (Sartorious).

The RH values at which an upward inflection in first HR and then core temperature occurred were determined (**Figure 1**) separately for each individual trial using segmented linear regression (GraphPad). These critical RH values and whole-body sweat rates were compared between fan and no fan trials at each temperature using paired-sample *t* tests ($P < .05$, 2-sided).

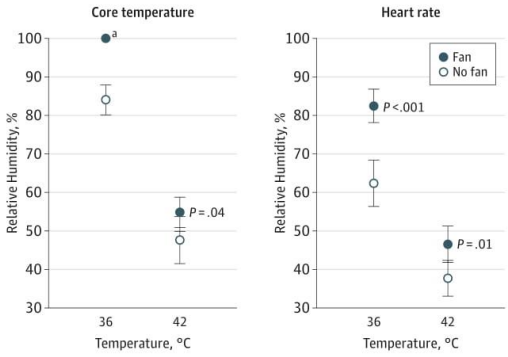
Results | Eight healthy males (mean [SD] age of 23 [3] years and weight of 80.7 [11.7] kg) participated between June 5 and November 6, 2013. The critical RH for an upward inflection in HR at 36°C was higher with fans (83%; 95% CI, 78%-87%) than without fans (62%; 95% CI, 56%-68%) ($P < .001$) and at 42°C (47% [95% CI, 42%-51%] vs 38% [95% CI, 33%-42%], respectively) ($P = .01$; **Figure 2**).

Figure 1. Changes in Core Temperature and Heart Rate With Stepwise Increases in Relative Humidity for 1 Participant at 42°C Without a Fan



Each trial consisted of 15 stepwise increases in absolute humidity of 2 mm Hg (3.33% relative humidity at 42°C) after an initial baseline period at 20% relative humidity. Each data point represents the average value during the last minute of each stage. The relative humidity values at which inflection points occurred for heart rate and core temperature were determined separately for each participant in each of his 4 trials using segmented linear regression.

Figure 2. Influence of Fans on Critical Humidity for Elevations in Core Temperature and Heart Rate



Error bars indicate 95% confidence intervals.

[a] No statistical comparison could be performed because an inflection in core temperature was observed in only 2 of 8 participants with fan use at 36°C.

An upward inflection in core temperature at 36°C only occurred in 2 participants with fans but in 7 participants without fans (RH, 84%; 95% CI, 80%-88%). At 42°C, the core temperature inflection occurred at a higher RH with fans (55%; 95% CI, 51%-59%) than without fans (48%; 95% CI, 42%-54%) (P = .04; Figure 2). Whole-body sweat rate was greater at 36°C with fans (180 g/h; 95% CI, 173-187 g/h) than without fans (153 g/h; 95% CI, 140-165 g/h) (P = .01) and at 42°C (399 g/h [95% CI, 381-417 g/h] vs 241 g/h [95% CI, 209-273 g/h], respectively) (P < .001).

Discussion | Our preliminary study is the first, to our knowledge, to demonstrate that electric fans prevent heat-related elevations in HR and core temperature in healthy young men up to approximately 80% RH at 36°C and 50% RH at 42°C. Thus, contrary to existing guidance,[3,4] fans may be effective cooling devices for those without air conditioning during hot and humid periods.

Only young participants were assessed, so critical RH values must be derived for other populations (eg, elderly with comorbidities) and those with diminished sweat production. However, sweat rates measured with fans were lower than values previously reported to be achievable in healthy 70-year-old adults (440 g/h).[6] Advice to the public to stop using fans during heat waves may need to be reevaluated.

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Author Contributions: Dr Jay had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Ravanelli, Hodder, Jay.
Acquisition, analysis, or interpretation of data: Ravanelli, Havenith, Jay.
Drafting of the manuscript: Ravanelli, Hodder, Jay.
Critical revision of the manuscript for important intellectual content: Ravanelli, Havenith, Jay.
Statistical analysis: Ravanelli, Hodder, Jay.
Obtained funding: Jay.
Administrative, technical, or material support: Ravanelli, Jay.
Study supervision: Ravanelli, Jay.

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COMMENT & RESPONSE

Fecal Microbiota Transplantation for *Clostridium difficile* Infection

To the Editor: Since the first description of successful fecal microbiota transplantation (FMT) via stool enemas for severe *Clostridium difficile* infection (CDI) in 1958,[1] FMT has consistently achieved treatment success rates of approximately 90%.[2] In previous work, Youngster et al[3] demonstrated that it is possible to freeze stool prior to FMT, thus greatly facilitating the process. In the most recent study, Dr Youngster and colleagues[4] have taken steps to transform FMT from an invasive, nonacute procedure to a potentially safe, instantly available bedside therapy for life-threatening CDI.

Even though the authors acknowledged that their small, preliminary study was primarily focused on feasibility and safety, we think they have compromised the phase 1 study design by emphasizing the efficacy of frozen FMT capsules. For example, the use of a sample size calculation in a proof-of-concept study is not appropriate in the absence of a recognized comparator. Data from a similar in-house study of frozen FMT administered via colonoscopy (n = 10; average age, 50.4 years)[3] cannot be compared statistically with oral

APPENDIX D: Acetaminophen ingestion and heat stress

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Acute acetaminophen ingestion does not alter core temperature or sweating during exercise in hot–humid conditions

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Acute acetaminophen (ACT) ingestion has been reported to reduce thermal strain during cycling in the heat. In this study, nine active participants ingested 20 mg of ACT per kg of total body mass (ACT) or a placebo (PLA), 60 min prior to cycling at a fixed rate of metabolic heat production (ACT: 8.3 ± 0.3 W/kg; PLA: 8.5 ± 0.5 W/kg), which was equivalent to 55 ± 6% VO_{2max}, for 60 min at 34.5 ± 0.1 °C, 52 ± 1% relative humidity. Resting rectal temperature (T_{re}; ACT: 36.70 ± 0.17 °C; PLA: 36.80 ± 0.16 °C, $P = 0.24$), esophageal temperature (T_{es}; ACT: 36.54 ± 0.22 °C; PLA: 36.61 ± 0.17 °C, $P = 0.50$) and mean skin temperature (T_{sk}; ACT: 34.00 ± 0.14 °C; PLA: 33.96 ± 0.20 °C, $P = 0.70$) were all similar among conditions. At end-exercise, no differences in ΔT_{re} (ACT: 1.12 ± 0.15 °C; PLA: 1.11 ± 0.21 °C, $P = 0.92$), ΔT_{es} (ACT: 0.90 ± 0.28 °C; PLA: 0.88 ± 0.23 °C, $P = 0.84$), ΔT_{sk} (ACT: 0.80 ± 0.39 °C; PLA: 0.70 ± 0.46 °C, $P = 0.63$), mean local sweat rate (ACT: 1.02 ± 0.15 mg/cm²/min; PLA: 1.02 ± 0.13 mg/cm²/min, $P = 0.98$) and whole-body sweat loss (ACT: 663 ± 83 g; PLA: 663 ± 77 g, $P = 0.995$) were evident. Furthermore, ratings of perceived exertion and thermal sensation and thermal comfort were not different between ACT and PLA conditions. In conclusion, ACT ingested 60 min prior to moderate intensity exercise in hot–humid conditions does not alter physiologic thermoregulatory control nor perceived strain.

Acetaminophen (ACT), also known as paracetamol, is a popular over-the-counter drug commonly used for pain relief and for reducing body temperature in febrile patients. Recently, the antipyretic properties of ACT have also been suggested to effectively reduce the thermal strain experienced during exercise (Burtscher et al., 2013; Mauger et al., 2014). Moreover, it has been demonstrated that ACT can be an ergogenic aid, because of an improved cycling performance in thermoneutral and hot conditions alike (Foster et al., 2014; Mauger et al., 2014). However, whether ACT truly reduces heat strain during cycling in hot conditions is not yet clear. All previous studies examining the use of ACT during exercise have employed performance-based experimental designs and any differences in exercise duration and/or metabolic heat production between conditions has not permitted the isolation of the independent effect of ACT on thermoregulatory responses. Most recently, Mauger et al. (2014) reported a slightly lower core temperature (–0.15 °C) during exercise following ACT ingestion despite a longer exercise duration. This observation could be attributed to an alteration of physiologic heat loss responses with ACT ingestion; however, thermoeffector responses such as local sweat rate were not measured. Furthermore, the lower skin temperature that was also reported in the same study with ACT would actually be detrimental to skin surface heat dissipation because of a reduction in the skin-to-air temperature gradient that governs dry heat loss and evaporative potential.

Like exercise, fever has the potential to produce dangerously high core temperatures. The fever response is triggered by mediators such as prostaglandin E_2 (PGE_2) (Ivanov, 2004) in the pre-optic area of the hypothalamus. These signals alter the firing rate of the pre-optic neurons and cause an elevation of the thermoregulatory set point (Boulant, 2000). ACT acts by inhibiting cyclooxygenase (COX) (Ayoub et al., 2004; Botting & Ayoub, 2005), which metabolizes arachidonic acid: the precursor to PGE_2 (Aronoff & Neilson, 2001). COX inhibition during a fever event should remove the stimulus to raise the thermoregulatory set point and the physiologic and behavioral responses that normally occur as a result will cease, consequently lowering the core temperature. During exercise, however, heat stored within the body results from heat produced by the aerobic and anaerobic metabolic processes that provide adenosine triphosphate to working muscles. It follows that as long as exercise continues, COX inhibition should not be able to reduce heat storage within the body in the same way that it can during a fever.

Given recent reports (Mauger et al., 2014), athletes may consider advocating the use of ACT to reduce the

risk of heat-related illnesses during competition in the heat. Indeed, some individuals may actually place themselves at a greater risk of heat-related illness while training or performing in the heat if they assume that ACT provides additional protection, when in fact, it may not. As such, there is a clear need for a comprehensive evaluation of the independent influences of ACT on human thermoregulatory responses during exercise in the heat.

The aim of present study was to determine whether acute ingestion of ACT prior to exercise alters thermoregulatory control in hot–humid conditions compared with a placebo (PLA) condition during exercise of a fixed duration (60 min) at a fixed metabolic heat production. Given that the mechanism of ACT is to inhibit the febrile response, it was hypothesized that thermoeffector responses would not be independently affected by ACT ingestion, resulting in similar changes in core temperature compared with a PLA condition.

Materials and methods

Participants

A power calculation using G*Power 3 software (Department of Psychology, University of Bonn, Bonn, Germany; Faul et al., 2007) was performed in order to determine the required sample size for the experiment. The effect size used was 1.42, as in a previous study (Patterson et al., 2004) using a similar design and primary outcome variables (i.e., esophageal temperature, whole-body sweat loss and local sweat rate), this was the smallest effect size of the three variables which resulted in a significant difference (local sweat rate on the arm after 9 days of heat acclimation), thereby assuring sufficient power for all primary outcome variables. Both the α and β were set at 0.05, as they respectively represent the probability of reporting a false positive or negative. Using these variables, the required sample size was nine participants.

Nine volunteers (eight men, one woman) participated in this study (VO_{2peak}: 3.87 ± 0.60 L/min; W_{peak}: 320 ± 51 W, age: 25 ± 4 years; mass: 70.1 ± 8.6 kg; height: 1.74 ± 0.05 m). Prior to experimentation, all participants provided written informed consent, and completed a Physical Activity Readiness Questionnaire as well as an American Heart Association/American College of Sports Medicine Health/Fitness Facility Pre-participation Screening Questionnaire. The experimental protocol was approved by the University of Ottawa Research Ethics Committee, and conformed with the guidelines set forth in the Declaration of Helsinki. Participants were instructed to avoid alcohol and strenuous exercise at least 24 h prior, to avoid caffeine at least 6 h prior, and to consume a light meal and ~ 500 mL of water (standardized for both experimental trials) at least 2 h prior to arrival to the laboratory for the preliminary and two experimental trials. All trials were separated by at least 48 h and no participants had taken part in heat stress exercise trials at least 30 days prior to their participation to minimize the potential for heat acclimation.

Preliminary trials

During a preliminary visit, each participant performed an incremental test to exhaustion on an upright cycle ergometer (Ergo Race, Kettler, Ense-Parsit, Germany) to determine their peak rate of oxygen consumption (VO_{2peak}) and peak external workload (W_{peak}). A standardized warm up involving four 4-min steps of increasing external workload beginning at 80 W and increasing by 20 W every step. The test required the participants to cycle at an initial external workload of 80 W with an increase of 20 W every minute thereafter until volitional exhaustion in accordance with guidelines from the Canadian Society for Exercise Physiology (CSEP, 1986). In both phases of the preliminary test (as well as the experimental trials, see later), expired gases were analyzed breath-by-breath using a metabolic cart (Vmax Encore, Carefusion, Yorba Linda, California, USA). Values of VO_{2peak} and W_{peak} were taken as the highest 1-min averages.

Experimental design

Participants performed two experimental trials, conducted at the same time of day to negate any influence of circadian rhythm. Upon arrival to the laboratory, participants voided their bladder and changed into standardized shorts and sandals. Participants were given 20 mg/kg of their total body weight of either ACT or a color- and taste-matched glucose PLA contained in identical pharmaceutical gelatin capsules (No. 000, Capella Enterprises, Carleton Place, Ontario, Canada). The dosage of 20 mg/kg of total body mass was chosen in order to standardize the dosage for all participants and to ensure that the concentration of ACT used in the current study was at least as strong as the 20 mg/kg of lean body mass dosage used by Mauger et al. (2014). Treatments were administered double-blinded in a random (coin toss) counterbalanced order. Capsules were ingested with ~ 175 mL of water 60 min prior to the onset of exercise to allow sufficient time for peak plasma concentrations to be reached (Singla et al., 2012). Immediately following ingestion, participants entered the climatic chamber (34.5 ± 0.1 °C, 52 ± 1% relative humidity) and were seated quietly for the remainder of instrumentation. These ambient conditions were chosen to elicit sufficiently large thermoeffector responses to detect an independent effect of ACT. Thirty minutes of baseline data were collected prior to the start of exercise, including a fully instrumented body mass measurement that was taken 5 min before exercise with a platform scale (Combics 2; Sartorius, Mississauga, Ontario, Canada). For each body mass measurement, sensor cables were secured to a nearby equipment cart in an identical spot. Participants then began the 60-min exercise bout on an upright cycle ergometer at an intensity that would elicit 8 W/kg of heat production (Cramer & Jay, 2014), thereby ensuring a consistent heat load was experienced by all participants despite morphologic differences. Three 46-cm mechanical fans stacked vertically and 1.25 m facing the participant elicited a mean air velocity of ~ 1.0 m/s, measured with a hot wire anemometer (HHF42, Omega Engineering, Stamford, Connecticut, USA). The absolute external workload was recorded at 1-min intervals so that an identical power profile could be replicated during the second experimental trial, and the same rate of heat production would be obtained. A final body mass measurement was taken immediately at the end of exercise.

Indirect calorimetry

Metabolic rate (M) was calculated every minute using the following equation:

$$M = VO_2 \cdot \frac{\left[\left(\frac{RER - 0.7}{0.3}\right)e_c\right] + \left[\left(\frac{1.0 - RER}{0.3}\right)e_f\right]}{(60)} \cdot 1000(W)$$

Where: VO_2 is the rate of oxygen consumption (L/min); RER is the non-dimensional respiratory exchange ratio; e_c and e_f are the energetic equivalents of carbohydrate (21.13 kJ/L of O_2) and fat (19.62 kJ/L of O_2), respectively. The rate of metabolic heat

production (H_{prod}) was calculated as the difference between M and external workload (W) and then converted into W/kg by dividing by total body mass.

Sweating

Whole-body sweat losses (WBSL) were estimated as the difference between pre- and post-exercise body mass measurements, corrected for metabolic and water vapor mass losses via respiration (Mitchell et al., 1972). Local sweat rates of the upper back (LSR_{back}) and forearm (LSR_{arm}) were measured using 4.1-cm^2 ventilated sweat capsules, which were secured to the skin using surgical tape (Transpore®, 3M, London, Ontario, Canada). Anhydrous air was supplied to each capsule at a constant flow rate of 1.00 L/min (Omega FMA-A2307, Omega Engineering, Stamford, Connecticut, USA) and the temperature and humidity of outflowing air were measured every 5 s using factory-calibrated capacitance hygrometers (HMT333, Vaisala, Vantaa, Finland). LSR_{back} and LSR_{arm} were calculated as the product of absolute humidity and flow rate, and expressed relative to the area under the capsule in $mg/cm^2/min$. Mean local sweat rate (LSR_{mean}) was calculated as an un-weighted average of LSR_{back} and LSR_{arm}.

Thermometry

Core temperature was measured in the esophagus (T_{es}) and rectum (T_{re}) using general-purpose pediatric thermistor probes (TM400, Covidien, Mansfield, Massachusettes, USA). T_{re} was measured at a depth of 12 cm past the anal sphincter and T_{es} was measured to a maximum depth of 40 cm, estimated to be at the level of the left ventricle (Mekjavic & Rempel, 1990). Skin temperature (T_{sk}) was measured at four sites on the left side of the body using T-type thermocouples (Concept Engineering, Old Saybrook, Connecticut, USA), secured to the skin using surgical tape, and expressed as a weighted average in accordance with Ramanathan (1964): chest 30%, triceps 30%, thigh 20%, and calf 20%. All thermometric measurements were sampled at a rate of 5 s (NI cDAQ-91722 module, National Instruments, Austin, Texas, USA) and displayed in real-time using LabView (v7.0, National Instruments).

Heart rate (HR)

HR was sampled every 5 s using a cardio-recorder (Polar RS 800, Polar electro Oy, Kempele, Finland) and coded transmitter (Polar Wearlink T31 coded, Polar electro Oy, Kempele, Finland). The data were downloaded with the manufacturer's software (Polar ProTrainer Versions 5.40.172, Kempele, Finland) and were expressed as 1-min averages.

Perceptual responses

Ratings of perceived exertion (RPE) (Borg, 1998), thermal sensation (TS; "slightly cool to "extremely hot"), and thermal comfort (TC; "not uncomfortable" to "very uncomfortable") (ASHRAE, 2009) were measured at baseline and every 15 min during exercise.

Statistic analysis

All data are reported as the mean ± standard deviation (SD). A two-way repeated measures analysis of variance (ANOVA), with the independent factors of treatment (ACT or PLA) and time (five levels: baseline, 15, 30, 45, 60 min) were used to analyze the independent variables of H_{prod}, T_{es}, T_{re}, T_{sk}, ΔT_{es}, ΔT_{re}, ΔT_{sk}, LSR_{back}, and $LSR_{forearm}$. A Greenhouse–Geisser correction was applied if assumptions of sphericity were not met. Additionally, the effect size of each ANOVA was calculated and reported as partial eta squared values (η^2). As defined by Cohen (1992), η^2 values of 0.01, 0.09, and 0.25 are indicative of small, medium, or large effect sizes, respectfully. When a significant main effect was detected, individual differences were compared using a t-test with a Bonferonni correction. Whole-body sweat loss, the ΔT_{es} onset sweating threshold and the thermosensitivity of sweating with further changes in T_{es} following onset were compared using a paired-sample Student's t-test. The effect sizes of these measures were determined using Cohen's d (d). As defined by Cohen (1992), d values of 0.2, 0.5, or 0.8 are indicative of small, medium, or large effect sizes, respectfully. The within-subject variation for these variables was determined using the coefficient of variation (CV) method (CV = SD/mean × 100). All statistic analyses were performed with Graphpad Prism 6 for Windows statistic software (version 6.01, La Jolla, California, USA).

Results

Partitional calorimetry

Power output on the cycle ergometer was maintained similarly between trials (ACT: 125 ± 18 W, PLA: 124 ± 18 W; $P = 0.98$, $d = 0.01$, CV = 0.65%). Consequently, metabolic heat production was similar between trials (ACT: 8.3 ± 0.3 W/kg, PLA: 8.5 ± 0.5 W/kg; $P = 0.46$, $d = 0.28$, CV = 4.0%).

Thermometry

Core temperature data are presented in Fig. 1. Resting T_{re} was not different between trials prior to the start of exercise (ACT: 36.70 ± 0.17 °C; PLA: 36.80 ± 0.16 °C, $P = 0.24$, $d = 0.40$). During exercise, there was no main effect of ACT on T_{re} ($P = 0.20$, $\eta^2 = 0.011$) nor was there an interaction between ACT ingestion and time on T_{re} ($P = 0.91$, $\eta^2 < 0.001$). The change in T_{re} after the 60-min exercise period was not different between trials (ACT: 1.12 ± 0.15 °C; PLA: 1.11 ± 0.21 °C, $P = 0.92$, $d = 0.03$) and the mean CV between ACT and PLA trials for ΔT_{re} was 12.1%. There was no difference between trials in resting T_{es} (ACT: 36.54 ± 0.22 °C; PLA: 36.61 ± 0.17 °C, $P = 0.50$, $d = 0.22$). During exercise, there was no main effect of ACT on T_{es} ($P = 0.38$, $\eta^2 = 0.011$) nor was there an interaction between ACT and time on T_{es} ($P = 0.82$, $\eta^2 = 0.002$). The 60-min ΔT_{es} was not different between trials (ACT: 0.90 ± 0.28 °C; PLA: 0.88 ± 0.23 °C, $P = 0.84$, $d = 0.07$) and the mean CV between ACT and PLA trials for ΔT_{es} was 8.1%. Skin temperature data are also displayed in Fig. 1. No difference in resting T_{sk} was found between trials (ACT: 34.00 ± 0.14 °C; PLA: 33.96 ± 0.20 °C, $P = 0.70$, $d = 0.14$). During exercise, there was no main effect of ACT on T_{sk} ($P = 0.49$, $\eta^2 = 0.009$) nor was there an interaction between ACT and time on T_{sk} ($P = 0.86$, $\eta^2 = 0.003$). The 60-min ΔT_{sk} was similar among trials (ACT: 0.80 ± 0.39 °C; PLA: 0.70 ± 0.46 °C, $P = 0.63$, $d = 0.16$) and the mean CV between ACT and PLA trials for ΔT_{sk} was 22.7%.

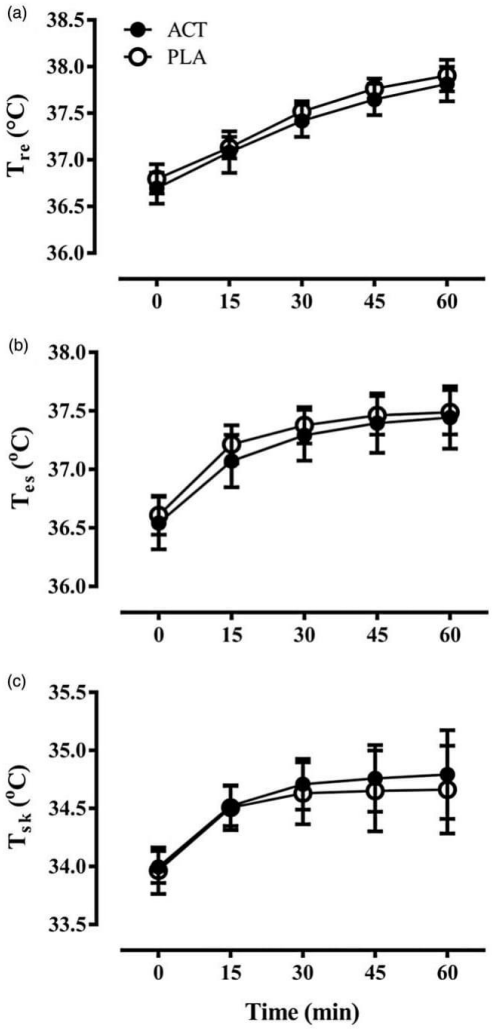

Fig. 1. Rectal temperature (T_{re} – panel a), esophageal temperature (T_{es} – panel b), and skin temperature (T_{sk} – panel c) during exercise in acetaminophen (ACT) and placebo (PLA) trials. All data are presented as mean ± standard deviation (SD).

Sweating

All sweating data are presented in Fig. 2. At end-exercise LSR_{back} (ACT: 1.09 ± 0.24 mg/cm^2/min; PLA: 1.05 ± 0.15 mg/cm^2/min, $P = 0.69$, $d = 0.12$) and LSR_{arm} (ACT: 0.95 ± 0.12 mg/cm^2/min; PLA: 0.99 ± 0.22 mg/cm^2/min, $P = 0.62$, $d = 0.18$) were similar between trials (Fig. 2(a, b)), resulting in no difference in end-exercise LSR_{mean} between trials (ACT: 1.02 ± 0.15 mg·cm^{-2}·min^{-1}; PLA: 1.02 ± 0.13 mg/cm^2/min, $P = 0.98$, $d = 0.01$). During exercise, there was no main effect of ACT on LSR_{mean} ($P = 0.85$, $\eta^2 < 0.001$) nor was there an interaction between ACT ingestion and time on LSR_{mean} ($P = 0.77$, $\eta^2 < 0.001$) and the mean CV between ACT and PLA trials for LSR_{mean} was 10.6%. Additionally, the onset threshold ΔT_{es} ($P = 0.58$, $d = 0.19$) and the thermosensitivity of sweating on the back (Fig. 2(c); $P = 0.56$, $d = 0.19$) and the onset threshold ΔT_{es} ($P = 0.64$, $d = 0.23$) and the thermosensitivity of sweating on the arm (Fig. 2(d); $P = 0.82$, $d = 0.10$) were not different between trials. Whole-body sweat losses were almost identical between trials (ACT: 663 ± 83 g; PLA: 663 ± 77 g, $P = 0.995$, $d < 0.01$, CV = 2.2%).

Perceptual responses

There was no main effect of ACT on RPE ($P = 0.97$, $\eta^2 < 0.001$) nor was there an interaction between ACT ingestion and time on RPE ($P = 0.76$, $\eta^2 = 0.003$) (Fig. 3(a)). The mean CV between ACT and PLA trials for RPE was 4%. There was no main effect of ACT on TS ($P = 0.99$, $\eta^2 < 0.001$) nor was there an interaction between ACT ingestion and time on TS ($P = 0.53$, $\eta^2 = 0.013$) (Fig. 3(b)). The mean CV between ACT and PLA trials for TS was 18%. Lastly, there was no main effect of ACT on TC ($P = 0.63$, $\eta^2 < 0.003$) nor was there an interaction between ACT ingestion and time on TC ($P = 0.54$, $\eta^2 = 0.009$) (Fig. 3(c)). The mean CV between ACT and PLA trials for TC was 13%.

HR

There was no main effect of ACT on HR ($P = 0.72$, $\eta^2 = 0.002$) nor was there an interaction between ACT ingestion and time on HR ($P = 0.78$, $\eta^2 = 0.001$) (Fig. 3(d)). The mean CV between ACT and PLA trials for HR was 4.0%.

Discussion

The main finding of this study was that ACT ingestion (20 mg/kg of total body mass) 60 min prior to exercising at a fixed rate of metabolic heat production in hot–humid conditions for 60 min does not alter thermoregulatory responses compared with a PLA condition. Compared with previous studies (Mauger et al., 2010, 2014), the present investigation used similar doses of ACT, a longer exercise duration and hotter ambient conditions, and therefore should have been sufficient to detect an effect of ACT on thermoregulatory control should one have existed. The lack of any independent effect of ACT on changes in core temperature or sweating responses suggests that another mechanism must have been responsible for the performance benefits following ACT ingestion previously reported in the literature.

The primary hypothesis of this study was that ACT would provide no thermoregulatory benefit, and as such, we took additional measures to ensure a type II error

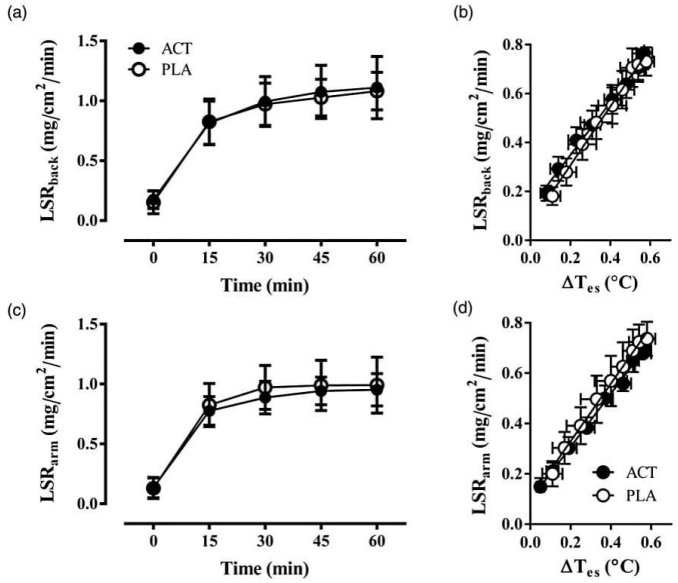

Fig. 2. Local sweat rate response of the upper back (LSR_{back} – panel a), and forearm (LSR_{arm} – panel c), and the ΔT_{es} onset threshold for LSR_{back} – (panel b) and LSR_{arm} (panel d) during exercise in acetaminophen (ACT) and placebo (PLA) trials. All data are presented as mean ± standard deviation (SD).

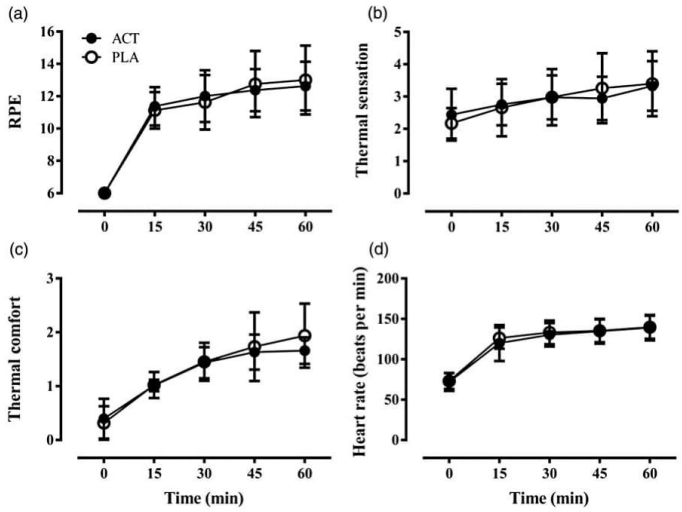

Fig. 3. Ratings of perceived exertion (RPE – panel a), thermal sensation (TS – panel b), thermal comfort (TC – panel c), and heart rate (panel d) during exercise in acetaminophen (ACT) and placebo (PLA) trials. All data are presented as mean ± standard deviation (SD).

(false negative) was not committed. First, when determining the required sample size for this investigation, both the α (chance of reporting a false positive) and β (chance of reporting a false negative) of our *a priori* effect size calculation were set at 0.05. Additionally, we used the smallest statistically significant effect size from a previous study using a similar design and outcome variables to power our study. Indeed, had we used the esophageal temperature ($d = 2.0$) or whole-body sweat loss ($d = 3.1$) data to power our study, only six or four

participants would have been required, respectfully. Thus, we simultaneously ensured that we did indeed have sufficient statistic power to detect a difference between groups had one occurred, while remaining 95% confident that had a false negative occurred, it would be rejected. Second, effect sizes were derived for all statistic analyses performed in order to provide statistics that were less sample size-dependent. With the exception of resting rectal ($d = 0.40$) and esophageal ($d = 0.22$) temperatures, all reported Cohen's d values fell below the definition of small effect size ($d = 0.2$) (Cohen, 1992) and the total variance described by ACT administration was less than 5% ($\eta^2 < 0.05$) for each ANOVA. Moreover, the Cohen's d statistic was lower than 0.1 for the primary outcome variables of ΔT_{es}, ΔT_{re}, and whole-body sweat losses following 60 min of exercise. These low values contrast strikingly with the effect sizes of other drugs known to affect changes in core temperature [cocaine: $d = 1.71$ (Crandall et al., 2002), melatonin: $d = 1.67$ (Atkinson et al., 2005)], as well as the effect sizes for non-pharmaceutical interventions that exert a significant [4% body weight dehydration: $d = 3.08$ (Montain & Coyle, 1992)] and non-significant [carbohydrate ingestion: $d = 0.30$ (Below et al., 1995)] influence on core temperature during exercise. Additionally, although the effect size was slightly larger for resting core temperatures, the 0.1 °C difference in rectal temperature between ACT and PLA conditions is considerably smaller than the reduction that is generally considered to be required for performance enhancement (Wegmann et al., 2012). Furthermore, the mean CV between ACT and PLA trials for each individual for nearly all physiologic variables was below 10%. Local sweat rate of the forearm has been previously demonstrated to have a day-to-day CV of 23% with no intervention (Kenefick et al., 2012). In light of these findings, we feel we can confidently state that there were no differences in thermoregulatory responses resulting from ACT ingestion beyond those that would be reasonably expected from normal day-to-day variation.

Compared with previous studies (Burtscher et al., 2013; Mauger et al., 2014), the present experimental design permitted an unbiased comparison of core temperature responses between conditions by fixing the rate of heat production over a standard exercise duration. As such, if any differences in thermoeffector responses (i.e., WBSL, LSR, skin blood flow (SkBF)) and changes in core temperature were observed, they could have been confidently attributed to the ACT treatment alone. Cycling power output was also maintained between conditions for each participant in order to determine if there was an effect of ACT on the mechanical efficiency of cycling, which would have altered the rate of metabolic heat production. Another potential reason for the disparity between the present findings and those of previous authors is that we analyzed our data using absolute time courses. The amount of heat stored in the body and the subsequent change in T_{re} and T_{es} depends on the duration and magnitude of imbalance between total heat production and heat loss. Comparing thermoregulatory responses over the same percentage of time to exhaustion leads to different absolute time intervals. In contrast, comparing these responses over fixed absolute time intervals permits a fair comparison from a heat balance perspective.

Mauger et al. (2014) suggested the analgesic properties of ACT were likely a contributing factor to the improved time to exhaustion in their study considering the concurrent reductions in core and skin temperature as well as TS reported in their study were small, but significant. The authors further speculated that another possible mechanism of ACT to reduce core body temperature could be through the moderation of inflammatory responses. Although exercise has been shown to increase the circulation of cytokines such as interleukin (IL)-1, tumor necrosis factor-α, and IL-6 (Bradford et al., 2007), it has also been demonstrated that the cytokine response to exercise contrasts that of a fever response as it is largely anti-inflammatory (Petersen & Pedersen, 2005). Therefore, the lack of differences between conditions in thermoregulatory responses in our study suggests that performance benefits following ACT administration may not be a result of altered thermoregulatory control, but rather a result of the increased pain threshold because of the analgesic properties of ACT.

In addition to the lack of influence of ACT on thermometric (Fig. 1) and sweating (Fig. 2) responses in the current study, there were also no differences between ACT and PLA conditions for the perceptual responses of RPE, TS, and TC (Fig. 3) assessed. It is clear, however, from previous performance-related work that elevations in the pain threshold likely allow athletes to up-regulate their power output to maintain a given RPE during self-paced exercise (Mauger et al., 2010) or to maintain a given RPE for longer, ultimately leading to faster time trials or longer times to exhaustion. While similar perceptual responses between ACT and PLA conditions were observed in the present study, a lower RPE value with ACT ingestion may only occur when exercising at or above the lactate threshold (Garcin et al., 2005) or possibly only when higher levels of core temperature and TS are reached. Future research should consider the exercise intensity level at which ACT can modulate perceptual responses in hot conditions, as this is a potential limitation of the current study given the moderate exercise intensity ($55 \pm 6\%$ VO_{2max}). Nonetheless, this intensity is comparable with other studies examining ACT and performance in the heat (Mauger et al., 2014).

In conclusion, the current study presents clear evidence that the ingestion of ACT (20 mg/kg of total body mass) 60 min prior to cycling for 60 min at a fixed rate of metabolic heat production (moderate intensity) does not independently alter thermoregulatory control or the associated perceptual responses in hot–humid conditions.

Perspectives

In response to recent evidence demonstrating improved repeated sprint cycling with ACT ingestion, Lippi and Sanchis-Gomar (2014) state that ACT should be listed under the World Anti-Doping Agency class of Therapeutic Use Exemption because of its ergogenic effects. From a thermoregulatory perspective, our current data suggest that ACT ingestion provides no benefit or elevated risk to athletes competing in hot–humid conditions. However, the effect of ACT on perceptual responses such as RPE and thermal sensation at higher exercise intensities warrants further investigation. Mauger et al. (2010) reported similar RPE at higher power outputs with greater blood lactate concentrations (> 5 mmol/L) following ACT ingestion compared with PLA. Therefore, at higher exercise intensities, potentially at or above the lactate threshold, ACT may attenuate perceived exertion and possibly discomfort, thereby allowing athletes to work harder and/or longer by maintaining central motor drive and force output (Amann & Dempsey, 2008). Previous literature may lead athletes to believe they are protected from thermal strain with ACT ingestion whereas the present study demonstrates that this does not seem to be the case. Yet this belief in conjunction with improved performance may place the athlete at a greater risk of heat strain.

Key words: Heat stress, hyperthermia, paracetamol, thermoregulation.

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Conflicts of interest: The authors of this study declare that they have no conflicts of interest.

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APPENDIX E: Electric fan use during heat waves

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FRONT MATTER: DISCOVERY

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Electric fan use in heat waves: Turn on or turn off?*

Comment on: Ravanelli NM, Havenith G, Hodder S, Jay O. Heart rate and body temperature responses to extreme heat and humidity with and without electric fans. *J Am Med Assoc* 2015; 313:724-25; http://dx.doi.org/10.1001/jama.2015.153.

Heat waves have been responsible for more deaths worldwide than all other natural disasters combined.[1] In Europe, this "silent killer" caused 70000+ excess deaths in 2003, and more recently 3500+ people died during 2 separate heat waves in India (May 2015) and Pakistan (June 2015) (Fig. 1). Groups among the most vulnerable include the elderly, poor, and people with cardiovascular disease.[1] Identifying simple and cost-effective cooling strategies are therefore an urgent priority. In this *Discovery* article, we highlight our study[2] which was the first to assess the efficacy of the humble electric fan for mitigating cardiovascular and thermal strain in humans during simulated heat wave conditions. Despite the high cooling capacity of air conditioners (AC), the millions of tonnes of CO_2 they generate annually potentially contribute to a vicious cycle of worsening future heat waves.[3] Mass AC-use has also led to electricity blackouts or brownouts during heat waves, and in some cases catastrophic exacerbations in morbidity and mortality.[4] By contrast, electric fans have an electricity requirement that is 50-fold lower than conventional AC units (55-100 W vs 1500-5000 W).

In South Korea, fans are equipped with an off-timer due to the unsubstantiated belief held since the mid-1920s that prolonged fan use can lead to asphyxiation. Meanwhile, all major international public health agencies warn against fan use during heat waves due to a similarly unsupported belief that they paradoxically increases the risk of heat related illness. Specifically, the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) state that electric fan use above ~35°C will critically exacerbate dehydration and "speed the onset" of heat exhaustion. In stark contrast, a 2012 Cochrane review[3] identified that no empirical evidence exists to support or refute the use of fans in heat waves.

In order to maintain body temperature, the human body must balance the rate of internal heat production with the rate of heat dissipation to the surrounding environment. One avenue of heat dissipation is sensible heat transfer, which in indoor environments primarily occurs via convection, following the temperature gradient between the skin surface and ambient air. When ambient air is less than skin temperature (~35°C), heat flows away from the body, but when the ambient air exceeds skin temperature this gradient is reversed and heat is instead added to the body.[5] Since convective heat transfer increases sharply with increases in air velocity, more heat flows *in* to the body with forced air movement (e.g. with a fan).

"*Not only do (fans) not work, they actually make (the risk of overheating) worse. We compare (fans) to a convection oven. By blowing hot air on a person, it heats them up rather than cools them down.*" – *Director of the Environmental Hazards and Health Effects Program at the CDC, USA (Scientific American, July 23, 2010).*

While convection in a hot [190°C (375°F)] oven is the ideal environment for cooking the main component of a typical thanksgiving dinner, there are two major limitations to this analogy. Firstly, the hottest day ever recorded on Earth was 57.6°C in Death Valley, California; a far cry from the interior of a conventional cooking vessel. Second and most importantly, humans are able to physiologically wet their skin surface with sweat secreted

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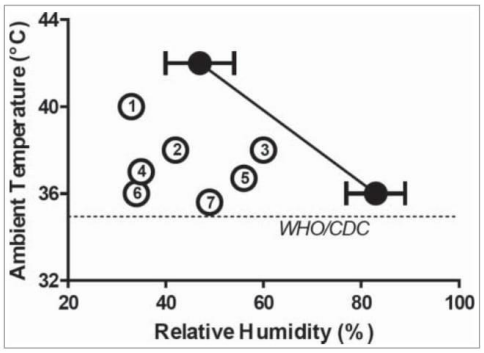

Figure 1. Mean critical environmental limits (with SD) for elevations in heart rate with fan use measured at 36°C and 42°C (solid circles). The dashed line represents the environmental limits for fan use proposed by the World Health Organization (WHO) and the Center for Disease Control and Prevention (CDC). Numbered circles identify the peak environmental conditions during some of the most severe recent heat waves; Karachi, Pakistan 2015 (1); New Delhi, India 2007 (2); Dhahran, Saudi Arabia 2003 (3); Paris, France 2003 (4); Chicago, USA 1999 (5); Frederick, USA 2010 (6); Washington, USA 2012 (7).

primarily from eccrine glands and the evaporation of this sweat promotes latent heat loss. Evaporation is enhanced greatly with higher air velocities, leading to the evaporation of sweat that would otherwise sit on the skin or drip off the body altogether and provide no cooling. However, sweat evaporation is greatly dependent on ambient humidity meaning that under more humid conditions fan use may not prevent heat related elevations in heart rate and core temperature.

We compared the maximum ambient humidity that could be physiologically tolerated with and without fan use at 36°C and 42°C – the range of temperatures typically experienced during heat waves.[5] Eight young healthy males wearing a t-shirt and shorts sat for 135 minutes facing an 18" diameter electric fan set at maximum speed (~4 m/s) from a distance of 1.0 m. The ambient humidity at which an upward inflection in heart rate (HR) and then in core temperature (T_{core}) were identified in each trial using an incremental humidity ramp protocol starting at 1.6 kPa and ending at 5.6 kPa. At 36°C, the ambient temperature above which the use of electric fans is discouraged by public health agencies, a clear benefit of electric fan use was evident. Specifically, the critical humidity for elevations in HR was much higher with a fan (4.9 ± 0.4 kPa, 83 ± 6% RH; Fig. 1) than without (3.7 ± 0.5 kPa, 62 ± 9% RH; $P<0.001$); whereas elevations in T_{core} were observed in only 2 of 8 participants with fan use, but 7 of 8 participants without fan use. At 42°C, which is ~7°C above the current recommendation for fan use worldwide, benefits of fan use, albeit of a smaller magnitude, were still observed for HR (fan: 3.8 ± 0.6 kPa, 47 ± 7% RH; no fan: 3.1 ± 0.6 kPa, 38 ± 7% RH; $P=0.01$; Fig. 1) and T_{core} (fan: 4.5 ± 0.5 kPa, 55 ± 6% RH; no fan: 3.9 ± 0.7 kPa, 48 ± 9% RH; $P=0.04$). In support of greater latent cooling, whole body sweat loss was greater with a fan at 36°C (fan: 398 ± 23 g, no fan: 337 ± 39 g; $P=0.01$) and 42°C (fan: 882 ± 58 g, no fan: 532 ± 102 g; $P<0.001$).

In summary, we clearly demonstrate the benefits of fan use during simulated heat wave conditions, however our findings do not yet apply to individuals with compromised thermoregulatory responses such as the elderly, or to very dry environments where the complete evaporation of sweat would occur even without fan use. Nevertheless, other simultaneous cooling strategies such as wetting the skin or garments with water may further improve the efficacy of fan use for different subpopulations in different types of heat waves. While fan use may hasten dehydration, based on our findings this can be easily negated by drinking between 25 to 175 ml/h of water. In sum, simply turning on a fan may yet prove to be an affordable and sustainable strategy for cooling down in a heat wave.

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APPENDIX F: Thermoregulatory responses during heat and hypoxia

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RESEARCH ARTICLE

Thermoregulatory responses to exercise at a fixed rate of heat production are not altered by acute hypoxia

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[1]*School of Human Kinetics, Faculty of Health Sciences, University of Ottawa, Ontario, Canada;* [2]*Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas and the University of Texas Southwestern Medical Center, Dallas, Texas; and* [3]*Thermal Ergonomics Laboratory, University of Sydney, Lidcombe, New South Wales, Australia*

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Coombs GB, Cramer MN, Ravanelli N, Imbeault P, Jay O. Thermoregulatory responses to exercise at a fixed rate of heat production are not altered by acute hypoxia. *J Appl Physiol* 122: 1198–1207, 2017. First published March 16, 2017; doi:10.1152/japplphysiol.00829.2016.—This study sought to assess the within-subject influence of acute hypoxia on exercise-induced changes in core temperature and sweating. Eight participants [1.75 (0.06) m, 70.2 (6.8) kg, 25 (4) yr, 54 (8) ml·kg^{-1}·min^{-1}] completed 45 min of cycling, once in normoxia (NORM; $F_{I_{O_2}} = 0.21$) and twice in hypoxia (HYP1/HYP2; $F_{I_{O_2}} = 0.13$) at 34.4(0.2)°C, 46(3)% RH. These trials were designed to elicit *1*) two distinctly different $\%\dot{V}O_{2peak}$ [NORM: 45 (8)% and HYP1: 62 (7)%] at the same heat production (H_{prod}) [NORM: 6.7 (0.6) W/kg and HYP1: 7.0 (0.5) W/kg]; and *2*) the same $\%\dot{V}O_{2peak}$ [NORM: 45 (8)% and HYP2: 48 (5)%] with different H_{prod} [NORM: 6.7 (0.6) W/kg and HYP2: 5.5 (0.6) W/kg]. At a fixed $\%\dot{V}O_{2peak}$, changes in rectal temperature (ΔT_{re}) and changes in esophageal temperature (ΔT_{es}) were greater at end-exercise in NORM [ΔT_{re}: 0.76 (0.19)°C; ΔT_{es}: 0.64 (0.22)°C] compared with HYP2 [ΔT_{re}: 0.56 (0.22)°C, $P < 0.01$; ΔT_{es}: 0.42 (0.21)°C, $P < 0.01$]. As a result of a greater H_{prod} ($P < 0.01$) in normoxia, and therefore evaporative heat balance requirements, to maintain a similar $\%\dot{V}O_{2peak}$ compared with hypoxia, mean local sweat rates (LSR) from the forearm, upper back, and forehead were greater (all $P < 0.01$) in NORM [1.10 (0.20) mg·cm^{-2}·min^{-1}] compared with HYP2 [0.71 (0.19) mg·cm^{-2}·min^{-1}]. However, at a fixed H_{prod}, ΔT_{re} [0.75 (0.24)°C; $P = 0.77$] and ΔT_{es} [0.63 (0.29)°C; $P = 0.69$] were not different in HYP1, compared with NORM. Likewise, mean LSR [1.11 (0.20) mg·cm^{-2}·min^{-1}] was not different ($P = 0.84$) in HYP1 compared with NORM. These data demonstrate, using a within-subjects design, that hypoxia does not independently influence thermoregulatory responses. Additionally, further evidence is provided to support that metabolic heat production, irrespective of $\%\dot{V}O_{2peak}$, determines changes in core temperature and sweating during exercise.

NEW & NOTEWORTHY Using a within-subject design, hypoxia does not independently alter core temperature and sweating during exercise at a fixed rate of heat production. These findings also further contribute to the development of a methodological framework for assessing differences in thermoregulatory responses to exercise between various populations and individuals. Using the combined environmental stressors of heat and hypoxia we conclusively demonstrate that exercise intensity relative to aerobic capacity (i.e., $\%\dot{V}O_{2max}$) does not influence changes in thermoregulatory responses.

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thermoregulation; hypoxemia; sweating; core temperature; skin blood flow; heat stress; cutaneous vascular conductance

THE CLASSIC 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 (26). While important, some of these physiological adjustments may influence the thermoregulatory responses to heat stress and exercise. For example, hypoxia may reduce plasma volume (45), which could impair sweating and lead to a redistribution of blood flow (8). Studies performing exercise at simulated high altitude have reported lower steady-state local sweat rates and thermosensitivities in hypoxic conditions using altitude-specific $\%\dot{V}O_{2peak}$ (32, 33), but exercise at fixed absolute workloads (and presumably fixed rates of heat production) have resulted in no differences between normoxia and hypoxia in steady-state sweating or its relationship to esophageal temperature (45). On the other hand, cutaneous vasodilation has been reported under normothermic hypoxic conditions (56), and an increased vasodilatory response to local heating after ~9 h of hypoxia has been observed at rest (36). Yet, a lower cutaneous vascular conductance has been reported on the forearm, but not the chest, during whole body passive heating (38) and exercise at a fixed external workload at 30°C (45). Whether any potential differences in cutaneous vasodilatory control in hypoxia are sufficient to alter the changes in core temperature during exercise in the heat at a fixed heat production is, however, unknown.

Additionally, the choice of exercise intensity for studies comparing thermoregulatory responses between participants is extremely important as confounding factors associated with differences in metabolic heat load and/or body size between individuals have the potential to either cause or mask differences in core temperature and sweating (11, 14, 27). It has been widely believed for many years that exercise intensity relative to an individual's rate of maximum oxygen uptake (i.e., $\%\dot{V}O_{2max}$) is a critical determinant of thermoregulatory responses (3, 20, 54). However, a recent series of studies by our research group has suggested that the importance of $\%\dot{V}O_{2max}$ may be greatly exaggerated (27). Nevertheless, our evidence to date has been exclusively derived from an independent group approach. While participant groups in these studies were carefully selected to isolate the independent influence of fitness and thus relative intensity [i.e., matched for body mass, body

surface area (BSA), and sex but with different levels of $\dot{V}O_{2peak}$], individual responses in core temperature are notoriously variable (24). A clear limitation is therefore that variation in other factors (e.g., partial acclimation status, adiposity) that inevitably arises when comparing different groups of participants could have obscured a potential influence of relative intensity. Indeed, there remain many recent examples of studies using $\%\dot{V}O_{2peak}$ to compare thermoregulatory responses between groups including obese individuals (1), children (37), and heart failure patients (4). Resolving whether $\%\dot{V}O_{2peak}$ exerts an influence independently of metabolic heat production and evaporative heat balance requirement is therefore an urgent priority.

One way to truly isolate the influence of relative intensity within an individual is to employ a hypoxic environment. By reducing the inspired fraction of oxygen ($F_{I_{O_2}}$) to create a normobaric hypoxic environment, the $\dot{V}O_{2peak}$ for a given individual will be lower (35, 41). Thus, $\%\dot{V}O_{2peak}$ can be manipulated for a given work rate (and therefore heat production) by altering $F_{I_{O_2}}$. This approach also permits the comparison of exercise in normoxia vs. hypoxia at a matched $\%\dot{V}O_{2peak}$, but with different rates of heat production. Given the traditional logic that core temperature (3, 54) and sweating (20) during exercise are altered, or even determined, by $\%\dot{V}O_{2peak}$, a higher core temperature would be expected in hypoxia compared with normoxia at the same rate of heat production. However, the evidence for such a phenomenon is weak (2, 21, 45), and observations of thermoregulatory responses to exercise in hypoxia have been inconsistent. Given these inconsistencies in the literature and the various protocols used to study thermoregulatory control in hypoxia (i.e., fixed $\%\dot{V}O_{2peak}$ vs. fixed workload), the independent influence of hypoxia on thermoregulatory responses warrants determination.

The aims of the present study were therefore to assess *1*) the independent influence of hypoxia on core temperature, sweating, and skin blood flow during exercise at a fixed metabolic heat load; and *2*) the within-subject influence of relative exercise intensity on the control of thermoregulatory responses independently of heat production and the evaporative requirement for heat balance (E_{req}) using hypoxia to differentiate relative vs. absolute workloads. It was hypothesized that thermoregulatory responses would not differ between normoxia and hypoxia during exercise at fixed rates of heat production and E_{req}, irrespective of large differences in $\%\dot{V}O_{2peak}$. However, during exercise at a fixed $\%\dot{V}O_{2peak}$, systematic differences in thermoregulatory responses were expected between normoxia and hypoxia secondary to different rates of heat production and E_{req} to maintain a given $\%\dot{V}O_{2peak}$.

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 and American Heart Association/American College of Sports Medicine Health/Fitness Facility Pre-participation Screening Questionnaire before participation.

Participants. Based on the mean effect sizes for 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 woman) nonheat-acclimated, healthy, and active participants [1.75 (0.06) m, 70.2 (6.8) kg, 25 (4) yr, 54 (8) $ml \cdot kg^{-1} \cdot min^{-1}$] were recruited to participate in the study; at the time of data collection the female participant was using constant-release hormonal contraception (IUD). All participants reported no history of cardiovascular, respiratory, metabolic, or neurological disorders and were asked to refrain from consuming any alcohol or caffeine, as well as performing any strenuous activity, 24 h before testing. 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: two preliminary trials and three experimental trials. During the first preliminary session, height and body mass were measured. Peak oxygen consumption ($\dot{V}O_{2peak}$) was measured in normoxia ($F_{I_{O_2}} = 0.21$) and again in normobaric (~743 mmHg) hypoxia ($F_{I_{O_2}} = 0.13$) during the preliminary sessions in a counterbalanced order. The maximal tests to determine $\dot{V}O_{2peak}$ were performed on a semirecumbent cycle ergometer (Lode; Corival, Groningen, Netherlands) and began at 100 W with increases of 20 W every minute thereafter until physical exhaustion, based on the recommendations from the Canadian Society for Exercise Physiology (13). The two $\dot{V}O_{2peak}$ tests were performed on separate days and in a counterbalanced order between participants.

All sessions were performed in an environmental chamber at the University of Ottawa. During hypoxia sessions, O_2 extractors (CAT12; Altitude Control Technologies, Lafayette, CO) connected to the climate-controlled chamber (volume of ~64 m^3) allowed for a stabilized $F_{I_{O_2}}$ level. Prior to each trial, urine specific gravity was measured to ensure that each participant was below the cut-off value for euhydration (<1.025) (29). The first two trials were performed in a counterbalanced order and consisted of 45 min of cycling at a fixed metabolic heat production (H_{prod}) of ~7 W/kg in either normoxia ($F_{I_{O_2}} = 0.21$; NORM) or normobaric hypoxia ($F_{I_{O_2}} = 0.13$; HYP1). Exercise intensity was set to elicit a fixed H_{prod} between trials as described previously by Cramer and Jay (11). The trials were completed in a compensable environment, at 34.4 (0.2)°C, 46 (3)% RH, to compare steady-state thermoregulatory responses. During a third trial ($F_{I_{O_2}} = 0.13$; HYP2), 45 min of cycling was completed to compare steady-state thermoregulatory responses at an intensity corresponding to the same $\%\dot{V}O_{2peak}$ as in NORM but at a lower rate of metabolic heat production. Subjects were clothed in standardized athletic shorts (and sports bra for the woman) and sandals. Once all equipment (see *Instrumentation* below) was in place and functioning, the participant rested in a seated position for a 30 min baseline period inside the chamber. Upon completion of exercise, there was a ~45 min postexercise rest period during which the participant was deinstrumented and measurements of maximum skin blood flow were recorded under normoxic conditions.

Heat balance parameters. Oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were measured by indirect calorimetry (Vmax Encore; Carefusion, San Diego, CA). Metabolic energy expenditure (M) was subsequently estimated by *Eq. 1*. H_{prod} was calculated by subtracting the rate of mechanical work (W) from M (*Eq. 2*), as follows:

$$M = \dot{V}O_2 \frac{\left(\frac{RER - 0.7}{0.3}\right)e_c + \left(\frac{1.0 - RER}{0.3}\right)e_f}{60(BSA)}(1{,}000)[W/m^2] \quad (1)$$

$$H_{prod} = M - W(W/m^2) \quad (2)$$

where RER is the respiratory exchange ratio ($\dot{V}CO_2$:$\dot{V}O_2$), and e_c and e_f are the caloric equivalents per liter of oxygen for the oxidation of carbohydrates (21.13 kJ) and fats (19.62 kJ), respectively.

Clothing insulation and evaporative resistance were considered negligible for all calculations given the minimal coverage of the ensemble. Heat losses via convection were determined by:

$$C = h_c(T_{sk} - T_a)[W/m^2] \quad (3)$$

$$h_c = 8.3v^{0.6}\left[W \cdot m^{-2} \cdot K^{-1}\right] \quad (4)$$

where h_c refers to the convective heat transfer coefficient and can be used for a seated subject facing an air velocity of 0.2–4.0 m/s (47), T_{sk} is the mean temperature of the skin (°C), T_a is the temperature of the ambient air (°C), and v is the air velocity, which was estimated to be 1.2 m/s in the chamber.

Radiative heat losses were calculated as follows:

$$R = h_r(T_{sk} - T_a)[W/m^2] \quad (5)$$

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

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 skin, set to 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), which can be estimated as 0.70 for seated subjects (31).

Total respiratory heat losses can be calculated by adding convective (C_{res}; *Eq. 7*) and evaporative (E_{res}; *Eq. 8*) respiratory heat loss (7, 23):

$$C_{res} = \frac{V_E \rho C_P (T_e - T_i)}{60(BSA)}[W/m^2] \quad (7)$$

$$E_{res} = \frac{V_E \rho (H_e - H_i)}{60(BSA)} h_v \left[W \cdot m^{-2}\right] \quad (8)$$

where $\dot{V}_E$ 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 ($kJ/kg \cdot K^{-1}$), 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 vaporization of water ($J/kg \cdot K^{-1}$).

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

$$E_{req} = H_{prod} - (C + R + C_{res} + E_{res})\left[W/m^2\right] \quad (9)$$

All heat balance parameters were calculated in W/m^2 but are displayed in either W or W/kg throughout this article.

Instrumentation. Rectal temperature (T_{re}) was monitored with a pediatric thermistor (TM400; Covidien, Mansfield, MA) inserted ~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 (42).

Skin temperature (T_{sk}) was measured at four sites (48) via thermistors integrated into heat flow sensors (2,252 Ohms; Concept Engineering, Old Saybrook, CT). The heat flow sensors were placed onto the skin with double-sided adhesive disks and surgical tape (Transpore; 3M, London, ON, Canada). All thermometry data were recorded on 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).

Local sweat rates (LSR) were measured from ventilated capsules placed on the skin of the upper back (lateral portion), forearm, and forehead. Influent anhydrous air flowed through the capsule at a rate of 1.00 l/min. Flow rates were measured with an Omega FMA-A2307 flow rate monitor (Omega Engineering, Stamford, CT). The vapor content of the effluent air was measured by capacitance hygrometers (series HMT333; Vaisala, Helsinki, Finland). LSR values were calculated from the recorded flow rate and the difference in vapor content of the influent and effluent air, normalized to the area of skin under the capsule (expressed in $mg \cdot cm^{-2} \cdot min^{-1}$).

In addition to LSR, whole body sweat losses (WBSL) were estimated from the difference of pre- and postexercise body mass measurements (Combics 2, Sartorius, Mississauga, ON, Canada), corrected for metabolic and vapor mass losses from respiration (44).

Heat-activated sweat gland density (HASGD) was determined using the iodine paper method (18) 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 (49). Forearm LSR was divided by HASGD to determine sweat gland output (SGO) expressed in $\mu g \cdot gland^{-1} \cdot min^{-1}$.

Blood pressure was monitored with an automated unit (Tango M2; SunTech, Raleigh, NC) and a 3-lead ECG setup (Q-Stress v3.3; Quinton, Bothell, WA). Mean arterial pressure (MAP) was calculated from the addition of 1/3 systolic blood pressure and 2/3 diastolic blood pressure at rest, while exercising values were calculated by a heart rate corrected formula as described by Razminia et al. (50). As an index of skin blood flow (SkBF), red blood cell flux (LDF) was measured on the forearm and upper back using laser-Doppler flowmetry (Periflux System 5000; Perimed, Järfälla, Sweden). Cutaneous vascular conductance (CVC) was calculated as LDF (AU)/MAP (mmHg) and expressed as both arbitrary units (AU/mmHg) and as a percentage of maximum values (%CVC_{max}) determined during 45 min of normoxic postexercise local heating of the measurement area (~1 cm^2) to 44°C. Oxygen saturation (SpO_2) and heart rate (HR) were recorded every 5 s with a Rainbow SET pulse oximeter (Radical-7, Masimo, Irvine, CA).

One blood sample of ~6 ml was taken at 0 and 45 min of exercise and was analyzed for hematocrit (Hct) and hemoglobin (Hb) using a photometer (HemoPoint H2 Meter; StanBio Laboratory, Boerne, TX) and microcuvettes (Alere, Orlando, FL). 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 (15).

Ratings of perceived exertion (RPE) were taken at rest and every 15 min during exercise using the Borg scale [6–20].

Statistical analysis. Two-way repeated-measures ANOVAs with the independent variables of condition (2 levels: normoxia or hypoxia) and time (four levels: 0, 15, 30, 45 min) were used to analyze the dependent variables of ΔT_{es}, ΔT_{re}, ΔT_{sk}, LSR_{arm}, LSR_{back}, LSR_{head}, CVC, $\%CVC_{max}$, HR, MAP, RPE, $\dot{V}_{O_2}$, RER, $\dot{V}_E$, and SpO_2. Separate ANOVAs were performed to compare fixed H_{prod} trials (i.e., NORM vs. HYP1) and trials matched for $\%\dot{V}O_{2peak}$ (i.e., NORM vs. HYP2). When a significant interaction between time and condition was detected, individual time points were compared by *t*-tests with a Holm-Bonferroni correction. Partial eta squared (η_p^2) was reported, where values of 0.01, 0.09, and 0.25 correspond to small, medium, and large effect sizes, respectively (9). Maximum CVC values were compared by a one-way ANOVA. Mean values throughout the trials for $\%\dot{V}O_{2max}$, H_{prod}, workload, mechanical efficiency, HASGD, SGO, respiratory heat losses, and changes in PV were compared by a paired-sample Student's *t*-test. Cohen's *d* values were reported for the *t*-tests where *d* values of 0.2, 0.5, 0.8 are indicative of small, medium, and large effect sizes, respectively (9). All data are reported as means (standard deviation). Alpha was set at the $P = 0.05$ level. All statistical analyses were performed with Prism GraphPad v6.0 for Windows (La Jolla, CA).

Table 1. *Workload, heat production, and relative exercise intensity (%$\dot{V}O_{2peak}$) while cycling in normoxia (NORM, 21% $F_{I_{O_2}}$), hypoxia at the same heat production as in NORM (HYP1, 13% $F_{I_{O_2}}$), and hypoxia at the same %$\dot{V}O_{2peak}$ as in NORM (HYP2, 13% $F_{I_{O_2}}$)*

	Workload, W	%$\dot{V}O_{2peak}$	H_{prod}, W	H_{prod}, W/kg	E_{req}, W/m^2
NORM	90 (5)	45 (8)	471 (37)	6.7 (0.6)	236 (15)
HYP1	87 (4)†	62 (7)†	488 (29)	7.0 (0.5)	246 (10)
HYP2	60 (8)*	48 (5)	384 (38)*	5.5 (0.6)*	188 (22)*

Values are means (standard deviation). H_{prod}, heat production; E_{req}, evaporative requirements for heat balance. *Significant difference between NORM and HYP2 ($P < 0.05$). †Significant difference between NORM and HYP1 ($P < 0.05$).

RESULTS

External workload, exercise intensity, and heat production. Mean values for H_{prod}, E_{req}, external workload, and %$\dot{V}O_{2peak}$ are presented in Table 1. By design, there was no difference in heat production ($P = 0.20$, $d = 0.49$) or E_{req} ($P = 0.17$, $d = 0.73$) in the fixed H_{prod} trials between NORM and HYP1 (Table 1), while workload was slightly lower in HYP1 than NORM ($P = 0.03$, $d = 0.61$) due to decrements in mechanical efficiency (NORM: 16.8 (1)%; HYP1: 15.7 (1)%; $P < 0.01$); however, %$\dot{V}O_{2peak}$ was significantly greater in HYP1 compared with NORM ($P < 0.001$, $d = 2.46$) due to a 27% reduction in $\dot{V}O_{2peak}$ from 3.78 (0.67) l/min in normoxia to 2.74 (0.36) l/min in hypoxia ($P < 0.001$, $d = 1.92$). Conversely, when the trials were matched for %$\dot{V}O_{2peak}$, heat production ($P < 0.001$), E_{req} ($P < 0.001$), and external workload ($P < 0.001$) were all significantly lower in HYP2 compared with NORM (Table 1).

Core and skin temperatures. During the fixed H_{prod} trials, while significant differences in %$\dot{V}O_{2peak}$ were observed, changes in T_{es} over time (Fig. 1*A*) were not different between conditions ($P = 0.69$, $\eta_p^2 = 0.07$) with a ΔT_{es} after 45 min of 0.64 (0.22)°C in NORM and 0.63 (0.29)°C in HYP1. There was also no interaction between time and condition on changes in T_{re} ($P = 0.77$, $\eta_p^2 = 0.05$) with a ΔT_{re} after 45 min of 0.76 (0.19)°C in NORM and 0.75 (0.24)°C in HYP1 (Fig. 1*B*). In contrast, when exercising at a matched %$\dot{V}O_{2peak}$ (but different H_{prod}), changes in T_{es} over time (Fig. 1*A*) were significantly smaller in HYP2 compared with NORM ($P < 0.01$, $\eta_p^2 = 0.52$), with a 45 min ΔT_{es} of 0.42 (0.21)°C in HYP2, while changes in T_{re} over time (Fig. 1*B*) were also smaller in HYP2 compared with NORM ($P < 0.01$, $\eta_p^2 = 0.85$), with a 45 min ΔT_{re} of 0.56 (0.22)°C in HYP2. The change in T_{sk} over time was not different between fixed H_{prod} trials ($P = 0.82$, $\eta_p^2 = 0.04$) with 45 min ΔT_{sk} values of 0.63 (0.26) °C in NORM and 0.58 (0.18)°C in HYP1, while ΔT_{sk} was significantly lower in HYP2 compared with NORM ($P = 0.04$, $\eta_p^2 = 0.32$) with 45 min ΔT_{sk} values of 0.50 (0.19)°C in HYP2.

Sweating. During the fixed H_{prod} trials (NORM and HYP1), again despite differences in %$\dot{V}O_{2peak}$, LSR on the forearm (Fig. 2, *left*) did not respond differently over time between conditions ($P = 0.30$, $\eta_p^2 = 0.18$) with values after 45 min of 1.21 (0.18) mg·cm^{-2}·min^{-1} in NORM and 1.28 (0.21) mg·cm^{-2}·min^{-1} in HYP1. There was also no significant interaction between time and condition on LSR of the upper back ($P = 0.93$, $\eta_p^2 = 0.02$) with values after 45 min of 1.06 (0.17) mg·cm^{-2}·min^{-1} in NORM and 1.05 (0.31) mg·cm^{-2}·min^{-1} in HYP1 (Fig. 2, *middle*), nor did an interaction exist between time and condition on LSR of the forehead ($P = 0.91$, $\eta_p^2 = 0.03$) with LSR values after 45 min of 1.01 (0.36) mg·cm^{-2}·min^{-1} in NORM and 1.03 (0.32 mg·cm^{-2}·min^{-1} in HYP1 (Fig. 2, *right*). However, in the %$\dot{V}O_{2peak}$-matched trials LSR was attenuated in HYP2 compared with NORM on the forearm ($P < 0.01$, $\eta_p^2 = 0.74$) with LSR after 45 min of 0.77 (0.20) mg·cm^{-2}·min^{-1} (Fig. 2, *left*). LSR on the upper back ($P < 0.01$, $\eta_p^2 = 0.77$) and the forehead LSR ($P < 0.01$, $\eta_p^2 = 0.65$) were also lower in HYP2 relative to NORM with values after 45 min of 0.76 (0.18) mg·cm^{-2}·min^{-1} (Fig. 2, *middle*) and 0.62 (0.29) mg·cm^{-2}·min^{-1} (Fig. 2, *right*), respectively.

Heat-activated sweat gland density and sweat gland output are displayed in Fig. 3. During fixed H_{prod} trials, HASGD was not different between conditions ($P = 0.51$, $d = 0.21$), with 93 (29) glands/cm^2 in NORM and 101 (45) glands/cm^2 in HYP1. When matched for %$\dot{V}O_{2peak}$ HASGD was lower in HYP2 than NORM with 70 (26) glands/cm^2 ($P = 0.01$, $d = 0.85$). Conversely, SGO was not different between conditions in fixed H_{prod} trials ($P = 0.64$, $d = 0.12$), with values of 13.2 (5.5) μg·gland^{-1}·min^{-1} in NORM and 12.6 (5.3) μg·gland^{-1}·min^{-1} in HYP1. Nor was SGO different when matched for %$\dot{V}O_{2peak}$ ($P = 0.48$, $d = 0.62$) with a value of 12.0 (1.8) μg·gland^{-1}·min^{-1}.

CVC. CVC data are displayed in Fig. 4. In the fixed H_{prod} trials, there tended to be an interaction between time and condition on CVC in AU at the forearm ($P = 0.06$, $\eta_p^2 = 0.33$), but not the back ($P = 0.35$, $\eta_p^2 = 0.14$), between NORM and HYP1. There was also a trend toward a significant interaction between time and condition on %CVC_{max} at the forearm ($P = 0.09$, $\eta_p^2 = 0.30$), suggesting %CVC_{max} in-

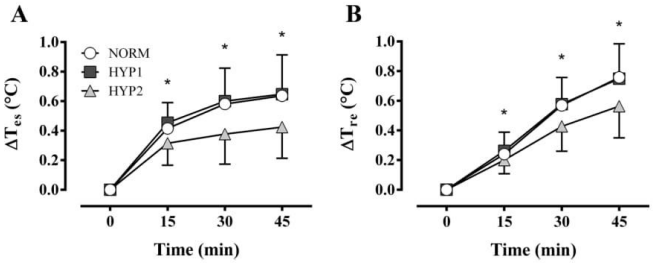

Fig. 1. Changes in esophageal (T_{es}, *A*) and rectal (T_{re}, *B*) temperatures as a function of time while cycling in normoxia (NORM, 21% $F_{I_{O_2}}$), hypoxia at the same heat production as in NORM (HYP1, 13% $F_{I_{O_2}}$), and hypoxia at the same %$\dot{V}O_{2peak}$ as in NORM (HYP2, 13% $F_{I_{O_2}}$). *Significant difference between NORM and HYP2 ($P < 0.05$).

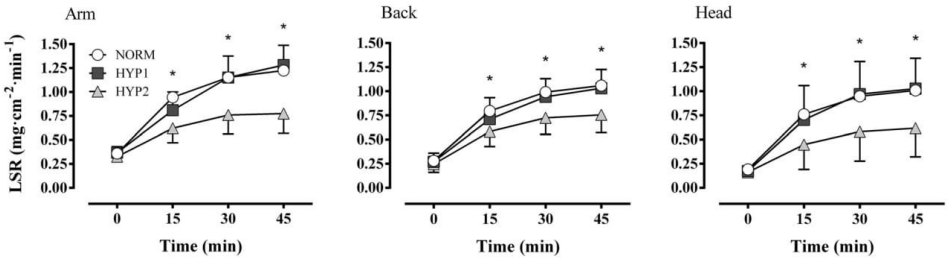

Fig. 2. Local sweat rates (LSR) from the forearm (*left*), upper back (*middle*), and forehead (*right*) as a function of time while cycling in normoxia (NORM, 21% $F_{I_{O_2}}$), hypoxia at the same heat production as in NORM (HYP1, 13% $F_{I_{O_2}}$), and hypoxia at the same $\%\dot{V}O_{2peak}$ as in NORM (HYP2, 13% $F_{I_{O_2}}$). *Significant difference between NORM and HYP2 ($P < 0.05$).

creased in a greater fashion over time in HYP1 than in NORM. While there was no evidence of an interaction at the upper back, there tended to be a main effect of hypoxia with steady-state $\%CVC_{max}$ ~30% higher in HYP1 compared with NORM ($P = 0.09$, $\eta_p^2 = 0.60$). At a fixed $\%\dot{V}O_{2peak}$, there was no interaction between time and condition on CVC in AU at the arm ($P = 0.64$, $\eta_p^2 = 0.09$) or back ($P = 0.99$, $\eta_p^2 < 0.01$), nor was there an interaction on $\%CVC_{max}$ at either the forearm ($P = 0.31$, $\eta_p^2 = 0.18$) or upper back ($P = 0.45$, $\eta_p^2 = 0.12$) between NORM and HYP2. Mean maximum CVC values in AU (Fig. 4) from the arm and back following local heating were not different between all trials [$P = 0.17$, $\eta_p^2 = 0.18$; NORM: 3.45 (1.04), HYP1: 2.64 (0.89), HYP2: 3.65 (0.73)].

Cardiovascular and hematological measurements. Mean MAP, Hb, Hct, and ΔPV values for both studies are all displayed in Table 2. In the fixed H_{prod} trials, the HR response was greater over time in HYP1 compared with NORM ($P < 0.01$, $\eta_p^2 = 0.71$) with mean values of 113 (18) beats/min in NORM and 134 (14) beats/min in HYP1 (Fig. 5*A*), MAP was not different between conditions ($P = 0.29$, $\eta_p^2 = 0.16$), SpO_2 decreased over time in HYP1 compared with NORM ($P < 0.01$, $\eta_p^2 = 0.54$) with mean values of 96 (1)% in NORM and 76 (4)% in HYP1 (Fig. 5*B*), and reductions in PV after 45 min of exercise tended to be greater in HYP1 compared with NORM ($P = 0.06$, $d = 0.81$). In the $\%\dot{V}O_{2peak}$-matched trials, hypoxia had no effect on HR ($P = 0.17$, $\eta_p^2 = 0.21$) with mean values of 113 (18) beats/min in NORM and 119 (16) beats/min in HYP2, and no effect on MAP ($P = 0.91$, $\eta_p^2 = 0.02$), or ΔPV ($P = 0.17$, $d = 0.41$), but SpO_2 decreased over time in HYP2 with mean values of 76 (3)% compared with NORM ($P < 0.01$, $\eta_p^2 = 0.56$).

Ventilatory responses and respiratory heat losses. Ventilatory and respiratory responses are displayed in Fig. 6. During the fixed H_{prod} trials, $\dot{V}O_2$ ($P = 0.12$, $\eta_p^2 = 0.38$) and RER ($P = 0.35$, $\eta_p^2 = 0.29$) were not different over time between NORM and HYP1, while minute ventilation ($P < 0.01$, $\eta_p^2 = 0.69$) was greater in HYP1 compared with NORM. Conversely, when matched for $\%\dot{V}O_{2peak}$, $\dot{V}O_2$ ($P < 0.01$, $\eta_p^2 = 0.95$) was lower in HYP2 compared with NORM, while RER was not different in HYP2 ($P = 0.56$, $\eta_p^2 = 0.19$), and the $\dot{V}_E$ ($P = 0.01$, $\eta_p^2 = 0.59$) was significantly lower in HYP2 than in NORM. Mean respiratory heat losses during exercise [NORM: 35 (2) W; HYP1: 41 (3) W] were greater ($P < 0.01$, $d = 2.74$) in HYP1 at a fixed H_{prod} and were lower [NORM: 35 (2) W; HYP2: 32 (3) W] in HYP2 when matched for $\%\dot{V}O_{2peak}$ ($P = 0.02$, $d = 1.07$).

RPE. In the fixed H_{prod} trials, RPE values (Borg) were higher over time in hypoxia ($P < 0.01$, $\eta_p^2 = 0.44$) with mean values of 11 (2) in NORM and 13 (2) in HYP1. Conversely, when exercising at a matched $\%\dot{V}O_{2peak}$ RPE values were lower over time in HYP2 ($P < 0.01$, $\eta_p^2 = 0.43$) with a mean value of 10 (1).

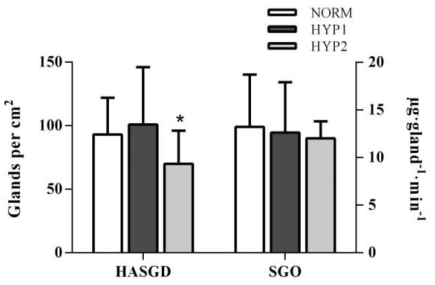

Fig. 3. Mean heat-activated sweat gland density (HASGD) and sweat gland output (SGO) while cycling in normoxia (NORM, 21% $F_{I_{O_2}}$), hypoxia at the same heat production as in NORM (HYP1, 13% $F_{I_{O_2}}$), and hypoxia at the same $\%\dot{V}O_{2peak}$ as in NORM (HYP2, 13% $F_{I_{O_2}}$). *Significant difference between NORM and HYP2 ($P < 0.05$).

DISCUSSION

The present results conclusively demonstrate, using a within-subject experimental design, that thermoregulatory responses of core temperature and sweating during exercise at a fixed rate of H_{prod}, and therefore fixed evaporative heat balance requirement (E_{req}), are unaffected by acute hypoxia. At the same time, we provide evidence illustrating that exercise at a fixed $\%\dot{V}O_{2peak}$ but different H_{prod} (and E_{req}), does not determine time-dependent changes in core temperature or local sweat rates.

The current study isolated the influence of hypoxia itself on thermoregulatory responses to exercise by fixing the rates of heat production between normoxia and hypoxia (NORM vs. HYP1). It follows that no independent effect of hypoxia on core temperature or sweat rates was observed. Previous assessments of thermoregulation at simulated high altitude (i.e., hypoxia) have compared thermo-effector responses at altitude-specific $\%\dot{V}O_{2peak}$ (32, 33) and found that exercise at 60% of altitude-specific $\dot{V}O_{2peak}$ attenuated steady-state forearm sweat

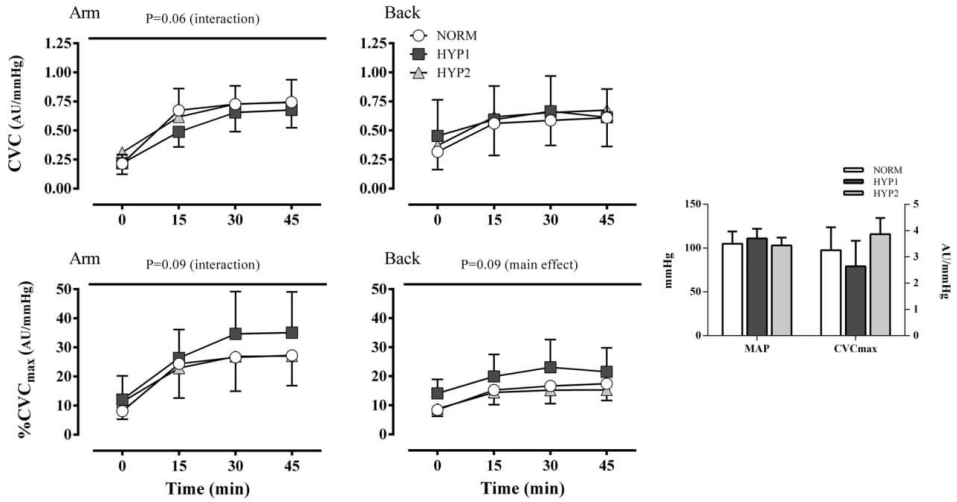

Fig. 4. Cutaneous vascular conductance (CVC) from the arm and upper back expressed as arbitrary units (AU) and as a percentage of maximum values (%CVC_{max}) while cycling in NORM (normoxia; 21% O_2), HYP1 (fixed Hprod hypoxia; 13% O_2), and HYP2 (matched %$\dot{V}O_{2peak}$ hypoxia; 13% O_2). Steady-state (30–45 min) mean arterial pressure (MAP) and maximum CVC values obtained during 45 min of local heating (CVC_{max}) are also displayed on *right*.

rates in the high-altitude trials (4,575 m). However, these observations (32, 33) can be attributed to differences in heat production and, therefore E_{req}, stemming from a reduced $\dot{V}O_{2peak}$ at high altitude (i.e., hypoxia) and not to hypoxia per se. Indeed, our current results demonstrate that LSR are the same when E_{req} is fixed (NORM vs. HYP1) and lower when E_{req} was reduced to match %$\dot{V}O_{2peak}$ in HYP2 (Fig. 2). Dipasquale et al. (16) examined LSR in normobaric hypoxia using pharmacological induction of sweating and reported that a peripheral effect of hypoxia suppressed sweating on the forearm by 16% compared with normoxia. However, in the current study, the lower steady-state LSR (at all sites) observed in HYP2 compared with NORM were mediated by fewer activated sweat glands and not differences in mean SGO (Fig. 3), which indicates that hypoxia did not have a peripheral influence on the sweat gland.

Table 2. *Cardiovascular and hematological measurements while cycling in normoxia (NORM, 21% $F_{I_{O_2}}$), hypoxia at the same heat production as in NORM (HYP1, 13% $F_{I_{O_2}}$), and hypoxia at the same %$\dot{V}O_{2peak}$ as in NORM (HYP2, 13% $F_{I_{O_2}}$)*

	MAP, mmHg	Hb, g/dl	Hct, %	ΔPV, %
		Rest		
NORM	89 (8)	14.5 (0.5)	43 (2)	
HYP1	89 (10)	14.6 (0.7)	43 (2)	
HYP2	88 (7)	14.5 (0.7)	43 (2)	
		Exercise		
NORM	105 (14)	15.1 (0.5)	44 (2)	−6.1 (4.8)
HYP1	111 (11)	15.4 (0.9)	45 (2)	−9.5 (3.2)
HYP2	103 (9)	14.9 (0.7)	44 (2)	−4.3 (4.1)

Values are means (standard deviation). MAP, mean arterial pressure; Hb, total hemoglobin; Hct, hematocrit; PV, plasma volume.

Other studies have previously reported no effect of hypoxia on core temperature during exercise at fixed absolute external workloads (2, 28, 34) and also no difference in chest LSR during fixed workload exercise between normoxia and hypoxia (45). However, two of these studies reported a higher LSR on the forehead during normothermic (~22°C) exercise in hypoxia compared with normoxia (28, 34). It is noteworthy, however, that while the same fixed workloads were used in normoxia and hypoxia in all of these studies, heat production was not measured. In the current study, different external workloads were required in NORM and HYP1 to generate a fixed heat production (Table 1) due to differences in mechanical efficiency. It was suggested that higher sweat rates in glabrous skin (i.e., forehead) may have been potentiated by greater perceived strain relating to nonthermal factors such as increased HR and dyspnea due to hypoxia (28). In support, greater forehead LSR have also been observed in normoxic conditions between groups of low and high aerobic fitness, independently of E_{req}, which was also associated with greater perceptual strain (10). The reasons for the absence of an influence of %$\dot{V}O_{2peak}$ on forehead LSR (Fig. 2, *right*) in the present study is unclear. It is possible that perceptual strain was insufficiently high to induce greater sweating from regions sensitive to such a stimulus as a result of low workloads in hypoxia. Indeed, cycling resistance was <100 W in the current study, and despite that workload tended to be lower in HYP1 compared with NORM at a fixed heat production, RPE was greater in the hypoxic condition given the greater %$\dot{V}O_{2peak}$ (Table 1). Yet RPE was also lower in HYP2 compared with NORM when matched for %$\dot{V}O_{2peak}$, which could potentially indicate a differential response between RPE and relative exercise intensity based on $\dot{V}O_{2peak}$. However, workloads were ~60 W in HYP2 compared with ~90 W in NORM, which suggests RPE

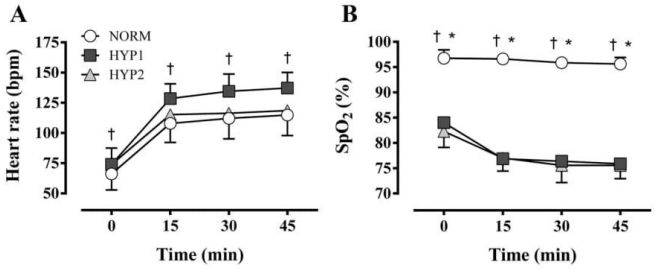

Fig. 5. Heart rate (*A*) and oxygen-hemoglobin saturation (SpO_2, *B*) responses as a function of time while cycling in normoxia (NORM, 21% $F_{I_{O_2}}$), hypoxia at the same heat production as in NORM (HYP1, 13% $F_{I_{O_2}}$), and hypoxia at the same $\%\dot{V}O_{2peak}$ as in NORM (HYP2, 13% $F_{I_{O_2}}$). *Significant difference between NORM and HYP2 ($P < 0.05$). †Significant difference between NORM and HYP1 ($P < 0.05$).

during cycling could also be influenced by peripheral sensation of force production relating to different cycling workloads (6).

Additionally, such large differences in $\dot{V}O_{2peak}$ within a given subject between normoxia and hypoxia allows for a unique situation in which the influence of $\%\dot{V}O_{2peak}$ on changes in core temperature and sweating can be assessed without potential confounding factors that arise when using a between-group experimental design (e.g., mass, BSA, body fat %, partial acclimation status) (7, 11). Recently, Jay et al. (27) demonstrated that differences in aerobic capacity between mass-matched groups of high and low fitness do not influence thermoregulatory responses during exercise at the same H_{prod}. The current study lends further support to this previous finding (27). It was found that despite differences in $\%\dot{V}O_{2peak}$ of 15–20%, core temperature (Fig. 1) and sweating (Fig. 2) were unaffected by hypoxia during exercise at a fixed H_{prod}. Conversely, to match $\%\dot{V}O_{2peak}$ in hypoxia to normoxia, H_{prod} (and thus E_{req}) was lowered, resulting in smaller changes in rectal and esophageal temperatures (Fig. 1), as well as attenuations of LSR in hypoxia at all sites (Fig. 2). This conclusively demonstrates that setting exercise intensity at a fixed percentage of $\dot{V}O_{2peak}$ to compare core temperature and sweating responses, as traditionally advised (3, 20, 54), should be avoided if H_{prod} is different between conditions, individuals, or groups. Rather, fixing H_{prod} [per unit mass, i.e., W/kg (8, 9)] has been demonstrated to be a more suitable method of setting exercise intensity when the change in core temperature is the primary outcome measure (11).

While it was not part of the specific design of the present study, we observed a very narrow range of oxygen-hemoglobin saturation values (SpO_2; Fig. 5*B*) in our participants with 95% confidence intervals of 74–79%. Therefore, we can confidently state that we successfully elicited a fixed level of hypoxemia in the present study. Accordingly, HR was higher during hypoxic exercise by ~20 beats/min at a fixed rate of heat production (and $\dot{V}O_2$) compared with normoxia (Fig. 5*A*). It is likely that the demand for oxygen delivery by skeletal muscles was greater given the reductions in oxygen saturation, such that increases in cardiac output via HR were necessitated. There is also evidence of a resetting of baroreflex control in hypoxia leading to an increased HR (22), which is consistent with higher resting HRs in both HYP1 and HYP2 by ~8 beats/min compared with NORM in the current study. Conversely, HR did not differ between NORM and HYP2 while exercising at a similar $\%\dot{V}O_{2peak}$, but much lower absolute $\dot{V}O_2$ in HYP2. While hypoxia exerts an autonomic reflex response, as evidenced by increased sympathetic vasoconstrictor nerve activity (52), many vascular beds also exhibit a vasodilator response including the coronary (58), cerebral (57), skeletal muscle (8), and cutaneous circulations (56). Yet reduced vascular resistance in beds such as the coronary and cerebral circulations must be accompanied by physiological compensations to maintain MAP, either by increases in HR, as currently observed, or perhaps due to sympathetic vasoconstrictor tone in other vascular beds (40).

Although hypoxia-mediated reductions in arterial partial pressure of oxygen stimulate higher $\dot{V}E$ (39, 59), which might be thought to contribute to greater rates of heat loss (21), the difference in ventilation (Fig. 6) observed in the current study only resulted in an extra 6 W of respiratory heat losses in HYP1 compared with NORM. A difference of this magnitude would be equivalent to <7 g of required sweat evaporation over 45 min, whereas mean WBSL after 45 min in HYP2 was 458 (107) g; thus any increases in respiratory heat loss related

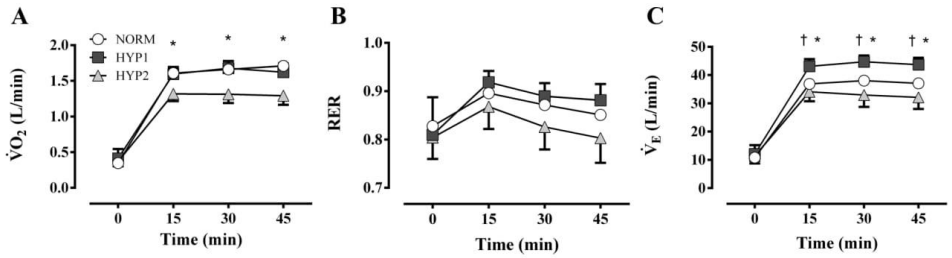

Fig. 6. The rate of O_2 consumption ($\dot{V}O_2$, *A*), respiratory exchange ratio (RER, *B*), and rate of ventilation ($\dot{V}E$, *C*) over time while cycling in normoxia (NORM, 21% $F_{I_{O_2}}$), hypoxia at the same heat production as in NORM (HYP1, 13% $F_{I_{O_2}}$), and hypoxia at the same $\%\dot{V}O_{2peak}$ as in NORM (HYP2, 13% $F_{I_{O_2}}$). *Significant difference between NORM and HYP2 ($P < 0.05$). †Significant difference between NORM and HYP1 ($P < 0.05$).

to hypoxia would be obscured by the variability of the measurement. Greenleaf et al. (21) also proffered that increases in respiratory heat loss must be compensated by reductions in heat loss via other physiological mechanisms to maintain a constant core temperature. They suggested peripheral blood flow was reduced because estimates of tissue conductance were correspondingly lower at 2,000 and 4,000 m of altitude in a hypobaric hypoxia chamber compared with increases in respiratory heat losses. However, their calculations of tissue conductance were most likely confounded by large reductions in skin temperature (−2.5°C) in the high altitude conditions as a result of the greater evaporative efficiency from high air velocities and actual peripheral blood flow was not measured.

In support of Greenleaf et al. (21), Miyagawa et al. (45) reported lower forearm blood flow (FBF) during hypoxic exercise in the heat (30°C, 50% RH) compared with normoxia; however, other studies have also reported no effect (51) or greater (5, 53, 56) cutaneous blood flow during hypoxic exposures. Rowell et al. (51) measured FBF during normothermic exercise and found no effect of hypoxia ($F_{I_{O_2}} = 0.12$), while Black and Roddie (5) and Sagawa et al. (53) both observed a greater FBF during passive hypoxic exposures. More recently, Simmons et al. (56) used laser-Doppler flowmetry (LDF) to directly measure SkBF on the forearm and found that CVC was higher during passive exposure to isocapnic hypoxia in normothermia. Lawley et al. (36) confirmed these findings in local heating (44°C) of the forearm during prolonged hypoxia exposure (9 h; $F_{I_{O_2}} = 0.12$). Alternatively, Low et al. (38) recently demonstrated the potential for regional differences in the measurement of SkBF during passive exposure to heat and hypoxia ($F_{I_{O_2}} = 0.13$). Using LDF, they reported no effect of hypoxia on CVC at the chest and lower CVC during hypoxia on the forearm. Ultimately, LSR in their study were unaffected by hypoxia, and core temperature was not compromised by possible reductions in CVC on the forearm during whole body heating.

The current study, which was apparently the most strenuous combination of hypoxia ($F_{I_{O_2}} = 0.13$) and exercise-heat stress (34.5°C, 46% RH) performed to date, also observed a potentially higher steady-state $\%CVC_{max}$ on the forearm and upper back in hypoxia compared with normoxia at a fixed H_{prod} (Fig. 4). It has previously been suggested that cutaneous blood flow is determined by the rate of heat production (17); therefore, differences in CVC between fixed H_{prod} trials (NORM vs. HYP1) might indicate an independent role of hypoxia in the regulation of SkBF. This lends partial support to the results of Simmons et al. (56) and Lawley et al. (36) and suggests a potential vasodilatory effect of hypoxia during exercise in the heat. However, it must be noted that CVC values in AU were not different between trials (Fig. 4). Mathematically, $\%CVC_{max}$ in the current study was probably higher primarily as a result of lower average maximum CVC values in HYP1 compared with NORM, but maximum CVC values in HYP2 were similar to NORM (Fig. 4), which indicates that the possible difference in maximum CVC values between NORM and HYP1 was not consistently driven by hypoxia. Several studies have suggested potential implications for heat dissipation from the skin when skin blood flow is altered (25, 30, 45, 55, 56); however, our current results demonstrate that this was not translated to differences in sweating or skin or core temperatures (Fig. 1). Although supraphysiological reductions in skin blood flow impair local sweat rates during passive heating (60), physiologically relevant differences in skin blood flow (such as in the present study) may not be as important for thermoregulatory capacity given the small temperature gradient between the skin and environment unless sweating is altered, which was not the case in the current study (Fig. 2).

Perspectives

Based on work from our research group over the last five years including the present study, it can be stated conclusively that relative exercise intensity ($\%\dot{V}O_{2peak}$) does not determine changes in core temperature (11, 12, 27). Our previous investigations used between-group designs, but the current study, using hypoxia, truly isolated the independent influence of $\%\dot{V}O_{2peak}$ within the same individual. Our previous studies have demonstrated that normalizing heat production for body mass eliminates systematic differences in core temperature that seem to arise from differences in body size (11). It has also been suggested that heat production relative to lean body mass might be a strong predictor of core temperature given the large "heat sink" effect of fat free mass (1, 19); however, we have recently provided evidence demonstrating that such an approach also leads to systematically different thermoregulatory responses (14).

While we demonstrated that thermoregulatory responses are not influenced by relative exercise intensity per se, that is not to say that there is no effect of physical training, which itself has the potential to induce partial acclimation. Any heat-related adaptations that may accompany training or repeated elevations in core temperature or sustained sweating may augment heat dissipation and therefore thermoregulatory capacity, particularly in hot and uncompensable conditions. The current study was performed in compensable conditions, so if an influence of relative exercise intensity exists on the upper limits of heat loss it would not have been observed.

Conclusions

This study isolated the independent influence of hypoxia on thermoregulatory responses to exercise in hot conditions and determined that acute hypoxia does not alter thermoregulatory control. It was also conclusively demonstrated that there is no within-subject influence of relative exercise intensity on changes in core temperature or sweating responses independently of heat production. Exercise set at a fixed $\%\dot{V}O_{2peak}$ led to systematic differences in core temperature and local sweat rates. On the other hand, exercise set at a fixed H_{prod} and E_{req} eliminated systematic differences in thermoregulatory responses, irrespective of large differences in $\%\dot{V}O_{2peak}$.

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DISCLOSURES

The authors declare no conflicts of interest, financial or otherwise.

AUTHOR CONTRIBUTIONS

G.B.C., P.I., and O.J. conceived and designed experiments; G.B.C., M.N.C., and N.R. performed experiments; G.B.C. analyzed data; G.B.C., M.N.C., N.R., P.I., and O.J. interpreted data; G.B.C drafted manuscript; G.B.C., N.R., M.N.C., P.I., and O.J. edited, revised, and approved final draft of the manuscript.

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APPENDIX G: Influence of body morphology during uncompensable heat stress

Physiological Reports

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ORIGINAL RESEARCH

The optimal exercise intensity for the unbiased comparison of thermoregulatory responses between groups unmatched for body size during uncompensable heat stress

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Keywords
Body morphology, core temperature, evaporation, hyperthermia, sweating.

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Abstract

We sought to identify the appropriate exercise intensity for unbiased comparisons of changes in rectal temperature (ΔT_{re}) and local sweat rates (LSR) between groups unmatched for body size during uncompensable heat stress. Sixteen males vastly different in body morphology were separated into two equal groups [small (SM): 65.8 ± 6.2 kg, 1.8 ± 0.1 m^2; large (LG): 100.0 ± 13.1 kg, 2.3 ± 0.1 m^2], but matched for sudomotor thermosensitivity (SM: 1.3 ± 0.6; LG: 1.1 ± 0.4 $mg \cdot cm^{-2} \cdot min^{-1} \cdot °C^{-1}$). The maximum potential for evaporation (E_{max}) for each participant was assessed using an incremental humidity protocol. On separate occasions, participants then completed 60 min of cycling in a 35°C and 70% RH environment at (1) 50% of VO_{2max}, (2) a heat production (H_{prod}) of 520 W, (3) H_{prod} relative to mass (6 $W \cdot kg^{-1}$), and (4) H_{prod} relative to mass above E_{max} (3 $W \cdot kg^{-1} > E_{max}$). E_{max} was similar between LG (347 ± 39 W, 154 ± 15 $W \cdot m^{-2}$) and SM (313 ± 63 W, 176 ± 34 $W \cdot m^{-2}$, $P > 0.12$). ΔT_{re} was greater in SM compared to LG at 520 W (SM: 1.5 ± 0.5; LG 0.8 ± 0.3°C, $P < 0.001$) and at 50% of VO_{2max} (SM: 1.4 ± 0.5; LG 0.9 ± 0.3°C, $P < 0.001$). However, ΔT_{re} was similar between groups when H_{prod} was either 6 $W \cdot kg^{-1}$ (SM: 0.9 ± 0.3; LG 0.9 ± 0.2°C, $P = 0.98$) and 3 $W \cdot kg^{-1} > E_{max}$ (SM: 1.4 ± 0.5; LG 1.3 ± 0.4°C, $P = 0.99$). LSR was similar between LG and SM irrespective of condition, suggesting maximum LSR was attained (SM: 1.10 ± 0.23; LG: 1.07 ± 0.35 $mg \cdot cm^{-2} \cdot min^{-1}$, $P = 0.50$). In conclusion, systematic differences in ΔT_{re} and LSR between groups unmatched for body size during uncompensable heat stress can be avoided by a fixed H_{prod} in $W \cdot kg^{-1}$ or $W \cdot kg^{-1} > E_{max}$.

Introduction

Assessing the influence of factors such as disease (Baker 2002; Davis et al. 2010; Benda et al. 2016) and injury (Petrofsky 1992; Crandall and Davis 2010; Pritchett et al. 2015) on the physiological capacity to regulate internal body temperature during exercise in hot and humid environments inevitably requires a comparison between independent (e.g., control and experimental) groups. If these participants are morphologically dissimilar, as is often the

case, selecting an exercise intensity that ensures no systematic differences in the change in core temperature and sweating due to factors associated with differences in body size and metabolic heat production (H_{prod}), is vital.

A recent series of studies from our laboratory has contributed to the development of a methodological framework for studies conducted under physiologically compensable conditions (i.e., temperate and relatively dry; ~25°C, <40% RH). Specifically, for comparisons of changes in core temperature, irrespective of maximum aerobic capacity (VO_{2max}) – between ~35 to 65 $mL \cdot kg^{-1} \cdot min^{-1}$ (Jay et al. 2011), body mass and body surface area (Cramer and Jay 2014), cycling efficiency (Jay et al. 2011; Cramer and Jay 2014) or running economy (Smoljanić et al. 2014), an exercise intensity should be chosen to elicit a fixed H_{prod} per unit total body mass (in $W \cdot kg^{-1}$). However, it is presently not known whether this approach is transferable to uncompensable heat stress conditions whereby independently of mass, the major determinant of heat loss capacity is the maximum rate of evaporation (E_{max}), which is ultimately limited by the absolute body surface area (BSA) that can be saturated with sweat.

Indeed, in uncompensable conditions a fixed H_{prod} in $W \cdot kg^{-1}$ of total body mass may systematically induce greater changes in core temperature in larger individuals secondary to their lower surface area-to-body mass ratio. That is, the H_{prod} in $W \cdot kg^{-1}$ at the limit of physiological compensation will be lower in a larger person, therefore, the rate of heat storage per unit mass (and therefore theoretically their rate of rise of core temperature) will be greater at fixed levels of H_{prod} in $W \cdot kg^{-1}$ in uncompensable environments. It follows that a fixed H_{prod} in $W \cdot kg^{-1}$ of total body weight at a level above each individual's limit of physiological compensation (i.e., $W \cdot kg^{-1} > E_{max}$) may be the optimal method for prescribing exercise intensity for between-group experimental designs. However, a fixed relative exercise intensity ($\%VO_{2max}$) has been traditionally favoured for such comparisons (Saltin and Hermansen 1966; Davies et al. 1976; Greenhaff 1989), whereas more recently a fixed absolute workload (and therefore absolute H_{prod}) has also been recommended (Mora-Rodriguez 2012).

It is now well established that absolute E_{req} (in W, (Gagnon et al. 2013)) and E_{req} relative to BSA (in $W \cdot m^{-2}$, (Cramer and Jay 2014)) primarily determine whole-body sweat rate (WBSR) and local sweat rate (LSR) in compensable conditions, respectively. In an uncompensable environment where progressive hyperthermia develops, LSR will be determined by the elevation in internal body temperature, eventually reaching a maximum (Davies 1979; Machado-Moreira et al. 2008). However, the same maximum LSR between two people of different body sizes will theoretically lead to a greater WBSR in the larger individual.

Similar to our previous work in compensable conditions (Jay et al. 2011; Cramer and Jay 2014), the aim of this study was to identify the optimal exercise intensity to eliminate inherent bias due to biophysical factors for the comparison of time-dependent changes in core temperature and sweating between groups of unequal body size during uncompensable heat stress. We compared the thermoregulatory responses of two groups differing greatly in body mass and BSA-to-mass ratio (large (LG), small (SM)) but matched for age, sex, operational parameters for the physiological control of sweating (i.e., thermosensitivity), and maximum rate of evaporation per unit BSA (i.e., E_{max}) during exercise in a hot and humid (i.e., T_a: 36°C; RH: 70%) environment. The LG and SM groups exercised at four different intensities: (1) a fixed H_{prod} per unit mass of 6 $W \cdot kg^{-1}$; (2) a fixed H_{prod} per unit mass above E_{max} of 3 $W \cdot kg^{-1} > E_{max}$; (3) a relative intensity of $50\%VO_{2max}$; and (4) an absolute H_{prod} of 520 W. It was hypothesized that H_{prod} per unit mass at a fixed level above E_{max} (i.e., $W \cdot kg^{-1} > E_{max}$) would yield similar changes in core temperature despite large differences in body mass and BSA-to-mass ratio, while systematic differences between LG and SM groups related to biophysical factors would be observed with exercise intensity prescribed at a fixed H_{prod} in W, $W \cdot kg^{-1}$ and $\%VO_{2max}$. It was also hypothesized that a same maximum LSR would be observed in both groups irrespective of the exercise intensity, and thus a greater WBSR in the LG group.

Methods

Participants

Ethical approval was obtained from the University of Ottawa Health Sciences Research Ethics Board (H12-11-05) conforming to the principles set forth in the Declaration of Helsinki 2013. All volunteers gave both verbal and written consent prior to any preliminary and experimental trials, and were required to fill out a Physical Activity Readiness Questionnaire and an American Heart Association Pre-Participation Screening Questionnaire.

A power calculation with G*Power (3.1.9.2) using α- and β- values set to 0.05 and 0.95, respectively, determined that a sample size of 16 subjects (eight per group) was required to report a significant difference between ΔT_{re} in two groups different in mass (~20 kg) following 60 min of exercise at 500 W of H_{prod} with a mean between-group difference of 0.5°C and a standard deviation of 0.2°C (Cramer and Jay 2014). A total of sixteen men separated equally into two groups (8 large, LG; 8

Table 1. Mean participant physical characteristics.

	Age (years)	Mass (kg)	BSA (m^2)	BSA/mass ($cm^2 \cdot kg^{-1}$)	Body fat (%)	VO_{2max} ($ml \cdot kg^{-1} \cdot min^{-1}$)
SM	25 ± 5	65.8 ± 6.2	1.8 ± 0.1	271 ± 17	12.3 ± 3.5	54.7 ± 4.6*
LG	25 ± 3	100.0 ± 13.1*	2.3 ± 0.1*	226 ± 17*	24.9 ± 8.2*	38.5 ± 9.0

LG, large body size group; SM, small body size group; BSA, body surface area; VO_{2max} maximum rate of oxygen uptake.
*Significant difference ($P < 0.05$).

small, SM) with a mean difference in body mass and BSA (estimated using the DuBois & DuBois equation (1916)) of ~30 kg and ~0.4 m^2, respectively (Table 1), participated in the study. Groups were matched for age, but not aerobic fitness to ensure differences in $\%VO_{2max}$ in trials with H_{prod} divisible by total body mass.

Preliminary session

Participants performed a preliminary session during which anthropometry and maximal aerobic capacity were assessed. Height and weight were also measured using a wall-mounted stadiometer (HR-200, Tanita, Arlington Heights, IL) and digital scale (BWB-800, Tanita, Arlington Heights, IL), respectively. Body composition was measured by dual-energy x-ray absorptiometry (GE-LUNAR Prodigy module, GE Medical Systems, Madison, WI). Aerobic fitness (VO_{2max}) was assessed using an incremental exercise test to exhaustion on an upright cycle ergometer (Kettler ErgoRace, Virginia Beach, VA) in accordance with guidelines from the Canadian Society of Exercise Physiology (CSEP, 1996). Following a self-paced warmup and at least 10-minute rest period, the protocol commenced with an external workload of 80 W that increased at a rate of 20 $W \cdot min^{-1}$ until physical or volitional exhaustion. Expired gases were measured via breath-by-breath indirect calorimetry using a metabolic cart (Vmax Encore, Care Fusion, Yorba Linda, CA).

Experimental design

Prior to all experimental sessions, participants were asked to abstain from alcohol, caffeine, and strenuous exercise for at least 12 h. In addition, they were asked to eat a light meal and drink ~500 mL of water 2 h before arrival. Experimental trials were conducted at the same time of day and separated by 48 h to eliminate any influence of circadian variation. Participants first completed the E_{max} assessment (described below) followed by the remaining four experimental trials in a counter-balanced order (i. 50% of VO_{2max}; ii. fixed H_{prod} of 520 W; iii. fixed H_{prod} of 6 $W \cdot kg^{-1}$; iv. fixed H_{prod} of 3 $W \cdot kg^{-1} > E_{max}$).

Instrumentation

Ambient temperature and absolute humidity were measured using a dew point mirror (473 RH Systems, Albuquerque, NM). Rectal temperature (T_{re}) and oesophageal temperature (T_{es}) were measured using paediatric grade thermistor probes (Mon-a-therm®, Mallinckrodt Medical, St. Louis, MO). The T_{re} probe was inserted to a depth of 20 cm past the anal sphincter and the T_{es} probe was inserted 40 cm through the nasal cavity into the oesophagus, estimated to be the region close to the left ventricle (Mekjavic and Rempel 1990). Four surface thermistors (Concept Engineering, Old Saybrook, CT) were affixed to the skin using surgical tape (Transpore®, 3M, London, ON). Mean skin temperature (T_{sk}) was calculated using the Ramanathan weighting coefficients (Ramanathan 1964): chest 30%, triceps 30%, thigh 20%, and calf 20%. All thermometric measures were sampled every 5 sec (NI cDAQ-91722 module, National Instruments, Austin, TX) and displayed in real-time on a desktop computer using customized LabView software (v7.0, National Instruments, Austin, TX).

Local sweat rates (LSR) of the upper back (inferior to the scapular spine and ~5 cm from the axilla) and forearm (midpoint of the anterior distal segment) were measured using ventilated sweat capsules. Anhydrous air was supplied to each 4.1-cm^2 capsule at a continuous flow rate of 1.00 L min^{-1} and 0.83 L min^{-1} for back and forearm, respectively (Omega FMA-A2307, Omega Engineering, Stamford, CT). Capsules were secured to the skin using skin glue (Collodion USP MD0002, Mavidon, Lake Worth, FL) and additional surgical tape. The temperature and humidity of outflowing air from the capsules were measured every 5 sec using factory-calibrated capacitance hygrometers (HMT333, Vaisala, Vantaa, Finland). Local sweat rate of the back and forearm were then calculated as the product of absolute humidity and flow rate, and expressed relative to the area under the capsule in milligrams per square centimetre per minute ($mg \cdot cm^{-2} \cdot min^{-1}$) and averaged between sites (LSR_{mean}). Sudomotor thermosensitivity was determined for each individual trial using linear regression of 1-min averages

of the change in mean body temperature (ΔT_b) calculated as a weighted average between T_{es} (80%) and T_{sk} (20%) (Vieth 1989; Cheuvront et al. 2009) with LSR_{mean}.

Protocol

Participants provided a urine sample immediately prior to all experimental trials. A refractometer (Reichert TS 400, Depew, NY) measured urine specific gravity (USG) and the cut-off value of greater than 1.025 was used to ensure pre-exercise euhydration (Kenefick and Cheuvront 2012). Participants where then given a pair of standardized running shorts and non-absorbent sandals to wear and inserted the T_{re} probe. Next, an initial body mass measurement was taken which was used to calculate the appropriate H_{prod} for exercise intensities fixed relative to body mass. Prior to entering the climatic chamber, a T_{es} probe was inserted and the two ventilated sweat capsules were affixed to the skin. Participants then entered the climate chamber where the remaining instrumentation was completed. Thirty minutes of rest then followed to equilibrate with the environment.

Experimental trial 1 (E_{max} Assessment)

We used an incremental humidity protocol first described by Kamon and Belding (1971) and subsequently revised and refined first by Kamon and Avellini (1976, 1979) and later by Kenney et al. (1993), Kenney and Zeman (2002), and Dougherty et al. (2009) to minimize trial duration and the number of tests required. The climate chamber was initially maintained at baseline conditions of 36.1 ± 0.3°C and 39.0 ± 1.8%RH (2.3 ± 0.1 kPa) with a fixed air velocity of 1.2 $m \cdot s^{-1}$. Participants began exercising on an upright cycle ergometer at a fixed external work rate of 100 W. After 30 min of exercise by which time a steady-state core temperature (and therefore presumably heat balance) had been reached, ambient vapour pressure was increased at a rate of 0.3 kPa (~5%RH) every 7.5 min in a stepwise fashion for up to 45 min, while ambient temperature remained fixed. E_{max} was derived using the absolute humidity at which an upward inflection in T_{es} was observed (Fig. 1) indicating a transition from a compensable (defined as a rate of rise in T_{es} of 0.1°C·15 min^{-1}) to an uncompensable condition. To verify this transition, participants continued to cycle for at least another 10 min (while ambient vapour pressure continued to increase) following the inflection of T_{es} to ensure T_{es} continued to rise. The critical absolute humidity at which this T_{es} inflection occurred was then objectively determined using segmental linear regression (Ravanelli et al. 2015) from the 30th min of exercise. One participant in the LG group was unable to insert a T_{es} thermistor, thus, his E_{max} was assumed to be equal to the mean of the LG group.

Experimental trials 2 to 5

For all remaining experimental trials, the environmental conditions were maintained at 36.2 ± 0.2°C and 69.7 ± 1.3%RH throughout. Following 30 min of rest, participants began exercising at one of the four predetermined exercise intensities for up to 75 min. All exercise sessions were at least 45 min; with early termination due to either volitional exhaustion (n = 12 of 64 trials) or T_{re} exceeding 39.5°C (n = 2 of 64 trials). The minimum exercise duration for each condition was 50 min for 50% VO_{2max} (SM: 70.6 ± 8.2 min, LG: 68.4 ± 9.4 min), 55 min for 520 W (SM: 68.8 ± 8.8 min, LG: 68.4 ± 9.4 min), and 45 mins for both 6 $W \cdot kg^{-1}$ (SM: 75 ± 0 min, LG: 67.5 ± 11.3 min) and 3 $W \cdot kg^{-1}$ > E_{max} (SM: 73.1 ± 5.3 min, LG: 65.6 ± 13.7 min). By design, some exercise intensities were equal to other conditions for some participants (i.e., 520 W was the equivalent of 6 $W \cdot kg^{-1}$ for LG). Core temperature (T_{re}), mean skin temperature (T_{sk}), and LSR were measured throughout the trial, while T_{es} was only measured for first 20 min of

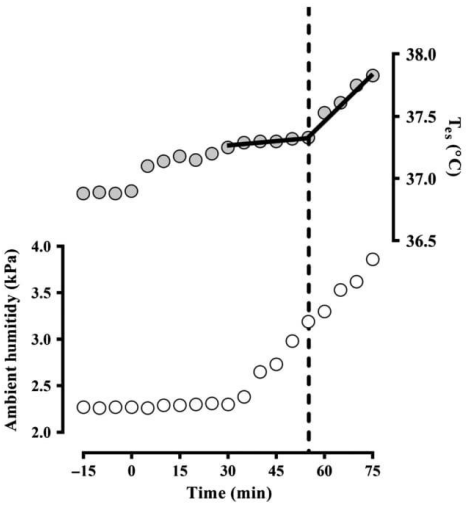

Figure 1. Example of method used to determine *K* coefficient from E_{max} assessment trial using segmental linear regression to assess the upward rise in oesophageal temperature (T_{es}). The slope of first segment was constricted such that it did not exceed a rate of change in T_{es} equivalent to 0.1°C·15 min^{-1}. Heat balance parameters coinciding with the point of inflection are used to derive K (Equation 8).

exercise to determine sudomotor thermosensitivity. Immediately before and after exercise, nude (unclothed but instrumented) body mass was measured in triplicate using a balance scale (Combics 2, Sartorius, Mississauga, ON, Canada); instrument wires were taped to an adjacent stand in an identical way for all measurements. The difference between pre- and post body mass (assumed to be total sweat loss) was divided by the time elapsed between the two measurements and expressed as WBSR in $g{\cdot}h^{-1}$.

Calculations

The evaporative requirement to maintain heat balance (E_{req}) in $W{\cdot}m^{-2}$ was estimated by rearranging the conceptual heat balance equation:

$$E_{req} = H_{prod} - \left(H_{dry} + H_{res}\right)\left[W \cdot m^{-2}\right] \quad (1)$$

The rate of metabolic heat production (H_{prod}) was calculated by subtracting the rate of external work regulated by the cycle ergometer (in W) from metabolic energy expenditure (M). M was estimated using the following equation (Nishi 1981):

$$M = \dot{V}O_2 \frac{\left(\left(\frac{RER-0.7}{0.3}\right)e_c\right) + \left(\left(\frac{1.0-RER}{0.3}\right)e_f\right)}{60 \cdot A_D} \cdot 1000\left[W \cdot m^{-2}\right] \quad (2)$$

Where: $\dot{V}O_2$ is the rate of oxygen consumption (L/min), e_c is the caloric equivalent per litre of oxygen for the oxidation of carbohydrates (21.13 kJ per L of O_2 consumed), e_f is the caloric equivalent per litre of oxygen for the oxidation of lipids (19.62 kJ per L of O_2 consumed), and respiratory exchange ratio (RER) is the ratio of carbon dioxide production and oxygen consumption (VCO_2/VO_2).

The rate of dry heat loss (H_{dry}) via convection and radiation is primarily governed by the temperature gradient between skin (T_{sk}) and air (T_a) and mean radiant (T_r) temperature, respectively. By design, the conditions of this study were selected to ensure a very small T_{sk}-T_a/T_r gradient (i.e., $T_a \approx T_{sk}$; and assuming $T_a = T_r$) so that absolute error associated with estimating dry clothing insulation and whole-body air velocity was minimized. Nevertheless, even though H_{dry} was not greater than 15 $W{\cdot}m^{-2}$ at any point for any participant, values were still calculated using the standard approach detailed in the literature (Parsons 2002).

The rate of respiratory heat loss (H_{res}) was estimated using the following:

$$H_{res} = 0.0173 \cdot \left(H_{prod}\right) \cdot (5.87 - P_a) + 0.0014 \cdot \left(H_{prod}\right) \cdot (34 - T_a)\left[W \cdot m^{-2}\right] \quad (3)$$

Where: P_a was the ambient vapour pressure (in kPa), and T_a was the ambient temperature (in °C).

Determining E_{max} (from Experimental trial 1)

The maximum rate of evaporation (E_{max}) is equal to:

$$E_{max} = \omega_{max}\left(P_{sk,s} - P_a\right)/\left(R_{e,cl} + [1/h_e * f_{cl}]\right)\left[W \cdot m^{-2}\right] \quad (4)$$

Where: ω_{max} is the maximum skin wettedness (Gagge 1937), which can theoretically range from 0.85 (or lower) to 1.00 (Candas et al. 1979b); P_a is the absolute ambient vapour pressure at E_{max} (in kPa), which is equal to P_{crit} measured in experimental trial 1 (Fig. 1). $P_{sk,s}$ (in kPa) was the saturated water vapour pressure at skin temperature and was derived using Antoine's equation:

$$P_{sk,s} = (\exp(18.956 - [4030.18/(T_{sk} + 235)]))/10[kPa] \quad (5)$$

Where: T_{sk} is mean skin temperature (°C).

$R_{e,cl}$ is the evaporative heat transfer resistance of the clothing ensemble in $kPa{\cdot}m^2{\cdot}W^{-1}$, which must be measured using a sweating thermal manikin or estimated from standardized tables (Oohori et al. 1984; Parsons 2002); f_{cl} is the clothing area factor (surface area of the clothed body divided by the surface area of the nude body; ND), which is estimated using the dry heat transfer resistance (Holmér et al. 1999; Parsons et al. 1999; Parsons 2002), which itself must be either measured using a hot plate or manikin, or estimated from tables; and h_e is the evaporative heat transfer coefficient in $W{\cdot}m^{-2}{\cdot}kPa^{-1}$ that is derived directly from the convective heat transfer coefficient which itself is dependent on an accurate measurement of whole-body air velocity.

To overcome these substantial limitations we defined E_{max} for each participant using a humidity ramp protocol in Experimental trial 1. The boundary of compensability is, by definition, the point at which E_{max} is equal to E_{req}. Thus, at the critical ambient vapour pressure point at which an inflection in T_{es} was observed (P_{crit}; Fig. 1), E_{max} can be substituted for E_{req}, therefore:

$$E_{req} = \omega_{max}\left(P_{s,sk} - P_{crit}\right)/\left(R_{e,cl} + [1/h_e * f_{cl}]\right)\left[W \cdot m^{-2}\right] \quad (6)$$

While one could estimate or measure ω_{max}, $R_{e,cl}$, h_e, and f_{cl}, any inaccuracies may be amplified. However, ω_{max}, $R_{e,cl}$, h_e, and f_{cl} can be combined into a single coefficient (K) for estimating E_{max} for our fixed experimental conditions, giving:

$$E_{req} = K\left(P_{sk,s} - P_{crit}\right) \quad (7)$$

And K can be derived for each individual using three directly measured variables from Experimental trial 1:

$$K = E_{req}/(P_{sk,s} - P_{crit})[ND] \quad (8)$$

Each individual K value (which was a combined term incorporating individual's ω_{max}, $R_{e,cl}$, h_e, and f_{cl} values) was then used to determine their predicted individual E_{max} value under the fixed environmental conditions (36°C, 70% RH with identical air velocity, clothing, and exercise mode to trial 1) in Experimental trials 2 to 5, using:

$$E_{max} = K(5.60-4.16) \quad (9)$$

Where: 5.60 (kPa) is the saturated water vapour pressure at the anticipated T_{sk} based on the inflection trial (35°C; (Alber-Wallerström 1985)); and 4.16 (kPa) is the ambient vapour pressure (70% RH at 36°C). The E_{max} value was then converted from $W{\cdot}m^{-2}$ to $W{\cdot}kg^{-1}$, and the H_{prod} for the 3 $W{\cdot}kg^{-1}$>E_{max} trial for each individual was determined.

Statistical analysis

All data are expressed as a mean with standard deviation (mean ± SD). Independent samples t-tests compared SM and LG for participant characteristics, K, E_{max}, H_{prod}, % VO_{2max}, WBSR, and sudomotor thermosensitivities. Two-way mixed analyses of variance (ANOVA) were used to compare 1-min averages of ΔT_{re}, ΔT_{sk}, and LSR with the repeated factor of time (7 levels: 0, 10, 20, 30, 40, 50, and 60 min) and the nonrepeated factor of body size (two levels: SM and LG) for experimental trials 2-5. In the case of a significant interaction, differences between groups were assessed using independent sample t-tests with a Holm-Bonferroni correction. All statistical analyses were conducted using GraphPad Prism Version 6.0 for Windows (Graphpad Software, La Jolla, CA).

Results

Participant characteristics

By design, a greater body mass ($P < 0.001$) and BSA ($P < 0.001$) were observed in the LG group (Table 1), whereas, a higher VO_{2max} ($P = 0.001$), BSA-to-mass ratio ($P < 0.001$), and lower body fat percentage ($P = 0.003$) were observed in the SM group (Table 1). No differences in USG ($P = 0.93$) were observed between SM (1.013 ± 0.006) and LG (1.012 ± 0.007) prior to all experimental sessions.

E_{max} assessment

The incremental humidity protocol in experimental trial 1 yielded similar P_{crit} values between groups (SM: 3.18 ± 0.35 kPa; LG: 3.00 ± 0.30 kPa, $P = 0.33$), and thus similar ($P = 0.12$) derived K coefficient values (Table 2), which were then utilized to derive E_{max} values under the fixed environmental conditions (36°C, 70% RH) in experimental trials 2-5. These estimated E_{max} values (Table 2) were similar when expressed in absolute terms (i.e., in W; $P = 0.22$) and relative to surface area (i.e., in $W{\cdot}m^{-2}$; $P = 0.12$). However as expected, due to differences in BSA-to-mass ratio between groups lower E_{max} values were observed in the LG group when expressed relative to body mass (i.e., in $W{\cdot}kg^{-1}$; $P = 0.006$).

Core and skin temperatures

The change in T_{re} (Fig. 2) was greater from 20 min onwards in the SM compared to LG group at both 50% of VO_{2max} ($P < 0.001$) and 520 W absolute H_{prod} ($P < 0.001$). In parallel, H_{prod} in $W{\cdot}kg^{-1}$ and $W{\cdot}kg^{-1}$>E_{max} was greater in the SM compared to the LG group at 50% of VO_{2max} ($P < 0.05$) and 520 W of H_{prod} ($P < 0.05$). In contrast, no differences were observed for the change in T_{re} between SM and LG at a H_{prod} of 6 $W{\cdot}kg^{-1}$ ($P = 0.88$) or 3 $W{\cdot}kg^{-1}$>E_{max} ($P = 0.92$). In addition, the change in T_{sk} was greater over time in LG compared to SM at a H_{prod} of 6 $W{\cdot}kg^{-1}$ ($P < 0.05$), while all other exercise intensities (50% VO_{2max}, 520 W, and 3 $W{\cdot}kg^{-1}$>E_{max}) yielded similar changes in T_{sk} between groups (Fig. 3).

Whole-body sweating

WBSR was similar between groups at 50% VO_{2max} (SM: 903 ± 362 $g{\cdot}h^{-1}$; LG: 855 ± 174 $g{\cdot}h^{-1}$, $P = 0.74$), 520 W (SM: 890 ± 368 $g{\cdot}h^{-1}$; LG: 857 ± 175 $g{\cdot}h^{-1}$, $P = 0.82$), 6 $W{\cdot}kg^{-1}$ (SM: 713 ± 192 $g{\cdot}h^{-1}$; LG: 871 ± 208 $g{\cdot}h^{-1}$, $P = 0.14$), or 3 $W{\cdot}kg^{-1}$>E_{max} (SM: 872 ± 362 $g{\cdot}h^{-1}$; LG: 892 ± 210 $g{\cdot}h^{-1}$, $P = 0.89$). Despite similar WBSR, E_{req} (in W) was greater in LG compared to SM at 50% VO_{2max} (SM: 531 ± 26 W; LG: 580 ± 54 W, $P = 0.04$), 6 $W{\cdot}kg^{-1}$ (SM: 408 ± 34 W; LG: 594 ± 65 W, $P < 0.001$), and 3 $W{\cdot}kg^{-1}$>E_{max} (SM:

Table 2. Mean E_{max} assessment characteristics.

		E_{max} at 36°C 70% RH		
	K coefficient	W	$W{\cdot}m^{-2}$	$W{\cdot}kg^{-1}$
SM	126.0 ± 24.3	322 ± 65	181 ± 34	4.9 ± 1.1*
LG	110.3 ± 11.1	357 ± 40	158 ± 15	3.6 ± 0.4

LG, large body morphology group; **SM**, small body morphology group; **E_{max}**, Maximum evaporative potential. Significantly greater than LG group ($P < 0.05$).

50% VO_{2max}

	$\dot{H}_{prod}$ W	$\dot{H}_{prod}$ W·kg^{-1}	$\dot{H}_{prod}$ W·kg^{-1}>E_{max}	%VO_{2max}
SM	527±27	8.0±0.5*	2.9±0.8*	50.8±3.4
LG	571±58	5.8±0.9	2.1±0.6	50.9±8.4

520 W

	$\dot{H}_{prod}$ W	$\dot{H}_{prod}$ W·kg^{-1}	$\dot{H}_{prod}$ W·kg^{-1}>E_{max}	%VO_{2max}
SM	523±15	8.0±0.6*	3.0±1.0*	50.7±6.2
LG	538±16	5.4±0.6	1.8±0.5	49.0±9.5

6 W·kg^{-1}

	$\dot{H}_{prod}$ W	$\dot{H}_{prod}$ W·kg^{-1}	$\dot{H}_{prod}$ W·kg^{-1}>E_{max}	%VO_{2max}
SM	392±33	5.9±0.4	1.2±0.7	36.7±3.5
LG	582±71*	5.8±0.3	2.2±0.5*	53.1±11.4*

3 W·kg^{-1}>E_{max}

	$\dot{H}_{prod}$ W	$\dot{H}_{prod}$ W·kg^{-1}	$\dot{H}_{prod}$ W·kg^{-1}>E_{max}	%VO_{2max}
SM	513±74	7.8±1.0*	2.7±0.4	48.3±5.9
LG	641±86*	6.5±0.4	2.6±0.2	58.4±10.9*

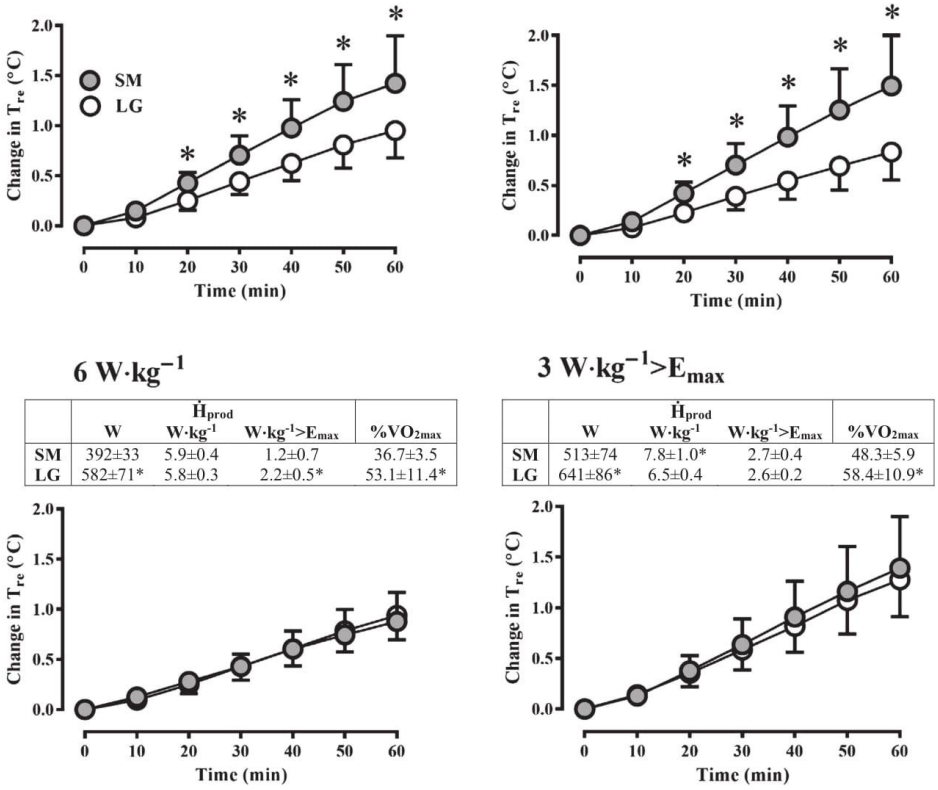

Figure 2. The mean change in rectal temperature (T_{re}) of the small (SM) and large (LG) group over time during exercise at 50%VO_{2max} (top-left), 520 W of heat production (H_{prod}; top-right), 6 W·kg^{-1} (bottom-left), and 3 W·kg^{-1}>E_{max} (bottom-right). The table above each panel displays mean H_{prod} expressed in absolute W, relative to body mass (W·kg^{-1}), relative to body mass above maximum evaporative potential (E_{max}), and %VO_{2max}. *Significant difference ($P < 0.05$).

519 ± 67 g·h^{-1}; LG: 642 ± 78, $P < 0.001$). By design, E_{req} was similar between SM and LG at 520 W (SM: 535 ± 16 W; LG: 548 ± 11 W, $P = 0.12$).

Local sweating

LSR was greater at the onset of exercise in LG compared to SM at 520 W (SM: 0.29 ± 0.07 mg·cm^{-2}·min^{-1}; LG: 0.49 ± 0.22 mg·cm^{-2}·min^{-1}, $P = 0.03$), with a trend for a greater LSR observed in LG at 50% of VO_{2max} (SM: 0.30 ± 0.07 mg·cm^{-2}·min^{-1}; LG: 0.46 ± 0.23 mg·cm^{-2}·min^{-1}, $P = 0.08$), 6 W·kg^{-1} (SM: 0.32 ± 0.08 mg·cm^{-2}·min^{-1}; LG: 0.48 ± 0.22 mg·cm^{-2}·min^{-1}, $P = 0.08$), and 3 W·kg^{-1}>E_{max} (SM: 0.32 ± 0.06 mg·cm^{-2}·min^{-1}; LG: 0.45 ± 0.23 mg·cm^{-2}·min^{-1}, $P = 0.10$). However, LSR from 10 min onwards was similar between groups at 50%

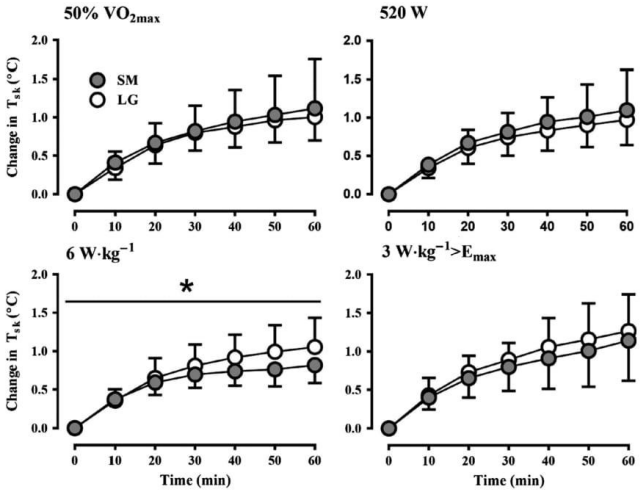

Figure 3. The mean change in skin temperature (T_{sk}) of the small (SM) and large (LG) group over time during exercise at 50%VO_{2max} (top-left), 520 W H_{prod} (top-right), 6 W·kg^{-1} H_{prod} (bottom-left), and 3 W·kg^{-1} H_{prod}>E_{max} (bottom-right). *Significant interaction (P = 0.01).

VO_{2max} (SM: 1.08 ± 0.28 mg·cm^{-2}·min^{-1}; LG: 1.09 ± 0.36 mg·cm^{-2}·min^{-1}, P = 0.97), 520 W (SM: 1.07 ± 0.29 mg·cm^{-2}·min^{-1}; LG: 1.05 ± 0.38, P = 0.95), 6 W·kg^{-1} (SM: 1.03 ± 0.20 mg·cm^{-2}·min^{-1}; LG: 1.03 ± 0.39 mg·cm^{-2}·min^{-1}, P = 0.99), and 3 W·kg^{-1} > E_{max} (SM: 1.21 ± 0.16 mg·cm^{-2}·min^{-1}; LG: 1.10 ± 0.30 mg·cm^{-2}·min^{-1}, P = 0.38). A similar LSR between LG and SM for both the forearm and upper back was observed for each condition. Meanwhile, values for E_{req} (in W·m^{-2}; relative to BSA) were greater in SM at 520 W (SM: 296 ± 13 W·m^{-2}; LG: 246 ± 13 W·m^{-2}, P < 0.001), 50% VO_{2max} (SM: 299 ± 12 W·m^{-2}; LG: 259 ± 29 W·m^{-2}, P = 0.003), and 6 W·kg^{-1} (SM: 229 ± 14 W·m^{-2}; LG: 265 ± 19 W·m^{-2}, P = 0.001), while a similar E_{req} was observed between groups at 3 W·kg^{-1}>E_{max} (SM: 292 ± 32 W·m^{-2}; LG: 286 ± 23 W·m^{-2}, P = 0.69).

LSR-T_b sensitivities

LSR-T_b sensitivity (Table 3) was similar between LG and SM at 50% VO_{2max} (P = 0.65), 520 W (P = 0.51), 6 W·kg^{-1} (P = 0.20) and 3 W·kg^{-1} > E_{max} (P = 0.51).

Discussion

This study demonstrates that in an uncompensable environment, large differences in body size independently leads to systematically different changes in core temperature during exercise at a fixed absolute H_{prod} in W. On the other hand, when exercise intensity is set to elicit the same H_{prod} in W·kg^{-1} of total body mass, any systematic difference in core temperature between LG and SM is eliminated; however, greater changes T_{sk} are observed in larger individuals. If exercise is conducted at a fixed H_{prod} in W·kg^{-1}>E_{max}, differences in both core temperature and T_{sk} between LG and SM are abolished. Exercise at a fixed 50% VO_{2max} resulted in much greater changes in core temperature in the SM group, as their H_{prod} per unit mass was greater secondary to their different VO_{2max}, which was higher in this study by design. Absolute E_{req} was similar at 520 W and different at all other intensities, while E_{req} in W·m^{-2} was only the same at 3 W·kg^{-1}>E_{max}. However, WBSR and LSR were similar

Table 3. Mean LSR thermosensitivity for LG and SM at each condition.

	Thermosensitivity (mg·cm^{-2}·min^{-1}·°C^{-1})			
	50% VO_{2max}	520 W	6 W·kg^{-1}	3 W·kg^{-1}>E_{max}
SM	1.3 ± 0.6	1.3 ± 0.6	1.4 ± 0.4	1.3 ± 06
LG	1.2 ± 0.4	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.4

LG, large body morphology group; **SM**, small body morphology group; **E_{max}**, Maximum evaporative potential.

between LG and SM at all intensities indicating maximum sweat rates were attained regardless of the uncompensable heat stress imposed. Collectively, the present data demonstrate that the methodological framework previously proposed by our group for performing unbiased comparisons of core temperature changes between independent groups in compensable conditions is largely transferable to uncompensable environments. However, for the assessment of local and whole-body sweating responses, our data indicate that once maximum sweat rates are reached the influence of the exercise intensity method used may be indistinguishable.

Core temperature

Although prescribing exercise intensity relative to an individual's VO_{2max} has been historically thought to normalize the putative effect of aerobic fitness on the exercise core temperature response (Saltin and Hermansen 1966; Davies et al. 1976; Greenhaff 1989), this approach does not yield similar changes in core temperature between groups differing in VO_{2max} during compensable heat stress when eliminating differences in body mass during cycle ergometry (Cramer and Jay 2014) and treadmill running (Smoljanić et al. 2014). For a given $\%VO_{2max}$, an aerobically fit individual will inevitably work at a greater H_{prod} per unit mass in comparison to an unfit person. Therefore, a greater change in core temperature should be observed in fitter individuals independently of body size (Mora-Rodriguez et al. 2010; Cramer et al. 2012). In this study, a greater rise in T_{re} was observed in the fitter SM group (Fig. 2) in the 50% VO_{2max} trial in parallel to a H_{prod} that was >2 $W{\cdot}kg^{-1}$ higher than the LG group. Meanwhile, when $\%VO_{2max}$ was different between groups in the 6 $W{\cdot}kg^{-1}$ and 3 $W{\cdot}kg^{-1}$>E_{max} trials, the rise in T_{re} was similar (Fig. 2). Taken together, these data further demonstrate that the use of a fixed relative intensity is unsuitable for assessing differences in core temperature changes between groups in an uncompensable environment.

Recent work from our laboratory has demonstrated that in compensable conditions, using a fixed H_{prod} in $W{\cdot}kg^{-1}$ of total body mass eliminates the systematic difference in ΔT_{re} observed at a fixed absolute H_{prod} in W between groups of different body sizes (Cramer and Jay 2014). In this study, the same systematic difference between LG and SM was expected and observed (Fig. 2) at a H_{prod} of 520 W. However, it was hypothesized that the utility of a fixed H_{prod} in $W{\cdot}kg^{-1}$ for fully eliminating systematic differences in ΔT_{re} may not fully translate to uncompensable conditions. In theory, even with a similar E_{max} in $W{\cdot}m^{-2}$ (Table 2), larger individuals who invariably have a lower BSA/mass ratio will have a lower E_{max} when expressed in $W{\cdot}kg^{-1}$. It follows that the H_{prod} in $W{\cdot}kg^{-1}$ needed to exceed E_{max} will thereby be lower in the LG group (Table 2). Thus, in an uncompensable environment a fixed H_{prod} in $W{\cdot}kg^{-1}$ would be expected to be *more* uncompensable (i.e., the gap between H_{prod} and E_{max} in $W{\cdot}kg^{-1}$ is wider) for a larger individual and therefore elicit a greater ΔT_{re} compared to a smaller person. It was therefore proposed that to account for this biophysical disparity in the degree of uncompensability between different body sizes exercise should be prescribed to elicit a fixed H_{prod} per unit mass *above* each individual's E_{max} (i.e., $W{\cdot}kg^{-1}$ >E_{max}). However, a similar ΔT_{re} was observed between LG and SM after 60 min of exercise in both the 6 $W{\cdot}kg^{-1}$ trial and the 3 $W{\cdot}kg^{-1}$>E_{max} trial (Fig. 2). These similar ΔT_{re} responses may be explained by the rather small difference in H_{prod} above E_{max} (~1 in $W{\cdot}kg^{-1}$ >E_{max}) between both groups despite a 45 $cm^2{\cdot}kg^{-1}$ difference in BSA/mass ratio in the 6 $W{\cdot}kg^{-1}$ trial. Nevertheless, a smaller ΔT_{sk} was observed in SM group in the 6 $W{\cdot}kg^{-1}$ condition (Fig. 3). Thus, to ensure no systematic bias when comparing changes in *both* core temperature and mean skin temperature during uncompensable heat stress, it is suggested that an exercise intensity that elicits a fixed H_{prod} above an individual's estimated E_{max} should be utilized. However, if changes in core temperature are the primary focus of a particular study, a fixed H_{prod} in $W{\cdot}kg^{-1}$ of total body mass can also be recommended. This latter approach is more straightforward as it does not require the somewhat complicated estimation (or measurement) of E_{max} for each individual.

The similar core temperature responses at fixed rates of heat production normalized for body mass between groups differing greatly in body size were observed despite a greater body fatness in the LG group (~25% vs. ~12%; Table 1). If body fatness provided an insulation effect, a greater rise in core temperature would have been expected in the LG group. Selkirk and McLellan (2001) reported a greater rise in core temperature in a trained higher adiposity group relative to a similarly trained lower adiposity group (~19% vs. ~11% body fat) with an ~10 kg smaller body mass from 40 min onwards during exercise at a similar heat production in $W{\cdot}kg^{-1}$. These opposing observations between studies may be due to stark differences in clothing. The participants in Selkirk and McLellan (2001) were likely closer to adiabatic in a semi impermeable protective ensemble than the semi-nude participants in this study. In a scenario with zero heat dissipation from the skin to the surrounding environment, it is possible that a lower mean specific heat capacity of the body, associated with greater body fatness, may exert a greater influence on the rise in core temperature.

Sweating

In order to identify the independent influence of body morphology on the time-dependent changes in thermoregulatory responses in an uncompensable environment it was ensured that LG and SM groups were similar in terms of their physiological control of sudomotor activity (i.e., thermosensitivity) and maximum capacity for evaporative heat loss when normalized to BSA (i.e., E_{max} in $W \cdot m^{-2}$). However, as hypothesized E_{max} was greater in the SM group when expressed relative to mass ($W \cdot kg^{-1}$) due to their greater BSA/mass ratio.

Under compensable conditions with 100% sweating efficiency, absolute E_{req} (in W) determines WBSR (Jay et al. 2011; Gagnon et al. 2013), and E_{req} (in $W \cdot m^{-2}$) primarily determines LSR (Cramer and Jay 2014), with some potential modification from very large differences in BSA/mass ratio (Notley et al. 2016). However, as the skin wettedness required for heat balance (i.e., proportion of BSA that must be saturated in sweat) increases, sweat efficiency declines (i.e., more sweat drips off the body) as a result of greater sweat rates for the attainment of heat balance (Candas et al. 1979a; Alber-Wallerström 1985). But, in an uncompensable heat stress situation once E_{req} exceeds E_{max} the rate of evaporative heat loss is essentially fixed even with different sweat rates. Nevertheless, greater sweating would still be expected with greater internal temperatures. We observed a similar WBSR and LSR between both groups in all conditions despite differences in E_{req} (in W and $W \cdot m^{-2}$) and ΔT_{re} in most conditions, which suggest maximum local sweat rates were attained. Theoretically, a similar LSR measured over a fixed surface area between two individuals differing greatly in BSA should result in a greater absolute WBSR (in $L \cdot h^{-1}$) in the larger individual as previously shown in compensable conditions with 100% sweating efficiency (Cramer and Jay 2014). The lack of dissociation between LSR and WBSR in this study is likely explained by the measurement methods and what they specifically represent; ventilated sweat capsules operate on the principle that complete evaporation occurs over a small surface area under the capsule, whereas the evaporation of sweat for a WBSR measurement is directly dependent on the ambient environment. Thus, decrements in sweating efficiency will not be observed under a capsule, even if sweating efficiency is greatly reduced over the rest of the body. In support, Gonzalez et al. (1974) demonstrated a progressive rise in core temperature and LSR with a ventilated sweat capsule, alongside an opposing decline in WBSR measured with continuous weighing, as sweating efficiency gradually reduced during an uncompensable heat stress. They and others (Peiss et al. 1956; Collins and Weiner 1962; Candas et al. 1983) have suggested excess saturation of the skin with sweat, as commonly observed in uncompensable conditions, suppresses sweating via mechanical obstruction lending to a reduced total sweat

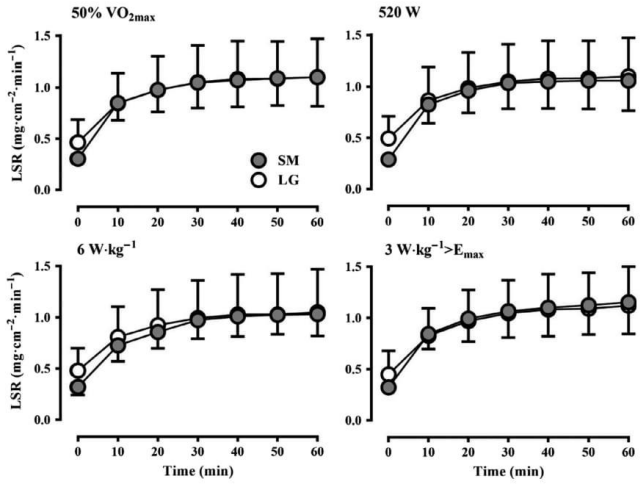

Figure 4. Mean local sweat rate (LSR) of the small (SM) and large (LG) group at 50%VO_{2max} (top-left), 520 W H_{prod} (top-right), 6 $W \cdot kg^{-1}$ H_{prod} (bottom-left), and 3 $W \cdot kg^{-1}$ $H_{prod} > E_{max}$ (bottom-right).

loss. Thus, the similar WBSR between SM and LG in this study may be associated with these previously reported phenomena, however, further evidence is required. Nevertheless, the similar LSR between both groups irrespective of exercise intensity demonstrates that matching for body size may not be required for unbiased comparisons of time-dependent changes in LSR during uncompensable heat stress.

Perspectives

This study expands our previous work and further demonstrates the importance of accounting for biophysical factors when comparing time-dependent changes in core temperature and sweating between groups unmatched for body size but with similar sudomotor function (i.e., thermosensitivity) during uncompensable heat stress. In contrast to compensable conditions (Jay et al. 2011; Gagnon et al. 2013; Cramer and Jay 2014), the present data indicate that it is not necessary to perform separate experiments with different exercise intensities for time-dependent comparisons of core temperature and sweating responses during uncompensable heat stress. Fixing H_{prod} in either $W{\cdot}kg^{-1}$ or $W{\cdot}kg^{-1}$>E_{max} during uncompensable heat stress results in similar ΔT_{re} (Fig. 2) and LSR (Fig. 4) between groups vastly different in body size, however, a systematic difference in ΔT_{sk} existed with the former method ($W{\cdot}kg^{-1}$; Fig. 3). Biophysical influences may explain differences in core temperature during uncompensable heat stress previously ascribed to other factors. For example, sex-related differences in core temperature have been reported with exercise at a $\%VO_{2max}$ (Horstman and Christensen 1982), however, the greater VO_{2max} in males compared to females would have resulted in a greater H_{prod} (in $W{\cdot}kg^{-1}$), which may have been responsible for the greater change in core temperature based on present findings. Furthermore, the present findings can potentially augment existing heat tolerance test protocols that employ a fixed treadmill walking speed on an incline (Moran et al. 2004; Druyan et al. 2013; Cheuvront 2014). While walking at the same speed and incline with a similar movement economy will lead to a similar $W{\cdot}kg^{-1}$ of H_{prod} between participants of different body masses, alterations in H_{prod} in $W{\cdot}kg^{-1}$ secondary to differences in walking efficiency would, according to the present observations (Fig. 2), result in systematic differences in ΔT_{re}. Indeed, differences in walking efficiency of ~15–20% at a fixed speed/incline have been previously reported as a function of body size (Browning et al. 2006) and age (Malatesta et al. 2003), therefore, we recommend heat tolerance tests should be specifically conducted at a fixed H_{prod} in $W{\cdot}kg^{-1}$, verified with indirect calorimetry measurements, in order to ensure the endogenous heat stress relative to the biophysical characteristics of the participant are standardized and an unbiased comparison of core temperature responses can be achieved between different individuals.

Finally, it was assumed that all participants were unacclimated to the heat. It has been well demonstrated a defining characteristic of heat acclimation is an increased ω_{max} from ~85% to 100% (i.e., complete saturation of skin in sweat) (Candas et al. 1979b), while differences in aerobic fitness can also theoretically alter ω_{max} secondary to a partial heat acclimation. However, the measured E_{max} in $W{\cdot}m^{-2}$ (and therefore ω_{max}; (Gagge 1937)) was similar between LG and SM groups (Table 2) despite a greater aerobic fitness in SM (Table 1) thereby suggesting a similar acclimation status between both groups independent of any fitness effect. While the greater aerobic fitness in SM did not appear to present any benefits from a core temperature or sweating perspective, their subjective tolerance to uncompensable heat stress (i.e., dropout rate due to volitional exhaustion) was better compared to LG individuals, as corroborated by others (McLellan 2001; Selkirk and McLellan 2001; McLellan et al. 2009).

Conclusion

In conclusion, exercise prescribed as either a fixed H_{prod} of $W{\cdot}kg^{-1}$ or $W{\cdot}kg^{-1}$>E_{max} yielded similar changes in ΔT_{re} during uncompensable heat stress between groups differing greatly in body size; however, the former method ($W{\cdot}kg^{-1}$) demonstrated systematic differences in ΔT_{sk}. Whole-body sweat rate and LSR were similar between LG and SM groups at all exercise intensities suggesting that a maximum sudomotor output and a similar degree of uncompensability were attained in all trials. This study expands our previously developed methodological framework to higher levels of hyperthermia.

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Conflict of Interest

No conflicts of interest, financial or otherwise, are declared by any of the authors.

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Appendix

Determining E_{max}

Step 1. Upon arrival, height and weight must be measured initially to estimate body surface area (BSA) using the DuBois & DuBois equation (Druyan et al. 2013).

Step 2. Following instrumentation of skin and oesophageal temperature, and breath-by-breath recording of oxygen consumption (See Methods), have the participant exercise at a predetermined intensity in a hot (36°C) but dry (40% RH; 2.3 kPa) environment. It is best to select an intensity that a participant can sustain for the duration of the humidity ramp protocol (75 min). For example, this study utilized a fixed external work of 100W which was equal to ~50% of VO_{2max}. Following 30 min of exercise where steady-state core temperature and sweating are achieved and observed, humidity in the room will increase at a rate of 0.3 kPa (~5%RH) every 7.5 min in a stepwise fashion.

Step 3. The transition from a compensable to an uncompensable state is determined as immediate and upward rise in oesophageal temperature; exemplifying the biophysical inability to maintain heat balance. The absolute humidity coinciding with the upward rise in oesophageal temperature is confirmed using segmental regression (Cheuvront et al. 2009) where the 1-minute averages of absolute oesophageal temperature are plotted

against the respective ambient humidity. The absolute humidity at the intercept of each slope is defined as P_{crit}.

Step 4. Using partitional calorimetry, one can then derive E_{req} for the minute of exercise coinciding with P_{crit} (Equation 1). E_{req}, P_{crit}, and $P_{sk,s}$ (see Equation 5) can then be substituted in to equation 8 to determine the individual's *K* coefficient.

Step 5. With the *K* coefficient, one can now derive the individual's actual E_{max} (in $W \cdot m^{-2}$) for the physical environment tested* by Equation 9. $P_{sk,s}$ is estimated using Equation 5 and P_a is the humidity of the prospective experimental conditions.

*Ambient air flow, exercise modality, and clothing must remain identical to that of the E_{max} assessment trial to ensure accuracy of the estimated E_{max} in any subsequent experimental session.

Determining net rate heat storage ($W \cdot kg^{-1} > E_{max}$):

In hot and humid conditions, the primary means for heat dissipation is the evaporation of sweat from the body surface, and thus the required heat loss can be defined as E_{req}. By definition, E_{req} will exceed E_{max} during uncompensable heat stress. By knowing the E_{max} in a given condition, and estimating E_{req} using partitional calorimetry (Equation 1), the difference will be the net rate of heat storage (in $W \cdot m^{-2}$). By further multiplying the net rate of heat storage by the participant's BSA, one can estimate the absolute net rate of heat storage, and this can be further expressed relative to the participant's mass ($W \cdot kg^{-1} > E_{max}$).

APPENDIX H: Functional relationship between sweating and skin blood flow

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RESEARCH ARTICLE | *Fluid and Electrolyte Homeostasis*

Sustained increases in skin blood flow are not a prerequisite to initiate sweating during passive heat exposure

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Ravanelli N, Jay O, Gagnon D. Sustained increases in skin blood flow are not a prerequisite to initiate sweating during passive heat exposure. *Am J Physiol Regul Integr Comp Physiol* 313: R140–R148, 2017. First published May 31, 2017; doi:10.1152/ajpregu.00033.2017.—Some studies have observed a functional relationship between sweating and skin blood flow. However, the implications of this relationship during physiologically relevant conditions remain unclear. We manipulated sudomotor activity through changes in sweating efficiency to determine if parallel changes in vasomotor activity are observed. Eight young men completed two trials at 36°C and two trials at 42°C. During these trials, air temperature remained constant while ambient vapor pressure increased from 1.6 to 5.6 kPa over 2 h. Forced airflow across the skin was used to create conditions of high (HiS_{eff}) or low (LoS_{eff}) sweating efficiency. Local sweat rate (LSR), local skin blood flow (SkBF), as well as mean skin and esophageal temperatures were measured continuously. It took longer for LSR to increase during HiS_{eff} at 36°C (HiS_{eff}: 99 ± 11 vs. LoS_{eff}: 77 ± 11 min, $P < 0.01$) and 42°C (HiS_{eff}: 72 ± 16 vs. LoS_{eff}: 51 ± 15 min, $P < 0.01$). In general, an increase in LSR preceded the increase in SkBF when expressed as ambient vapor pressure and time for all conditions ($P < 0.05$). However, both responses were activated at a similar change in mean body temperature (average across all trials, LSR: 0.26 ± 0.15 vs. SkBF: 0.30 ± 0.18°C, $P = 0.26$). These results demonstrate that altering the point at which LSR is initiated during heat exposure is paralleled by similar shifts for the increase in SkBF. However, local sweat production occurs before an increase in SkBF, suggesting that SkBF is not necessarily a prerequisite for sweating.

body temperature; heat stress; sudomotor; thermoregulation; vasodilation

THE REGULATION of internal body temperature during heat stress relies on sweat production and cutaneous vasodilation. Although both responses promote the exchange of heat between the body and the surrounding environment, evaporation of sweat provides by far the greatest potential for heat loss (1, 12, 23, 47). In contrast, cutaneous vasodilation and subsequent increases in skin blood flow (SkBF) are generally thought to transfer heat from core tissues to the periphery, therefore providing the heat to be removed by sweat evaporation (6, 14).

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A functional relationship between sweating and SkBF has long been hypothesized, beginning with the theory that bradykinin released by activated sweat glands leads to cutaneous vasodilation (11). Although this hypothesis was later refuted (20), a number of studies provide evidence for a functional relationship between sweating and SkBF. Most notably, Brengelmann et al. (4) reported a lack of active cutaneous vasodilation during passive heating in individuals with a congenital absence of sweat glands (i.e., anhidrotic ectodermal dysplasia). In addition, manipulations of local skin temperature (and probably SkBF) affect the onset threshold and thermal sensitivity of the sweating response during heat stress (2, 5, 31, 32). Finally, the sweating response to heat stress is attenuated when SkBF is prevented from increasing by using arterial occlusion (7, 25) or pharmacological blockade (49). Regardless of the potential mechanism, such observations clearly highlight a functional relationship between SkBF and sweating, in that one response becomes compromised when the other is absent or prevented from increasing.

The implications of a functional relationship between SkBF and sweating during physiologically relevant conditions remain unclear. This question has been examined by comparing the onset threshold of both responses when they are allowed to increase normally during heat exposure. Most recently, Smith et al. (42) reported that the onset threshold for SkBF precedes the one for sweat rate and suggested that an increase in SkBF may be required to initiate sweat production during whole body passive heat stress. Other studies have provided conflicting evidence that SkBF increases before (40, 41), after (24), or simultaneously (45) with sweat production. However, these studies did not manipulate one heat loss response to observe if parallel changes are observed in the other. Recently, we demonstrated that fan use delays the critical humidity at which elevations in heart rate are observed during stepwise increases in humidity in warm and hot conditions (36, 37). The delayed increase in heart rate was paralleled by improved sweating efficiency and lower levels of local sweat rate (LSR) during fan use relative to a still airflow condition (36). These observations suggest that increased air velocity delays the point at which sweating is activated, which provided us with a unique opportunity to examine the relationship between SkBF and sweating when sudomotor activity is manipulated through changes in sweating efficiency. If, as previously suggested (42), increased SkBF is a prerequisite for sweating during heat exposure, one might expect that *1*) SkBF consistently increases prior the

initiation of sweating, and *2*) manipulating the activation of sweating would lead to parallel changes in the activation of SkBF. Furthermore, the stepwise increase in humidity protocol elicits a slow and gradual heating stimulus, which we hypothesized would allow more resolution to detect subtle differences between the point at which sustained increases in sweating and SkBF occur. We hypothesized that increases in SkBF would precede increases in sweat production implying a functional dependency of sweating on changes in local SkBF.

METHODS

The data presented in this manuscript were collected as part of a larger study examining the effectiveness of fan use during exposure to extreme heat and humidity, the results of which have been published previously (36, 37). The study participants included eight healthy normotensive and nonsmoking men, with no preexisting cardiovascular, metabolic, or neurological diseases (age: 24 ± 3 y; body mass: 80.69 ± 11.68 kg; height: 1.77 ± 0.05 m; body surface area: 1.98 ± 0.14 m^2). None of the subjects were taking medications. All participants provided written informed consent. The experimental protocol was approved by the University of Ottawa Research Ethics Committee and conformed to the guidelines set forth in the Declaration of Helsinki. Participants were instructed to avoid vigorous physical activity 24 h before, refrain from alcohol 12 h before, eat a light meal, and avoid any caffeinated beverages at least 6 h before testing.

Instrumentation. Esophageal temperature was measured using a pediatric thermistor probe (Mon-a-therm, Mallinckrodt Medical, St. Louis, MO) inserted through the nasal cavity into the esophagus to a depth estimated to be nearest the left ventricle (27). Skin temperature was measured using four thermistors (Concept Engineering, Old Saybrook, CT), which were secured to the skin by using surgical tape (Transpore, 3M, London, Canada). Mean skin temperature was calculated as the weighted average of four sites (35): chest 30%, triceps 30%, thigh 20%, and calf 20%. Temperature measurements were sampled every 5 s (NI cDAQ-91722 module, National Instruments, Austin, TX) and recorded to a desktop computer by using customized LabView software (v7.0, National Instruments). LSR was measured on the chest and forearm by using ventilated sweat capsules. Anhydrous air was supplied through 4.1-cm^2 capsules at a rate of 1.2–1.4 l/min. Capsules were secured to the skin with surgical tape. The temperature and humidity of the air leaving both capsules were measured with factory calibrated capacitance hygrometers (HMT333, Vaisala, Vantaa, Finland) every 5 s. LSR was calculated as the product of absolute humidity and flow rate, and expressed relative to the amount of skin surface covered by the capsule. SkBF was measured using laser-Doppler flowmetry probes (Small Angled Thermostatic Probe no. 457, Perimed, Järfälla, Sweden) placed on the chest and forearm in close proximity to the ventilated sweat capsules. SkBF was sampled at a rate of 60 Hz by the Transcutaneous Oxygen Monitoring System (Periflux System 5000, Perimed) and recorded in real time (Perisoft for Windows Version 2.5.5, Perimed) before being exported to an Excel Spreadsheet (Excel 2000, Microsoft) at a sampling rate of 5 s. Blood pressure was measured using an automated cuff (E-Sphyg II 9002, American Diagnostics, Hauppauge, NY). Urine specific gravity was measured using a refractometer (Reichert TS 400, Depew, NY). Ambient air velocity was measured using a hot-wire anemometer (VelociCalc 9535, TSI, Shoreview, MN).

Experimental protocol. The participants volunteered for four experimental trials performed in a climatic chamber that precisely regulated air temperature and humidity. For all trials, participants provided a urine sample on arrival before entering the climatic chamber regulated at a temperature of either 36 or 42°C and a standardized ambient vapor pressure of 1.6 kPa, where they were fully instrumented. After a 45-min baseline period, ambient vapor pressure within the chamber was increased in a stepwise fashion by ~0.3 kPa every 7.5 min until reaching 5.6 kPa, a comparable protocol to previous studies (3, 19, 22). The stepwise increases in ambient vapor pressure therefore lasted a total of 120 min. For both air temperatures, the participants performed the trial without and with forced air flow across the skin to manipulate sweating efficiency (S_{eff}) and thus the physiological requirement for sweat production to attain heat balance (36). During the trials with a low sweating efficiency at 36°C and 42°C (i.e., $36LoS_{eff}$ and $42LoS_{eff}$), respectively, participants sat behind a 122-cm barrier made of foamcore boards (122 × 250 cm) placed in a "V" shape against a wall. The barrier minimized airflow across the skin to less than 0.1 m/s, confirmed by a hot-wire anemometer placed ~30 cm anterior to the participant's torso. During the trials with a high sweating efficiency at 36°C and 42°C (i.e., $36HiS_{eff}$ and $42HiS_{eff}$), respectively, an 18-in.diameter mechanical fan (High velocity orbital air circulator, Whirlpool, Benton Harbor, MI) set at full speed (generating a free space air velocity of ~4.0 m/s) was placed 1 m in front of the participant and turned on following the baseline period. The trials were performed in a balanced order and were separated by a minimum of 48 h. During the trials, participants wore a standardized T-shirt and shorts and sat on a plastic chair, which covered their back and upper rear thighs.

Data analysis. Mean body temperature was calculated as esophageal temperature × 0.9 + mean skin temperature × 0.1 (32). Mean arterial pressure was calculated as the weighted sum of systolic (1/3) and diastolic (2/3) blood pressures. Cutaneous vascular conductance (CVC) was calculated as SkBF divided by mean arterial pressure. Stepwise increases in ambient vapor pressure elicited relatively stable values of mean body temperature, SkBF, CVC, and sweating until a critical ambient vapor pressure was attained where an upward inflection in each variable occurred (3). The critical ambient vapor pressure at which the inflection point occurred was determined separately for SkBF and sweating by using segmented regression analysis of the minute-averaged data (21, 22, 37). For CVC values, only one data point per ambient vapor pressure stage was used for segmented regression as blood pressure was measured at the end of each stepwise increment. Figure 1 depicts the segmented regression analysis for one participant using one data point per ambient vapor pressure stage. The inflection point was also characterized based on corresponding time (in minutes) and change in mean body temperature from baseline. No statistical differences were observed between the forearm and chest for SkBF and LSR. Therefore, values from both sites were averaged to yield one value for each variable.

Statistical analysis. Mean skin, esophageal, and mean body temperatures, as well as mean arterial pressure, were analyzed within each air temperature (i.e., 36 and 42°C) by using two-way repeated-measures ANOVA with the repeated factors of time (9 levels: baseline, 15, 30, 45, 60, 75, 90, 105, and 120 min) and condition (LoS_{eff} vs. HiS_{eff}). To determine if sweating efficiency affected the inflection point for LSR, SkBF, and CVC, differences between conditions (at a given air temperature) were compared using paired samples *t*-tests. The α was set to 0.05 and corrected for multiple comparisons by using the Holm-Bonferroni approach. All data are presented as means ± SD.

RESULTS

Baseline urine specific gravity was similar between conditions ($36HiS_{eff}$: 1.012 ± 0.006 vs. $36LoS_{eff}$: 1.012 ± 0.006; $42HiS_{eff}$: 1.013 ± 0.005 vs. $42LoS_{eff}$: 1.016 ± 0.002, $P > 0.24$). Baseline mean skin, esophageal, and mean body temperatures also did not differ between conditions at 36 and 42°C ($P > 0.15$, Fig. 2). Manipulations of sweating efficiency did not affect esophageal and mean body temperatures during the conditions performed at 36°C ($P > 0.20$). In contrast, time × condition interactions for esophageal and mean body temperatures were observed at 42°C ($P < 0.01$, Fig. 2).

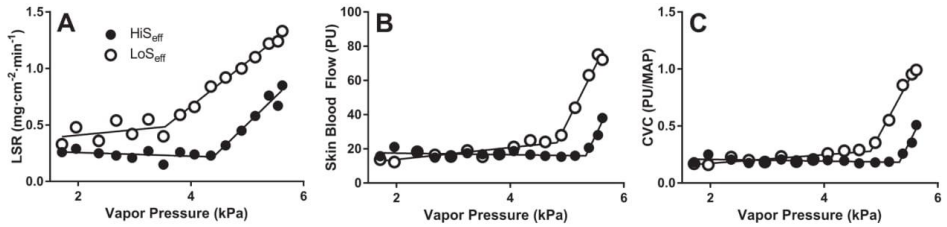

Fig. 1. Individual tracings used to determine the critical vapor pressure for the upward rise in local sweat rate (LSR) (*A*), skin blood flow (*B*), and cutaneous vascular conductance (CVC) (*C*). Data are from a participant resting at 36°C during conditions permitting a high (HiS$_{eff}$) or low (LoS$_{eff}$) sweating efficiency. The inflection point was determined using segmented linear regression.

However, none of the post hoc comparisons reached statistical significance (all $P > 0.12$). A time × condition interaction was also observed for mean skin temperature at 36°C ($P < 0.05$), but not at 42°C ($P = 0.24$). Again, no post hoc comparisons at 36°C reached statistical significance (all $P > 0.12$). Overall, the change in mean skin temperature did not exceed 1.5°C during any condition (36HiS$_{eff}$: 0.74 ± 0.32°C vs. 36LoS$_{eff}$: 1.16 ± 0.41°C; 42HiS$_{eff}$: 1.01 ± 0.33°C vs. 42LoS$_{eff}$: 1.30 ± 0.36°C). Mean arterial pressure remained unchanged throughout the protocols at 36 and 42°C (main effects of time, $P > 0.44$). Furthermore, mean arterial pressure was similar between high and low sweating efficiency conditions at 36°C and 42°C (main effects of condition, $P > 0.20$).

Tables 1 and 2 present the ambient vapor pressure (kPa), time (min), and change in mean body temperature corresponding with increases in LSR, SkBF, and CVC at 36 and 42°C, respectively. Individual responses for the time corresponding with the upward rise in LSR and SkBF for all four conditions are presented in Fig. 3. Figures 4 and 5 illustrate SkBF and sweat rate as a function of kPa, time, and mean body temperature for both conditions and both air temperatures. Manipulations of sweating efficiency resulted in different ambient vapor pressure inflection points for LSR at 36°C ($P < 0.01$) and 42°C ($P < 0.01$). The inflection point for LSR also differed when expressed as time at both air temperatures ($P < 0.01$). When expressed as a change in mean body temperature, different onset thresholds for LSR were observed at 42°C ($P = 0.03$), but not 36°C ($P = 0.20$). In general, increases in LSR occurred later when sweating efficiency was high, regardless of how it was expressed (see Tables 1 and 2).

Manipulating sweating efficiency also resulted in different inflection points for SkBF and CVC. When expressed as ambient vapor pressure (SkBF, $P = 0.04$; CVC, $P = 0.01$) and time (SkBF, $P = 0.02$; CVC, $P < 0.01$), the inflection points for SkBF and CVC differed between conditions at 36°C. A similar trend was observed at 42°C, although differences did not reach statistical significance for SkBF (ambient vapor pressure: $P = 0.09$; time: $P = 0.07$), whereas a statistical difference was observed for CVC (ambient vapor pressure: $P < 0.01$; time: $P < 0.01$). When expressed as a change in mean body temperature, the onset threshold for SkBF and CVC did not differ between conditions at 36°C (SkBF, $P = 0.80$, CVC, $P = 0.10$), whereas it was different at 42°C (SkBF, $P = 0.05$; CVC, $P = 0.03$). Increases in SkBF and CVC generally

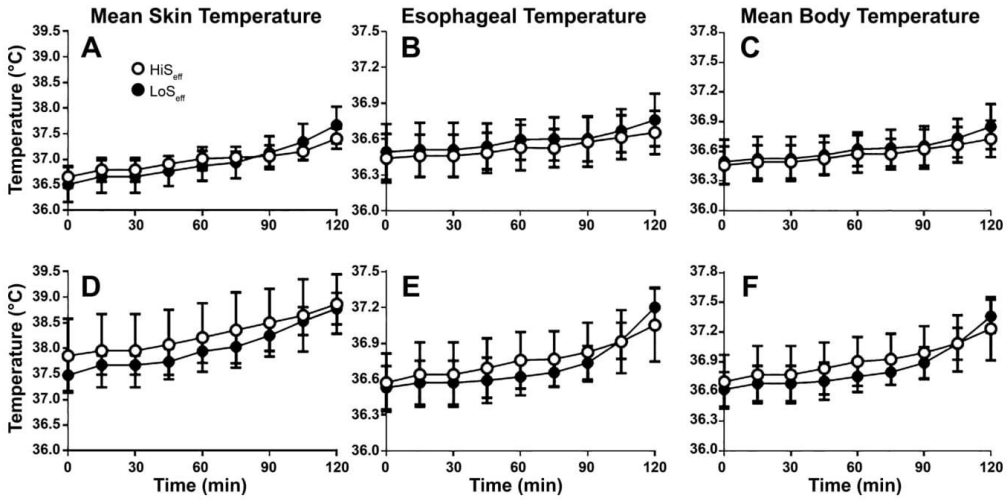

Fig. 2. Mean skin temperature (*A*: 36°C; *D*: 42°C), esophageal temperature (*B*: 36°C; *E*: 42°C), and mean body temperature (*C*: 36°C; *F*: 42°C) during passive exposure to an air temperature of 36 or 42°C with conditions permitting a high (HiS$_{eff}$) or low (LoS$_{eff}$) sweating efficiency. Values are means ± SD.

Table 1. *Inflection points for sweating, SkBF, and CVC expressed as ambient vapor pressure, ΔT_b, and time during HiS_{eff} and LoS_{eff} sweating efficiency conditions at 36°C air temperature*

	$36HiS_{eff}$			$36LoS_{eff}$		
	Sweating	SkBF	CVC	Sweating	SkBF	CVC
Vapor pressure, kPa	$4.96 \pm 0.36^{a,b}$	5.34 ± 0.22^{b}	5.02 ± 0.50^{b}	$3.96 \pm 0.42^{c,d}$	4.68 ± 0.37	4.50 ± 0.36
ΔT_b, °C	0.27 ± 0.15	0.27 ± 0.14	0.26 ± 0.14	0.20 ± 0.13^{c}	0.26 ± 0.17	0.23 ± 0.13
Time, min	$99 \pm 11^{a,b}$	111 ± 6^{b}	102 ± 15^{b}	$70 \pm 11^{c,d}$	91 ± 11	85 ± 9

Values are means ± SD. SkBF, skin blood flow; CVC, cutaneous vascular conductance; ΔT_b, change in mean body temperature; $36HiS_{eff}$, high sweating efficiency at 36°C air temperature; $36LoS_{eff}$, low sweating efficiency at 36°C air temperature. $^{a}P < 0.05$ vs. SkBF during $36HiS_{eff}$; $^{b}P < 0.05$ vs. $36LoS_{eff}$; $^{c}P < 0.05$ vs. SkBF during $36LoS_{eff}$; and $^{d}P < 0.05$ vs. CVC during $36LoS_{eff}$.

occurred later with high sweating efficiency (see Tables 1 and 2).

When expressed in terms of ambient vapor pressure and time, the inflection point for LSR differed from the one for SkBF ($P < 0.01$), but not CVC ($P = 0.86$), at $36HiS_{eff}$ (Table 1). During $36LoS_{eff}$, the time and ambient vapor pressure associated with the inflection point for LSR differed from SkBF ($P < 0.001$) and CVC ($P < 0.01$). During $42HiS_{eff}$, the inflection points for LSR (expressed as time and ambient vapor pressure) did not differ statistically from the ones for SkBF ($P > 0.06$), but were different from the ones for CVC ($P < 0.03$, Table 2). Similarly, the time and ambient vapor pressure inflection points for LSR were not statistically different from the ones for SkBF ($P > 0.12$), but were different than the ones for CVC ($P < 0.02$) during $42LoS_{eff}$ (Table 2). In general, increases in LSR preceded increases in SkBF and CVC. During the conditions performed at 36°C, all subjects exhibited an earlier inflection point in LSR compared with the one for SkBF (Fig. 3). At an air temperature of 42°C, the inflection point for sweating preceded the one for SkBF in 75% of the trials (Fig. 3). When expressed as a change in mean body temperature, the onset threshold for LSR occurred at a lower change in mean body temperature than the one for SkBF during 36LoSeff ($P = 0.04$, see Table 1). However, the mean body temperature onset thresholds for LSR, SkBF, and CVC were similar for all other conditions ($P > 0.10$).

DISCUSSION

This study examined the relationship between SkBF and LSR during physiologically relevant conditions when sweat production is manipulated through changes in sweating efficiency. Furthermore, changes in mean skin and esophageal temperatures occurred gradually over an extended period of time. Although the inflection points of both responses changed in parallel, the increase in LSR preceded an increase in SkBF. These results suggest that increases in SkBF are not necessarily a prerequisite to initiate sweat production.

On the basis of early reports of a close temporal relationship between sweating and cutaneous vasodilation, it has been hypothesized that a functional relationship exists between vasomotor and sudomotor activities (50). Fox and Hilton (11) initially suggested that bradykinin released from activated sweat glands mediates cutaneous vasodilation, thus providing a physiological basis for the functional relationship between sweating and SkBF. However, a role for bradykinin was later refuted (20), and it remains unclear whether sudomotor and vasomotor activity are controlled by common or independent nerves (17, 18, 44, 50). Regardless of the potential underlying mechanism, a functional relationship between SkBF and sweating is observed under certain conditions. Brengelmann et al. (4) observed a lack of active cutaneous vasodilation in individuals with a congenital absence of sweat glands. In that study, neurological abnormalities were ruled out, and the cutaneous vasculature retained the ability to vasodilate in response to local heating and vasoconstrict in response to lower body negative pressure (4). Furthermore, occluding limb blood flow attenuates the increase in sweat rate during heat exposure (7, 25), and Wingo et al. (49) observed that the sensitivity of the sweating response to changes in body temperature is substantially reduced when the increase in SkBF is blocked pharmacologically. Taken together, these observations demonstrate that full expression of either heat loss response is not achieved when the other response is absent (4) or prevented from increasing (7, 25, 49). However, the nature of a functional relationship between sweating and SkBF during more common and physiologically relevant conditions remains less clear. For example, we recently reported that an ~20% reduction in SkBF, such as those associated with healthy aging (15, 42, 43), does not affect sweat rate or the critical environmental limit for heat balance (8). It is therefore debatable whether the functional relationship between SkBF and sweating is relevant when both responses operate within a physiological range (as opposed to a complete absence of one heat loss response).

Table 2. *Inflection points for sweating, SkBF, and CVC expressed as ambient vapor pressure, ΔT_b, and time during HiS_{eff} and LoS_{eff} sweating efficiency conditions at 42°C air temperature*

	$42HiS_{eff}$			$42LoS_{eff}$		
	Sweating	SkBF	CVC	Sweating	SkBF	CVC
Vapor pressure, kPa	$3.83 \pm 0.57^{a,b}$	4.29 ± 0.45	4.38 ± 0.26^{a}	3.00 ± 0.65^{c}	3.54 ± 0.78	3.63 ± 0.43
ΔT_b, °C	0.36 ± 0.16^{a}	0.44 ± 0.18^{a}	0.45 ± 0.17^{a}	0.19 ± 0.12	0.25 ± 0.20	0.27 ± 0.18
Time, min	$72 \pm 16^{a,b}$	87 ± 12	92 ± 8^{a}	51 ± 15^{c}	64 ± 24	66 ± 13

Values are means ± SD. $42HiS_{eff}$, high sweating efficiency at 42°C air temperature; $42LoS_{eff}$, low sweating efficiency at 42°C air temperature. $^{a}P < 0.05$ vs. $42LoS_{eff}$; $^{b}P < 0.05$ vs. CVC during $42HiS_{eff}$; and $^{c}P < 0.05$ vs. CVC during $42LoS_{eff}$.

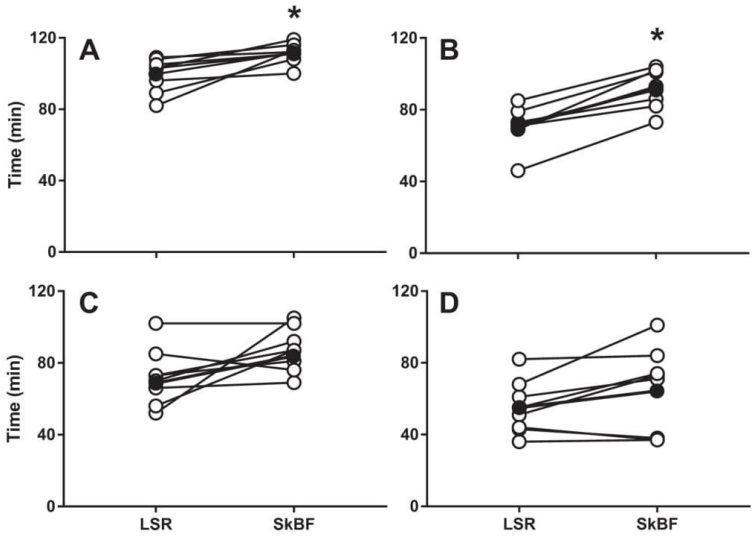

Fig. 3. Individual inflection points (○) for local sweat rate (LSR) and skin blood flow (SkBF) expressed as a function of time. The inflection points were derived using segmented regression analysis during four experimental conditions: 36°C and high sweating efficiency (*A*); 36°C and low sweating efficiency (*B*); 42°C and high sweating efficiency (*C*); and 42°C and low sweating efficiency (*D*). Mean values indicated by ●; $^{*}P < 0.05$ vs. LSR for the mean value.

A few studies have considered the relationship between SkBF and sweating during physiologically relevant conditions by examining the onset threshold of both responses when they are allowed to increase normally during heat exposure. With the use of this approach, early studies provide conflicting evidence with some reporting that SkBF increases before (40, 41), after (24), or simultaneously (45) with the increase in sweat production. Most recently, Smith et al. (42) examined whether differences in local SkBF could explain regional differences in LSR. Although regional differences in sweat rate could not be explained by regional differences in SkBF, they suggested that an increase in SkBF is necessary for the initiation of sweating since the onset threshold for SkBF occurred before the one for sweat rate. However, these studies did not manipulate sweating or SkBF to determine if and/or how the other response is affected. Furthermore, an important consideration of the study by Smith et al. (42) is the use of the water-perfused suit model of heat stress that elicits large (~4–5°C) and very rapid (~10–15 min) changes in mean skin temperature. Such large and rapid changes in skin temperature may have provided a potent local temperature-dependent increase in SkBF, which could explain the apparent dependency of sweating on an increase in SkBF. In contrast, the present protocol resulted in gradual and moderate changes in mean skin temperature. Importantly, sudomotor activity was manipulated through the use of forced airflow across the skin surface which affects sweating efficiency. Using this approach, we observed a delayed inflection point for LSR during conditions of high sweating efficiency, which was paralleled by a delayed inflection point for SkBF. This occurred whether air temperature was warm or hot and was most evident when the inflection point was expressed in terms of ambient vapor pressure and time. These findings support, at the very least, a temporal relationship between sweating and SkBF (24, 45). However, the main finding of the present study is that an increase in local sweat production generally preceded the increase in SkBF. This was also most evident when the inflection point was expressed in terms of ambient vapor pressure and time, and it was evident at both air temperatures. In contrast to our hypothesis, these results suggest that an increase in SkBF is not a prerequisite for increases in sweat production under the conditions examined.

An interesting observation of the present study is the substantial difference in the inflection points for LSR and SkBF when expressed as ambient vapor pressure and time. For example, the increase in sweat production occurred 15 ± 9 min before an increase in SkBF when averaged across all conditions. This observation cannot be attributed to differences in mean skin and esophageal temperatures between conditions (Fig. 2). In fact, the mean body temperature onset thresholds for LSR and SkBF were generally similar. Because of the nature of the experimental protocol, the increase in mean body temperature occurred very gradually. As such, mean body temperature remained at stable levels for prolonged periods, despite substantial increases in ambient vapor pressure and time. This resulted in a decoupling between the mean body temperature onset threshold and the inflection point when expressed as time and ambient vapor pressure. Had we solely examined onset thresholds, we would have concluded that LSR and SkBF increase simultaneously. As such, any potential relationship between SkBF and sweating may not be fully characterized if only examined through mean body temperature onset thresholds. It is well established that sweating and SkBF are stimulated by changes in skin and deep body temperatures (26, 29, 30, 34, 46, 51). Therefore, an earlier inflection point for LSR compared with SkBF, despite similar changes in mean body temperature, may suggest that increases in SkBF occur secondary to an increase in sweating to support sudomotor activity (rather than being a prerequisite). However, future studies are needed to evaluate this possibility.

As expected from the experimental design, sweating efficiency markedly affected the point at which LSR was initiated.

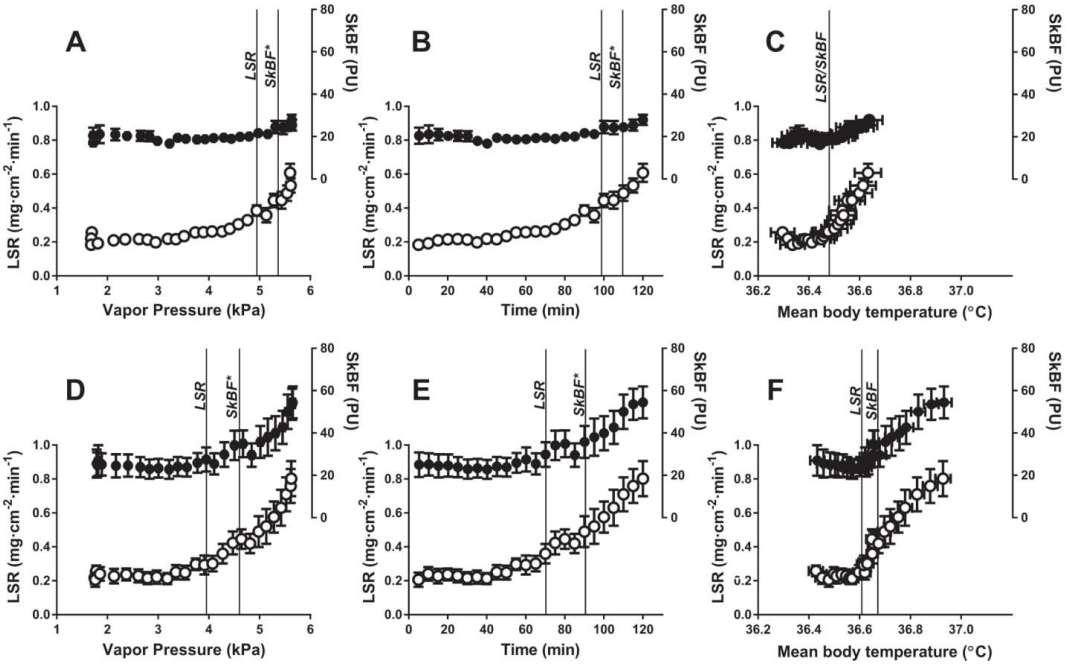

Fig. 4. Local sweat rate (LSR; open circles) and skin blood flow (SkBF; closed circles) expressed as a function of ambient vapor pressure (kPa), time (min), and mean body temperature (°C) during passive exposure to 36°C with conditions permitting a high (*A*, *B*, and *C*) or low (*D*, *E*, and *F*) sweating efficiency. Vertical lines indicate the mean inflection points for LSR and SkBF. Values are means ± SD. *$P < 0.05$ vs. LSR.

For example, the inflection point for LSR during the low efficiency condition occurred 29 ± 9 min earlier compared with when sweating efficiency was high at an air temperature of 36°C. Increased airflow across the skin surface promotes sweat evaporation, thereby reducing skin wettedness. The results of the present study suggest that the accumulation of sweat, and therefore increased skin wettedness, is associated with an earlier ambient vapor pressure/time inflection for sweat production. This was documented by Mole (28), who reported that sweat rate increases in proportion with the required skin wettedness to maintain heat balance. Alternatively, when sweat is removed from the skin surface by wiping the skin dry, sweat rates increase to counterbalance the absence of potential heat loss via evaporation (33). Placed within the context of the present study, the stepwise increases in ambient vapor pressure progressively reduced the ambient vapor pressure gradient between the skin surface and the surrounding air, resulting in a greater required skin wettedness to maintain heat balance. This necessity for a greater skin wettedness resulted in a greater drive for sweating at a given mean body temperature, as evidenced by the earlier inflection point for LSR during the low sweating efficiency conditions.

Considerations. During heat exposure, SkBF initially increases because of withdrawal of vasoconstrictor tone, and sustained increases are subsequently mediated by active cutaneous vasodilation (10, 17, 38). It is possible that withdrawal of vasoconstrictor tone explains why some studies have observed an earlier increase in SkBF relative to sweating. In the present study, subjects were exposed to a 36 or 42°C environment for ~60 min before the stepwise increases in ambient vapor pressure. It is assumed that all vasoconstrictor tone was withdrawn with this approach and that the inflection points for SkBF/CVC represent active cutaneous vasodilation. It should therefore be considered that the present results suggest that sustained increases in SkBF (i.e., active cutaneous vasodilation) are not required to initiate sweat production. It is also likely that the temporal relationship between SkBF and sweating is dependent on the experimental model of heat stress employed and the environmental conditions. For example, SkBF may increase before sweating when heat stress is induced using the water-perfused suit model (42). An increase in SkBF was also observed before any evidence of sweating on the decision to move from a warm (~40°C) to a cool (~17°C) environment (39). The results of the present study therefore suggest that sustained increases in SkBF do not always precede the initiation of sweating during heat exposure. It should also be considered that sweating and SkBF were not measured from the exact same location. Although we maintained close proximity (~1 cm) between both measures, it is unknown if this distance would alter our observations. Finally, we only examined sweating and SkBF on the forearm and chest. Although similar patterns were observed when each area was examined separately, we cannot determine if our findings would be similar or different in other areas not measured (e.g., back, lower limbs, forehead).

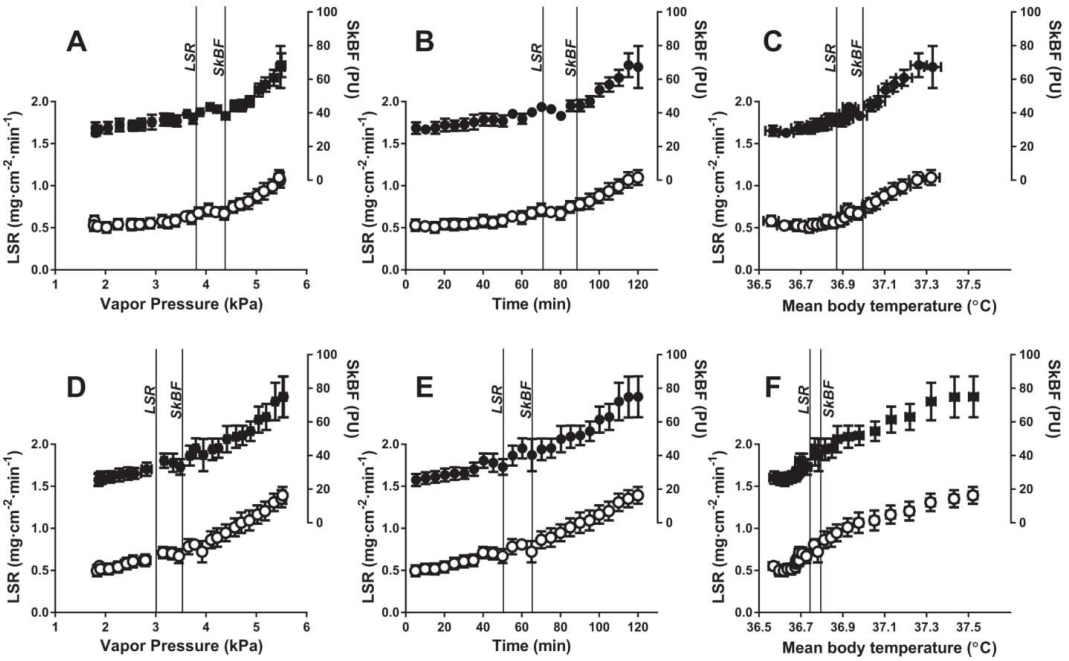

Fig. 5. Local sweat rate (LSR; open circles) and skin blood flow (SkBF closed circles) expressed as a function of ambient vapor pressure (kPa), time (min), and mean body temperature (°C) during passive exposure to 42°C with conditions permitting a high (*A*, *B*, and *C*) or low (*D*, *E*, and *F*) sweating efficiency. Values are means ± SD. Vertical lines indicate the mean inflection points for LSR and SkBF.

Perspectives and Significance

Determining whether the functional relationship between sweating and SkBF has implications during physiologically relevant conditions is important for our understanding of thermoregulatory control in various scenarios and/or populations. For example, a number of conditions (primary aging, heart failure, and diabetes) limit the ability of the skin to vasodilate during heat stress resulting in attenuated SkBF (9, 13, 16, 48). If the functional relationship between SkBF and sweating is relevant under physiological conditions, reduced SkBF in these populations may affect sweat production and ultimately the control of internal body temperature since sweat evaporation provides by far the greatest potential for heat loss during heat exposure (1, 12, 23, 47). The findings of the present study suggest that sustained increases in SkBF are not a prerequisite to initiate local sweat production within the conditions tested. Alternatively, reduced SkBF could compromise sweating if increases in SkBF support the increase in sweat rate. However, we recently reported that an ~20% reduction in SkBF does not affect sweat production or the critical environmental limits for heat balance (8). Combined, the findings of our present and previous (8) studies suggest that the functional relationship between SkBF and sweating may not have implications during physiologically relevant conditions. That said, we have only examined young healthy adults exposed to extreme heat and humidity. These findings may not be applicable to other populations and/or conditions. Future studies are therefore required to determine if physiological reductions in SkBF associated with primary aging or various health conditions has an impact, if any, on sweat production in environments that may be encountered by these populations.

Conclusion. The present study examined if a sustained increase in SkBF occurs before the initiation of local sweating during stepwise increases in ambient vapor pressure in warm (36°C) and hot (42°C) environments. By changing sweating efficiency, the point at which LSR was activated was manipulated to determine if parallel changes in SkBF would be observed. Although directional changes in the inflection point for LSR and SkBF were similar, sweat production preceded any sustained increase in SkBF. This was particularly noticeable when inflection points were quantified as ambient vapor pressure and time, while the mean body temperature onset thresholds for LSR and SkBF were generally similar. These results suggest that a sustained increase in SkBF is not always a prerequisite for sweating to be initiated during passive heat exposure.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

N.R. and O.J. conceived and designed research; N.R. performed experiments; N.R. analyzed data; N.R., O.J., and D.G. interpreted results of experiments; N.R. prepared figures; N.R. and D.G. drafted manuscript; N.R., O.J., and D.G. edited and revised manuscript; N.R., O.J., and D.G. approved final version of manuscript.

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APPENDIX I: Biophysical and physiological effects of fan use during heat stress

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ORIGINAL PAPER

The biophysical and physiological basis for mitigated elevations in heart rate with electric fan use in extreme heat and humidity

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Abstract Electric fan use in extreme heat wave conditions has been thought to be disadvantageous because it might accelerate heat gain to the body via convection. However, it has been recently shown that fan use delays increases in heart rate even at high temperatures (42 °C) in young adults. We here assess the biophysical and physiological mechanisms underlying the apparently beneficial effects of fan use. Eight males (24 ± 3 y; 80.7 ± 11.7 kg; 2.0 ± 0.1 m^2) rested at either 36 °C or 42 °C, with (F) or without (NF) electric fan use (4.2 m/s) for 120 min while humidity increased every 7.5 min by 0.3 kPa from a baseline value of 1.6 kPa. Heart rate (HR), local sweat rate (LSR), cutaneous vascular conductance (CVC), core and mean skin temperatures, and the combined convective/radiative heat loss (C+R), evaporative heat balance requirements (E_{req}) and maximum evaporative potential (E_{max}) were assessed. C+R was greater with fan use at 36 °C (F 8 ± 6, NF 2 ± 2 W/m^2; $P = 0.04$) and more negative (greater dry heat gain) with fan use at 42 °C (F −78 ± 4, NF −27 ± 2 W/m^2; $P < 0.01$). Consequently, E_{req} was lower at 36 °C (F 38 ± 16, NF 45 ± 3 W/m^2; $P = 0.04$) and greater at 42 °C (F 125 ± 1, NF 74 ± 3 W/m^2; $P < 0.01$) with fan use. However, fan use resulted in a greater E_{max} at baseline humidity at both 36 °C (F 343 ± 10, NF 153 ± 5 W/m^2; $P < 0.01$) and 42 °C (F 376 ± 13, NF 161 ± 4 W/m^2; $P < 0.01$) and throughout the incremental increases in humidity. Within the humidity range that a rise in HR was prevented by fan use but not without a fan, LSR was higher in NF at both 36 °C ($P = 0.04$) and 42 °C ($P = 0.05$), and skin temperature was higher in NF at 42 °C ($P = 0.05$), but no differences in CVC or core temperatures were observed (all $P > 0.05$). These results suggest that the delayed increase in heart rate with fan use during extreme heat and humidity is associated with improved evaporative efficiency.

Keywords Heat waves · Cardiovascular strain · Thermoregulation · Sweating

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Introduction

Over the past 20 years, heat waves—characterized by extended bouts of extreme heat and humidity—have led to high levels of excess morbidity and mortality in the USA (Whitman et al. 1997), Europe (Fouillet et al. 2006), Australia (Nitschke et al. 2011), and most recently India and Pakistan (Lancet 2015). Cardiovascular events are consistently identified as an underlying cause of heat-related mortality and morbidity (Bouchama et al. 2007; Hajat et al. 2010), with those who do not have access to air conditioning being particularly vulnerable. Moreover, the high electricity requirements associated with widespread air conditioning use by the majority of households in urban areas during heat waves have in some cases led to massive power failures (Luber and McGeehin 2008), and a consequent surge in morbidity and mortality rates (Schuman 1972; Hartz et al. 2012). It is

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therefore evident that affordable and energy efficient cooling strategies (Kravchenko et al. 2013) are urgently needed to mitigate cardiovascular strain during heat waves.

Electric fans provide a simple cooling intervention at a fraction of the price and energy requirement of modern air conditioning (Gupta et al. 2012; Salamanca et al. 2014). However, current heat management guidelines from public health agencies such as the World Health Organization, US Environmental Protection Agency, and The Centers for Disease Control and Prevention typically advise against fan use at air temperatures above 35 to 37 °C as they are thought to, at best, be ineffective (Wolfe 2003; CDC 2004), and at worst, exacerbate physiological strain and the risk of heat illness and dehydration (Wolfe 2003; Matthies et al. 2008; Victorian Government Department of Health 2013). We recently demonstrated that electric fan use at air temperatures up to 42 °C delays heat-induced elevations in heart rate in young healthy males (Ravanelli et al. 2015). However, the underlying physiological and biophysical mechanisms for the protective effect of electric fans at high air temperatures and humidity were not determined.

When ambient temperature exceeds skin temperature, which in a hot environment will typically be ~35 °C (Gagge et al. 1937), heat will be gained via convection. With fan use, this environmental heat load will be added to the body at a faster rate. However, fan use favors elevated rates of sweat evaporation. Importantly, increased levels of sweat evaporation with fan use can be achieved without the need for greater sweat production through improvements in evaporative efficiency—the amount of sweat that evaporates relative to the amount produced (Adams et al. 1992). In contrast, not using a fan would lead to decrements in evaporative efficiency and therefore greater sweat rates to overcome compromised sweat evaporation (Candas et al. 1979b). Since greater sweat rates are generally accompanied by greater cutaneous vasodilation (Wingo et al. 2010; Smith et al. 2013), it is possible that the delayed increase in heart rate with fan use during passive heat exposure is associated with less peripheral vasodilation and therefore less of a need for cardiac output to increase in order to maintain blood pressure.

The purpose of the present study was to (i) evaluate how changes in physiological heat loss responses and human heat balance are altered by electric fan use during simulated extreme heat wave conditions, and (ii) identify how fan use previously resulted in a lower heart rate (Ravanelli et al. 2015) at air temperatures equal to (36 °C) and far exceeding (42 °C) the limits for fan use presently stated in public health recommendations (CDC 2004; WHO 2009). It was hypothesized that improved sweat evaporation with fan use outweighs greater convective heat gain, leading to a lower requirement for skin blood flow and sweat production.

Methods

The data presented in the current manuscript were collected as part for a larger study examining humidity inflection points for heart rate and core temperature with and without fan use (Ravanelli et al. 2015). Eight healthy, normotensive, non-smoking young males, with no pre-existing cardiovascular, metabolic, or neurological issues participated in the study (age 24 ± 3 years; mass 80.7 ± 11.7 kg; height 1.77 ± 0.05 m; BSA 1.98 ± 0.14 m^2). All participants completed one preliminary visit and four experimental trials. The experimental protocol was approved by the University of Ottawa Research Ethics Board and conformed to the guidelines set forth in the 1964 Declaration of Helsinki. All participants provided written informed consent prior to their participation in the study. Participants were instructed to avoid vigorous exercise or physical activity 24 h prior, refrain from alcohol 12 h prior, eat a light meal, and avoid any caffeinated beverages at least 6 h prior to testing. The preliminary visit consisted of providing informed consent and anthropometric measurements (weight and height) to estimate body surface area (DuBois and Dubois 1916).

Instrumentation

Rectal temperature was measured using a thermistor probe (Mon-a-therm®, Mallinckrodt Medical, St. Louis, MO) inserted to a depth of 20 cm past the anal sphincter. Esophageal temperature was measured using a thermistor probe (Mon-a-therm®, Mallinckrodt Medical, St. Louis, MO) inserted through the nasal cavity into the esophagus. The end of the thermistor probe was estimated to be located at a region nearest the left ventricle (Mekjavic and Rempel 1990). Skin temperature was measured using four thermistors (Concept Engineering, Old Saybrook, CT, USA), which were secured to the skin using surgical tape (Transpore®, 3M, London, ON). Mean skin temperature was calculated as the weighted average of four sites using the formula reported by Ramanathan (1964): chest 30 %, triceps 30 %, thigh 20 %, and calf 20 %. Temperature measurements were sampled every 5 s (NI cDAQ-91,722 module, National Instruments, Austin, TX) and displayed in real-time on a desktop computer using customized LabView software (v7.0, National Instruments, Austin, TX).

Heart rate was measured using cardio-recorder (Polar RS 800, Polar electro Oy, Kempele, Finland) and coded transmitter (Polar wearlink T31 coded, Polar electro Oy, Kempele, Finland), which recorded every 5 s. The recording was downloaded to a desktop computer using the manufacturer's software (Polar ProTrainer Versions 5.40.172, Kempele, Finland) and averaged every minute. Systolic and diastolic blood pressures were measured using an automated cuff (E-Sphyg II 9002, American Diagnostic Corporation,

Hauppauge, NY, USA) at baseline and at the end of each humidity stage during the ramp protocol. Mean arterial pressure was subsequently calculated as:

$$(1/3 \times \text{systolic blood pressure}) + (2/3 \times \text{diastolic blood pressure})\ [\text{mmHg}] \quad (1)$$

Skin blood flow was measured using Laser Doppler Flowmetry probes (Small Angled Thermostatic Probe no. 457, Perimed, Järfälla, Sweden) placed on the chest and forearm. Skin blood flow perfusion units were displayed by the Laser Doppler Perfusion Monitor (Periflux System 5000, Perimed, Järfälla, Sweden) and simultaneously recorded at a sampling rate of 5 s by the manufacturers software (Perisoft for Windows version 2.5.5, Perimed, Järfälla, Sweden). Skin blood flow was averaged between recordings from the chest and the forearm and expressed as (i) absolute values and (ii) cutaneous vascular conductance, which was derived as the quotients of perfusion units and mean arterial pressure.

Local sweat rates of the chest and forearm were measured using ventilated sweat capsules. Anhydrous air was supplied through each 4.1-cm^2 capsule at a rate of 1.2 L/min (chest) and 1.4 L/min (forearm). Capsules were secured to the skin using surgical tape. The temperature and humidity of the air leaving both capsules were measured by individually factory calibrated capacitance hygrometers (HMT333, Vaisala, Vantaa, Finland). Local sweat rates were calculated as the product of flow rate and effluent absolute humidity, and expressed relative to the amount of skin surface covered by the capsule ($mg/cm^2/min$). Local sweat rate was expressed as the average between chest and forearm.

Experimental protocol

All trials were performed in a climatic chamber that precisely regulated ambient air temperature and absolute humidity, situated at the Thermal Ergonomics Laboratory at the University of Ottawa in Canada. During the fan trials, an 18″ diameter mechanical fan (Whirlpool, Benton Harbor, MI, USA) was set at full speed and placed 1.0 m directly in front of the participant. The mean whole body air velocity (4.2 m/s) generated by the fan was derived from calculations of the convective heat transfer coefficient (h_c—see Eq. 4) using measurements of convective heat loss (see Eq. 3) in a 15 °C environment using a 34 zone thermal manikin (NEWTON; Measurement Technology Northwest, Seattle, USA) at the Environmental Ergonomics Centre at Loughborough University, UK. The four experimental trials were (i) 36 °C with fan (36F), (ii) 36 °C with no fan (36NF), (iii) 42 °C with fan (42F), and (iv) 42 °C with no fan (42NF). The experimental trials were presented in a balanced order determined using a Latin square design. All trials were separated by at least 48 h. Upon arrival at the laboratory, participants provided a urine sample to ensure euhydration and similar hydration states between trials by measuring urine specific gravity with a refractometer (Reichert TS 400, Depew, NY). All urine specific gravity measurements were lower than 1.025 (Kenefick and Cheuvront 2012) and were similar between experimental trials for each person (±0.002). Each participant wore a standardized t-shirt and shorts and sat on a plastic chair that covered part of their back and upper rear thigh. The dry insulation (with fan 0.04 clo; without fan 0.10 clo) and evaporative resistance (0.01 m^2kPa/W) of this standardized ensemble was measured using a thermal manikin at Loughborough University, UK. During the 36NF and 42NF trials, participants sat behind a 122-cm high barrier to ensure still (<0.1 m/s) airflow around them. Throughout all trials, ambient air velocity was measured using a hot wire anemometer (VelociCalc 9535, TSI Inc., Shoreview MN, USA) positioned ~20 cm anterior to the participants torso.

Each trial began with the participant entering the climatic chamber regulated at a temperature of either 36 °C or 42 °C, an ambient vapor pressure of 1.6 kPa, and sitting quietly for 45 min. An initial body mass measurement was then taken using a platform scale (Combics 2, Sartorius, Mississauga, ON, Canada). Following a further 20 min at a vapor pressure of 1.6 kPa, vapor pressure was increased in a stepwise fashion by 0.3 kPa every 7.5 min (Kenney et al. 1993) until 5.6 kPa, at which point the participant's body mass was once again measured and a urine sample was obtained. The duration of each trial (excluding the 45-min baseline rest) was 120 min. Table 1 illustrates the ambient temperature and absolute humidity for each stepwise increase in humidity.

Partitional calorimetry

Heat balance was estimated using partitional calorimetry, and parameters are presented as the mean values for each condition. Metabolic heat production (H_{prod}) was not measured and was assumed to be 1.2 W/kg of total body based on the following equation:

$$H_{prod} = \frac{VO_2\left(\left(\frac{RER-0.7}{0.3}\right)e_c\right) + \left(\left(\frac{1.0-RER}{0.3}\right)e_f\right)}{60 \cdot A_D} \cdot 1000\left[W/m^2\right] \quad (2)$$

where oxygen consumption (VO_2) was estimated as 3.5 ml/kg/min, the respiratory exchange ratio (RER) was assumed to be 0.85, e_c is the caloric equivalent per liter of oxygen for the oxidation of carbohydrates (21.13 kJ/L of O_2 consumed), e_f is the caloric equivalent per liter of oxygen for the oxidation of lipids (19.62 kJ/L of O_2 consumed).

Table 1 Ambient temperature (T_a) and absolute humidity (AH) for each stepwise increase in humidity at 36 and 42 °C expressed as mean ± standard deviation

Stage	36°C - Fan		36°C – No fan		42°C - Fan		42°C – No fan	
	T_a (°C)	AH (kPa)	T_a (°C)	AH (kPa)	T_a (°C)	AH (kPa)	T_a (°C)	AH (kPa)
1	36.6 ± 0.2	1.7 ± 0.2	36.2 ± 0.3	1.7 ± 0.1	42.8 ± 0.1	1.8 ± 0.1	41.3 ± 0.4	1.9 ± 0.1
2	36.7 ± 0.3	2.0 ± 0.0	36.3 ± 0.3	2.0 ± 0.0	42.8 ± 0.1	2.0 ± 0.1	41.4 ± 0.3	2.0 ± 0.1
3	36.6 ± 0.4	2.4 ± 0.1	36.4 ± 0.2	2.4 ± 0.1	42.8 ± 0.1	2.3 ± 0.2	41.5 ± 0.3	2.3 ± 0.2
4	36.6 ± 0.4	2.7 ± 0.1	36.4 ± 0.3	2.7 ± 0.1	42.8 ± 0.1	2.6 ± 0.3	41.5 ± 0.3	2.5 ± 0.3
5	36.6 ± 0.4	3.0 ± 0.1	36.4 ± 0.2	3.0 ± 0.1	42.8 ± 0.0	2.9 ± 0.1	41.6 ± 0.2	2.9 ± 0.2
6	36.6 ± 0.4	3.3 ± 0.0	36.5 ± 0.3	3.3 ± 0.1	42.8 ± 0.1	3.2 ± 0.1	41.6 ± 0.2	3.3 ± 0.1
7	36.6 ± 0.4	3.5 ± 0.0	36.5 ± 0.3	3.5 ± 0.1	42.8 ± 0.1	3.4 ± 0.1	41.6 ± 0.2	3.5 ± 0.1
8	36.7 ± 0.3	3.8 ± 0.0	36.6 ± 0.2	3.8 ± 0.0	42.8 ± 0.1	3.7 ± 0.1	41.6 ± 0.2	3.7 ± 0.1
9	36.7 ± 0.3	4.1 ± 0.0	36.6 ± 0.2	4.1 ± 0.0	42.8 ± 0.1	3.9 ± 0.1	41.6 ± 0.2	4.0 ± 0.1
10	36.7 ± 0.3	4.4 ± 0.0	36.6 ± 0.2	4.4 ± 0.1	42.8 ± 0.1	4.1 ± 0.0	41.7 ± 0.3	4.2 ± 0.1
11	36.7 ± 0.3	4.6 ± 0.0	36.7 ± 0.2	4.7 ± 0.1	42.8 ± 0.1	4.3 ± 0.0	41.6 ± 0.3	4.4 ± 0.1
12	36.7 ± 0.2	4.9 ± 0.0	36.7 ± 0.2	5.0 ± 0.1	42.8 ± 0.1	4.6 ± 0.1	41.7 ± 0.3	4.7 ± 0.1
13	36.7 ± 0.2	5.2 ± 0.1	36.7 ± 0.2	5.2 ± 0.1	42.8 ± 0.1	4.8 ± 0.0	41.7 ± 0.3	4.9 ± 0.1
14	36.7 ± 0.2	5.4 ± 0.1	36.8 ± 0.2	5.4 ± 0.1	42.8 ± 0.1	5.1 ± 0.1	41.8 ± 0.3	5.2 ± 0.1
15	36.7 ± 0.2	5.6 ± 0.1	36.8 ± 0.2	5.6 ± 0.1	42.8 ± 0.1	5.3 ± 0.0	41.7 ± 0.3	5.4 ± 0.1
16	36.7 ± 0.2	5.6 ± 0.2	36.9 ± 0.2	5.7 ± 0.1	42.7 ± 0.1	5.6 ± 0.1	41.7 ± 0.4	5.6 ± 0.1

Shaded rows denote the stages coinciding with an upward rise in heart rate

Convective heat exchange from the skin, C, was calculated as (Kerslake 1972):

$$C = h_c \cdot (T_{sk} - T_a)\ [W/m^2] \quad (3)$$

where h_c is the convective heat transfer coefficient for an individual facing an air velocity (Mitchell 1974):

$$h_c = 8.3 \cdot v^{0.6}\ \left[W/m^2/K\right] \quad (4)$$

where v is mean air velocity derived using a thermal manikin (4.2 m/s). During the 36NF and 42NF trials, air velocity was less than 0.2 m/s and h_c was assumed to be 3.1 $W/m^2/K$ (Parsons 2002).

Radiant heat transfer (R) was estimated by:

$$R = h_r \cdot (T_{sk} - T_r)\ [W/m^2] \quad (5)$$

where h_r (radiant heat transfer coefficient) in $W/m^2/K^1$ is estimated using the following:

$$h_r = \varepsilon \cdot 4\sigma \cdot \left(A_r/A_D\right) \cdot \left((T_{sk} + T_r)/2 + 273.15\right)^3\ \left[W/m^2/K\right] \quad (6)$$

where ε is the area weighted emissivity of the body surface (0.95), σ is the Stefan-Boltzmann constant (5.67×10^{-8} $W/m^2/K^4$), A_r/A_D is the effective radiative surface area (ND), which can be estimated as 0.70 for a seated person (Fanger 1967), and $T_{sk} + T_r$ is the sum of the mean skin temperature and mean radiant temperature (°C), assumed to be equivalent to T_a (°C).

Respiratory heat loss was estimated using the following:

$$E_{res} + C_{res} = \left[0.0173 \cdot (H_{prod}) \cdot (5.87 - P_a)\right] + \left[0.0014 \cdot (H_{prod}) \cdot (34 - T_a)\right]\ [W/m^2] \quad (7)$$

The evaporative requirement to maintain heat balance (E_{req}) in W/m^2 was estimated by rearranging the conceptual heat balance equation:

$$E_{req} = H_{prod} - (C + R + C_{res} + E_{res})\ [W/m^2] \quad (8)$$

Required skin wettedness (ω_{req}), defined by Gagge (1937), was estimated as:

$$\omega_{req} = E_{req}/E_{max}\ [ND] \quad (9)$$

where E_{max} is the theoretical maximum rate of evaporation in the prevailing climate when 100 % of the skin surface is saturated in sweat and can be calculated using:

$$E_{max} = (P_{sk,sat} - P_a)/(R_{e,cl} + [1/(f_{cl} \cdot h_e)])\ [W/m^2] \quad (10)$$

where $R_{e,cl}$ is the evaporative heat transfer resistance of the clothing layer (in m^2kPa/W), f_{cl} is the clothing area factor (surface area of the clothed body divided by the surface area of the nude body; ND), and h_e is the evaporative heat transfer coefficient (in W/m^2/kPa). $P_{sk,sat} - P_a$ is the difference in water vapor pressure between the skin and air in kPa. While P_a is a measured in absolute terms (in kPa), $P_{sk,sat}$ can be derived from Antoine's equation:

$$P_{sk,sat} = (\exp(18.956 - [4030.18/(T_{sk} + 235)]))/10\ [kPa] \quad (11)$$

where T_{sk} is mean skin temperature (°C).

For Eq. 10, the evaporative heat transfer coefficient (h_e) (in W/m^2/kPa) can be estimated using the product of the Lewis number (16.5 ND) and h_c:

$$h_e = 16.5\ h_c \quad (12)$$

Statistical analysis

Based on a power calculation (G*Power 3.1.9.2) with β- and α-values equal to 0.95 and 0.05, respectively, a minimum sample size of five participants was required based on evidence from critical vapor pressures of 4.16 ± 0.19 and 4.60 ± 0.13 kPa for unacclimated (Kenney and Zeman 2002) and heat acclimated (Kamon and Avellini 1976) women, respectively. All thermometric, cardiovascular, and heat loss measurements were averaged over the last minute of each humidity stage and expressed as means (±standard deviation).

As reported previously (Ravanelli et al. 2015), the critical humidity, at which elevations in heart rate were observed, was higher with fan use at both 36 °C (F 4.9 ± 0.4 kPa, NF 3.7 ± 0.5 kPa; $P < 0.001$) and 42 °C (F 3.8 ± 0.6 kPa, NF 3.1 ± 0.6; $P = 0.01$). The temperature and humidity ranges for stages during which an elevation in heart rate was observed are presented in Table 1. At the stage corresponding to the upward rise in heart rate, paired *t* tests were used to assess differences between groups (36F vs 36NF; 42F vs 42NF) for C + R, E_{req}, E_{max}, and ω_{req}. Moreover, paired *t* tests were used to assess the change from baseline to the end of the humidity ramp protocol between fan conditions (i.e., 36F vs 36NF; 42F vs 42NF) for heart rate, and esophageal, rectal, and mean skin temperatures.

To compare physiological variables across humidity levels during which elevations in heart rate were observed during the NF condition but not the F condition, three separate humidity "zones" were identified for each participant (Fig. 1) at 36 °C and 42 °C. These zones were defined as: zone 1 (Z1): heart rate not elevated from baseline during both fan conditions; zone 2 (Z2): heart rate elevated during NF but not during the F condition; and zone 3 (Z3): heart rate elevated during both fan conditions. A two-way repeated measures ANOVA was used to analyze the data using the repeated factor of humidity "zone" (rest, Z1, Z2, Z3, and end-trial) and the non-repeated factor of fan use (levels: F and NF) to compare heart rate, MAP, skin, esophageal, and rectal temperatures, as well as local sweat rate and cutaneous vascular conductance. When significance was found, individual differences were assessed using a Student's *t* test. For all multiple comparisons a fixed probability (5 %) of making a type I error was maintained throughout using a Holm-Bonferroni correction. All analysis was conducted using Graphpad Prism 6 for Windows statistical software (version 6.01, La Jolla, CA, USA).

Results

Alterations in human heat balance with fan use

At 36 °C, dry heat loss was greater with fan use ($P = 0.04$), which led to a lower E_{req} (Fig. 2a). E_{max} at baseline was increased more than twofold during fan use compared to no fan ($P < 0.01$). During the subsequent stepwise increases in humidity, E_{max} declined to a greater ($P < 0.01$) extent with fan use before an upward inflection in heart rate was observed (Fig. 2a). The ω_{req} at baseline was lower ($P < 0.001$) with fan use (0.13 ± 0.02) compared to the no fan condition (0.28 ± 0.04). At the critical humidity at which an upward inflection in heart rate was observed, ω_{req} remained lower ($P < 0.01$) with a fan (0.38 ± 0.13) than without a fan (0.52 ± 0.11).

At 42 °C, dry heat gain was ~70 W/m^2 greater ($P < 0.01$) with fan use (Fig. 2b), which resulted in a greater E_{req} ($P < 0.01$). However, E_{max} was twofold greater with fan use

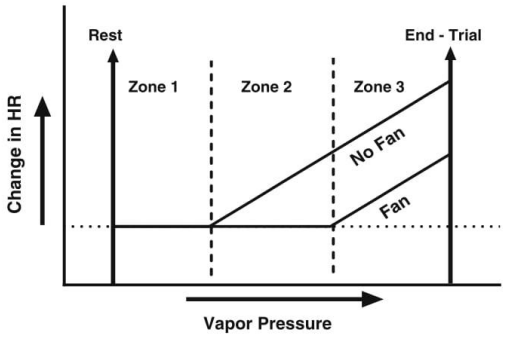

Fig. 1 Graphical representation of how zones 1, 2, and 3 were derived and analyzed for each participant. Zones were subject specific and were separated by the humidity coinciding with the upward rise in HR with (F) and without a fan (NF) for a given ambient temperature (36 °C and 42 °C). Within zones 1, 2, and 3, T_{es}, T_{re}, T_{sk}, MAP, cutaneous vascular conductance, and local sweat rate were compared between F and NF within each ambient temperature (36 °C, Table 2; 42 °C, Table 3)

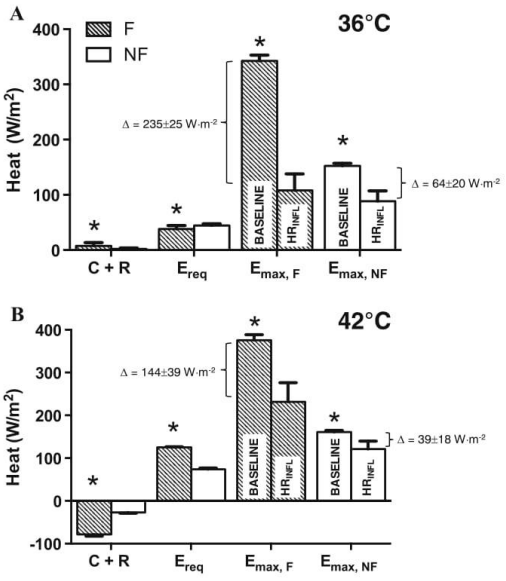

Fig. 2 The mean partitional calorimetric values at the stage prior to each participant's upward rise in HR at 36 °C (**a**) and 42 °C (**b**) with (*F*) and without a fan (*NF*). *C* + *R* dry heat loss, E_{req} evaporative requirement for heat balance, E_{max} theoretical maximum potential evaporative heat loss, *BASELINE* E_{max} at 1.6 kPa, HR_{INFL} E_{max} at inflection, *Significantly different to NF ($P < 0.05$)

at baseline and declined a greater extent compared to the no fan condition ($P < 0.01$) before an upward rise in heart rate was observed (Fig. 2b). At baseline, ω_{req} was lower ($P < 0.01$) with fan use (0.35 ± 0.02) compared to the no fan condition (0.45 ± 0.03). The ω_{req} at the critical humidity at which an upward inflection in heart rate was observed was similar ($P = 0.34$) with a fan (0.56 ± 0.14) compared to the no fan condition (0.61 ± 0.07).

Heart rate

The range of humidity, which captured Z1, Z2, and Z3, is outlined in Tables 2 and 3 for 36 °C and 42 °C, respectively. While Z2 demonstrates overlap in humidity due to individual variability for the critical humidity at which an inflection in heart rate occurred, no overlap is present between Z1 and Z3 for 36 and 42 °C. Prior to beginning the humidity-ramp protocol, heart rate was similar between conditions at 36 °C ($P = 0.60$) and 42 °C ($P = 0.35$). In humidity Z1, heart rate remained similar between conditions at both 36 °C ($P = 0.27$) and 42 °C ($P = 0.20$). By definition, heart rate was greater during the no fan condition at both 36 °C ($P = 0.002$) and 42 °C ($P = 0.05$) in Z2. In Z3, heart rate was elevated from baseline during both conditions but was greater during the no fan condition at both 36 °C ($P = 0.003$) and 42 °C ($P = 0.01$). At the end of the humidity-ramp protocol, heart rate was greater during the no fan condition at both 36 °C ($P = 0.02$) and 42 °C ($P < 0.001$).

Core and mean skin temperatures

At 36 °C, esophageal and rectal temperatures were similar ($p > 0.05$) between conditions at baseline. Core temperatures were also similar between conditions across the three zones (Table 2). At the end of the humidity-ramp protocol, esophageal temperature was greater without fan use ($P = 0.01$), but rectal temperature was similar ($P = 0.08$) to when a fan was used (Table 2). Similarly, at 42 °C, esophageal and rectal temperatures were similar ($P > 0.05$) between conditions at baseline and at each zone (Table 3). At the end of the humidity-ramp protocol, esophageal temperature was greater without a fan ($P = 0.03$), but rectal temperature was similar ($P = 0.21$) between conditions (Table 3).

At 36 °C, mean skin temperature was similar ($P > 0.05$) between conditions at baseline, heart rate zones 1 and 2 (Table 2) but became greater during the no fan condition during heart rate zone 3 ($P = 0.01$) and at the end of the humidity-ramp protocol ($P = 0.007$). At 42 °C, mean skin temperature was greater ($P < 0.05$) with fan use at baseline, and during all three zones (Table 3). By the end of the humidity-ramp protocol, mean skin temperature was similar between conditions ($P = 0.14$) due to a greater ($P = 0.04$) increase in mean skin temperature from baseline during the no fan condition (Table 3).

Mean arterial pressure

Mean arterial pressure was similar ($P > 0.05$) between conditions throughout the humidity-ramp protocol at both 36 °C (Table 2) and 42 °C (Table 3).

Sweating

At 36 °C, local sweat rate was similar between conditions at baseline and during Z1 but was greater ($P < 0.05$) without fan use during Z2 and Z3, as well as at the end of the humidity-ramp protocol (Table 2). At 42 °C, local sweat rate was also similar between conditions at baseline and during Z1 but became greater ($P < 0.05$) without fan use during Z2 and Z3, as well as at the end of the humidity-ramp protocol (Table 3). As previously reported (Ravanelli et al. 2015), whole body sweat rate was greater at 36 °C with a fan (180 ± 10 g/h) than without (153 ± 18 g/h; $P = 0.01$). Similarly, at 42 °C, whole body sweat rate was greater with a fan (399 ± 26 g/h) than without (241 ± 46 g/h; $P < 0.001$).

Table 2 Mean thermal and cardiovascular responses at the rest, during zone 1 (Z1), zone 2 (Z2), and zone 3 (Z3), and at the end of the protocol at 36 °C with (fan) and without (no fan) a fan

36 °C		HR (BPM)	T_{es} (°C)	T_{re} (°C)	T_{sk} (°C)	LSR (mg/cm^2/min)	MAP (mm Hg)	SkBF (PU)	CVC (PU/mm Hg)
Baseline									
	Fan	64 ± 7	36.4 ± 0.2	36.6 ± 0.3	36.7 ± 0.2	0.19 ± 0.04	88 ± 6	16.7 ± 3.3	0.18 ± 0.01
	No fan	66 ± 10	36.5 ± 0.2	36.7 ± 0.3	36.5 ± 0.3	0.21 ± 0.12	84 ± 7	27.4 ± 17.6	0.34 ± 0.23
Z1									
Relative humidity 49 ± 13 %	Fan	66 ± 8	36.5 ± 0.2	36.7 ± 0.3	36.9 ± 0.1	0.23 ± 0.03	88 ± 6	17.6 ± 2.7	0.19 ± 0.01
Range 28 ± 2 to 62 ± 9 %	No fan	67 ± 10	36.5 ± 0.2	36.7 ± 0.2	36.7 ± 0.3	0.23 ± 0.10	86 ± 7	23.3 ± 13.3	0.29 ± 0.17
Z2									
Relative humidity 74 ± 14 %	Fan	68 ± 8	36.6 ± 0.2	36.8 ± 0.2	37.1 ± 0.1	0.29 ± 0.06	89 ± 4	18.8 ± 2.4	0.21 ± 0.03
Range 62 ± 9 to 83 ± 6 %	No fan	75 ± 8*	36.6 ± 0.2	36.8 ± 0.2	37.1 ± 0.2	0.42 ± 0.19*	86 ± 6	31.4 ± 14.6	0.40 ± 0.18
Z3									
Relative humidity 89 ± 8 %	Fan	74 ± 9	36.7 ± 0.2	36.9 ± 0.2	37.3 ± 0.1	0.49 ± 0.11	88 ± 6	27.1 ± 7.2	0.30 ± 0.04
Range 83 ± 6 to 91 ± 3 %	No fan	84 ± 9*	36.7 ± 0.2	37.0 ± 0.2	37.6 ± 0.3*	0.67 ± 0.26*	85 ± 6	47.4 ± 18.2*	0.58 ± 0.26*
End-trial									
	Fan	78 ± 14	36.7 ± 0.2	36.9 ± 0.2	37.4 ± 0.2	0.60 ± 0.15	86 ± 8	34.2 ± 17.7	0.34 ± 0.06
	No fan	89 ± 10*	36.8 ± 0.2*	37.1 ± 0.3	37.8 ± 0.4*	0.80 ± 0.30*	83 ± 7	54.1 ± 20.1*	0.62 ± 0.27*
Δ Rest—end-trial									
	Fan	14 ± 14	0.3 ± 0.2	0.4 ± 0.2	0.8 ± 0.3	–	–	–	–
	No fan	23 ± 7*	0.4 ± 0.2*	0.4 ± 0.2	1.3 ± 0.4*	–	–	–	–

HR heart rate, *BPM* beats per minute, T_{es} esophageal temperature, T_{re} rectal temperature, T_{sk} mean skin temperature, *LSR* mean local sweat rate, *SkBF* mean skin blood flow, *CVC* cutaneous vascular conductance

*Significantly greater than NF ($P < 0.05$)

Table 3 Mean thermal and cardiovascular responses at rest, during zone 1 (Z1), zone 2 (Z2), and zone 3 (Z3), and at the end of the protocol (end-trial) at 42 °C with (fan) and without (no fan) a fan

42 °C		HR (BPM)	T_{es} (°C)	T_{re} (°C)	T_{sk} (°C)	LSR (mg/cm^2/min)	MAP (mmHg)	SkBF (PU)	CVC (PU/mmHg)
Baseline									
	Fan	73 ± 7	36.6 ± 0.3	36.7 ± 0.3	38.1 ± 0.4*	0.53 ± 0.20	86 ± 6	29.9 ± 9.3	0.36 ± 0.13
	No fan	71 ± 11	36.5 ± 0.2	36.7 ± 0.3	37.5 ± 0.3	0.50 ± 0.19	86 ± 6	27.3 ± 9.9	0.32 ± 0.11
Z1									
Relative humidity 31 ± 7 %	Fan	75 ± 7	36.6 ± 0.3	36.8 ± 0.3	38.3 ± 0.2*	0.53 ± 0.18	87 ± 6	32.0 ± 9.1	0.38 ± 0.12
Range 22 ± 1 to 38 ± 7 %	No fan	72 ± 10	36.6 ± 0.2	36.8 ± 0.2	37.7 ± 0.2	0.56 ± 0.19	86 ± 5	30.8 ± 10.1	0.36 ± 0.12
Z2									
Relative humidity 44 ± 9 %	Fan	76 ± 7	36.7 ± 0.3	37.0 ± 0.3	38.5 ± 0.2*	0.60 ± 0.20	87 ± 6	35.4 ± 9.4	0.41 ± 0.12
Range 38 ± 7 to 47 ± 7 %	No fan	81 ± 7*	36.6 ± 0.1	37.0 ± 0.2	37.9 ± 0.3	0.75 ± 0.20*	85 ± 7	38.5 ± 16.8	0.40 ± 0.15
Z3									
Relative humidity 57 ± 8 %	Fan	87 ± 8	36.9 ± 0.3	37.2 ± 0.3	38.9 ± 0.3*	0.86 ± 0.25	86 ± 6	49.9 ± 9.2	0.61 ± 0.13
Range 47 ± 7 to 67 ± 3 %	No fan	94 ± 9*	37.0 ± 0.1	37.2 ± 0.2	38.5 ± 0.3	1.13 ± 0.29*	85 ± 5	59.8 ± 23.4	0.69 ± 0.29
End-trial									
	Fan	96 ± 11	37.2 ± 0.3	37.4 ± 0.3	39.1 ± 0.3	1.09 ± 0.25	87 ± 8	73.1 ± 31.2	0.85 ± 0.34
	No fan	109 ± 11*	37.4 ± 0.2*	37.5 ± 0.2	38.9 ± 0.3	1.39 ± 0.29*	87 ± 5	71.1 ± 29.6	0.82 ± 0.34
Δ Rest—end-trial									
	Fan	23 ± 8	0.6 ± 0.2	0.6 ± 0.1	1.0 ± 0.3	–	–		
	No fan	38 ± 13*	0.9 ± 0.1*	0.8 ± 0.2	1.4 ± 0.4*	–	–		

HR heart rate, *BPM* beats per minute, T_{es} esophageal temperature, T_{re} rectal temperature, T_{sk} mean skin temperature, *LSR* mean local sweat rate, *SkBF* mean skin blood flow, *CVC* cutaneous vascular conductance

*Significantly greater than other condition ($P < 0.05$)

Skin blood flow

At 36 °C, skin blood flow (absolute values) and cutaneous vascular conductance were similar between conditions at baseline and during Z1 and Z2 but became greater without a fan during Z3 and at the end of the protocol (Table 2). At 42 °C, skin blood flow (absolute units) and cutaneous vascular conductance were similar between conditions throughout the humidity-ramp protocol (Table 3).

Discussion

The current study examined potential biophysical and physiological factors associated with the delayed increase in heart rate with fan use during extreme heat and humidity conditions. Biophysically, a greater air velocity across the skin surface with fan use led to negligible changes in dry heat exchange at 36 °C, whereas ~70 W/m^2 of additional dry heat was gained via convection at 42 °C (Fig. 2). However, at both ambient temperatures, the greater potential for evaporation with fan use increased evaporative efficiency. While evaporative efficiency was not directly quantified, the additional ~70 W/m^2 of dry heat gain with fan use at 42 °C must have been offset by at least an equally greater evaporative heat loss as the increase in core temperature was delayed relative to the no fan condition (Ravanelli et al. 2015). From a physiological perspective, the different inflection points for increases in heart rate between the fan and the no fan conditions seemed to coincide with elevations in sudomotor output at both 36 °C and 42 °C. Collectively, the delayed increase in heart rate with electric fan use was associated with increased evaporative efficiency and lower sudomotor output.

At 36 °C, air temperature was similar to mean skin temperature. Therefore, differences in dry heat loss and thus the evaporative requirement for heat balance were trivial (<5 W/m^2) between conditions. The influence of fan use on the potential for evaporative heat loss however was profound (i.e., ~250 W/m^2 greater with a fan; Fig. 2a) due to a greater convective and therefore evaporative heat transfer coefficient (Nelson et al. 1948; Clifford et al. 1959). As ambient humidity progressively increased during the humidity-ramp protocol, E_{max} naturally declined due to a shrinking humidity gradient between the skin and air. The E_{max} value at which elevations in heart rate occurred was slightly greater with fan use. However, because E_{max} started at a much greater level with fan use it took longer, and therefore a greater relative humidity (i.e., 83 ± 6 % RH; Ravanelli et al. 2015) for E_{max} to reach a similar level as that observed during the no fan condition. This greater "buffer" for increases in humidity with fan use at 36 °C can be explained in terms of greater evaporative efficiency. The work of Candas et al. (1979a, 1979b) and Alber-Wallerström (1985) demonstrate that if E_{req} is small relative to E_{max}, evaporative efficiency is greater, but as E_{req} approaches E_{max} evaporative efficiency rapidly declines. Prior to the start of the humidity ramp protocol at 36 °C, E_{req} was ~10 % of E_{max} with fan use but ~30 % of E_{max} without fan use (Fig. 2a). Decrements in evaporative efficiency would have therefore occurred at a lower relative humidity (i.e. earlier during the ramp protocol) during the no fan condition. In order to maintain heat balance during heat stress, E_{req} must be sustained. With reductions in evaporative efficiency, a concomitant rise in sweating must occur to sustain E_{req} which was reflected by greater local sweat rate values (Table 2).

The main argument proposed by public health agencies for not using a fan during heat waves is that additional air flow across the skin will accelerate dry heat gain (Wolfe 2003; CDC 2004; WHO 2009). Indeed, this was observed during the 42 °C trial as fan use resulted in ~70 W/m^2 greater dry heat gain. However, an often neglected advantage of fan use in the public health literature is that it also promotes evaporation by increasing evaporative efficiency. In this study, fan use resulted in an evaporative heat loss potential that was 160 W/m^2 greater relative to no fan use. As such, the required evaporation for heat balance only accounted for ~35 % of the maximum evaporative potential during fan use, which is relative to ~45 % with no fan. According to the findings of Alber-Wallerström (1985), decrements in evaporative efficiency would have occurred even before the humidity ramp protocol started during the no fan condition, whereas fan use would have maintained sweat evaporation at ~100 %. Moreover, the critical skin wettedness (ω_{crit}; E_{req}/E_{max}) at which elevations in heart rate were observed by Berglund and Gonzalez (1977) was lower with air movement relative to still air. The present results partially concur with these findings with lower ω_{crit} when the inflection in heart rate occurred at 36 °C (F 0.38 ± 0.13; NF 0.52 ± 0.11) but not 42 °C (F 0.56 ± 0.14; NF 0.61 ± 0.07). The reason for differences in ω_{crit} between fan conditions at 36 °C but not 42 °C is unclear; however, it must be acknowledged that partitional calorimetric estimates of heat transfer values are based on several assumptions and subject to variability. Despite these limitations, we propose that fan use facilitated a greater evaporative efficiency during the humidity-ramp protocol, which is further supported by the lower local sweat rate values (Table 3).

The underlying physiological mechanisms responsible for the delayed increase in heart rate with fan use are difficult to determine from the present data. It was hypothesized that earlier heart rate elevations without fan use would be preceded by greater peripheral vasodilation, leading to a greater heart rate requirement for the maintenance of blood pressure. Indirect evidence suggests that this may be the case. Assuming that stroke volume was similar between fan and no fan conditions, greater heart rate during the no fan conditions presumably lead to greater cardiac output. Given that blood pressure was similar between fan and no fan conditions, it is possible that a

greater cardiac output would be associated with greater peripheral vasodilation during the no fan conditions. In theory, this could be due to greater cutaneous vasodilation, although we cannot rule out the possibility of greater vasodilation within other vascular beds. While this hypothesis is supported by greater cutaneous vasodilation during the no fan condition when elevations in heart rate were observed at 36 °C, a separation in heart rate between fan conditions (Z2) was observed without any preceding differences in cutaneous vasodilation at 42 °C (Table 3). Alternatively, a higher mean skin temperature at 42 °C with fan use could have theoretically led to greater cutaneous vasodilation (Rowell et al. 1970; Wyss et al. 1975; Wingo et al. 2010) and heart rate via stimulation of cutaneous thermoreceptors (Shibasaki et al. 2015), but this was not observed. In fact, heart rate was lower with fan use at 42 °C.

It should be noted that cutaneous vasodilation was only measured at two local sites, and it is therefore possible that differences in other body regions were not detected. Rowell et al. (1970) reported that elevations in heart rate during aggressive passive heating (47.5 °C water perfused suit) were not lowered following the restoration of mean arterial pressure to normothermic levels, suggesting that blood pressure maintenance is not necessarily the primary driver of heat-related elevations in heart rate. This notion was further supported by Cui et al. (2002) who observed only a minor decrease in heart rate during passive heating (46 °C water perfused suit) following the reestablishment of normothermic blood pressure with phenylephrine infusion. Collectively, these and other studies (Kamon and Belding 1971; Wyss et al. 1974; Gorman and Proppe 1982) suggest that heart rate elevations during passive heating are partially driven by direct effects of temperature upon the heart (Jose et al. 1970; Gorman and Proppe 1982). However, core temperatures were similar between fan and no fan conditions and were actually unchanged from baseline when the elevations in heart rate occurred at both ambient temperatures. Differences in core temperature therefore cannot explain the earlier elevations in heart rate observed without fan use. The only physiological response measured that differed between fan conditions at both ambient temperatures when the elevation in heart rate occurred without fan use was local sweat rate (Tables 2 and 3).

Perspectives

The present results suggest that the different critical humidities at which elevations in heart rate are observed with and without fan use are potentially associated with an elevated sudomotor drive, secondary to decrements in evaporative efficiency. While future studies are required to examine whether this is a direct cause and effect or indirect link, cooling interventions during extreme heat exposure (i.e., heat waves) that strive to mitigate elevations in heart rate could possibly focus on reducing the heat balance requirement for sweat production. Under circumstances that air conditioning is not available, which is a commonplace for most vulnerable populations during heat waves (Bouchama et al. 2007; Basu and Ostro 2008; Kravchenko et al. 2013), the propagation of convective flow across the skin coupled with external moistening of the skin may suppress the need for sweating. Empirical evidence supporting this notion however is needed. If supplemental air flow is not available, a combination of external skin wetting and conductive cooling (e.g., cold water forearm or foot immersion) that provides ~80–90 W/m^2 of heat loss would minimize the evaporative requirement for heat balance and therefore reduce the necessity for sweating at 42 °C (Fig. 2b).

Limitations and future studies

The present data pertain only to young, healthy males; they therefore do not account for age-related decrements in sweating capacity of older individuals (Kenney and Hodgson 1987; Inoue et al. 1991) nor the lower maximum evaporative capacity of females (Gagnon and Kenny 2011). The potential benefit of fan use has also only been demonstrated in hot/humid conditions. Inhabitants of some geographical regions (e.g., South Australia) often experience very hot (>45 °C) and dry (RH <10 %) heat waves. In such environments, most secreted sweat would readily evaporate in relatively still air and fan use may therefore not increase evaporative efficiency while creating additional dry heat gain. The efficacy of fan use under hot/dry versus hot/humid conditions must therefore be evaluated. Moreover, metabolic heat production was not measured directly and assumed to be constant. While this assumption may be limited, Hardy and Stolwijk (1966) observed very minor differences in metabolic rate between the ambient temperatures tested in the present study. It is also difficult to provide a comprehensive explanation for the different heart rate responses between fan conditions without measurements of cardiac output, therefore further research incorporating this measure is warranted. Finally, only one fan speed, diameter, orientation, and distance from the participant was tested, and further research is required to assess the influence of these variables on thermal and cardiovascular strain.

Conclusion

In conclusion, delayed elevations in heart rate with fan use during extreme heat and humidity conditions are associated with (i) a greater increase in evaporative efficiency relative to the increase in convective heat gain; and (ii) a lower sudomotor output.

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Author contributions N.M.R., O.J., S.H., and G.H. were involved in the concept and design of the research question and methodology; N.M.R. performed all data collection; N.M.R. analyzed the data; N.M.R., O.J., S.H., G.H., and D.G. interpreted the results; N.M.R. prepared the figures; N.M.R. and O.J. drafted the manuscript; N.M.R. and O.J. edited the manuscript; N.M.R., O.J., D.G., S.H., and G.H. approved the final version of manuscript.

Compliance with ethical standards All participants provided written informed consent prior to their participation in the study.

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

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APPENDIX J: Persistant organic pollutants in sweat

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Can POPs be substantially popped out through sweat?

In an elegant review by Lee et al. (Lee et al., 2017), the authors emphasize the role of adipose tissue as a repository site for low dose chemical mixtures and its importance in carcinogenesis and the prognosis of cancer patients. Additionally, the authors propose that physical activity may improve the prognosis among cancer survivors via the excretion of persistent organic pollutants (POPs) via sweat. Although this hypothesis is certainly appealing, the evidence supporting sweat as a medium for meaningful POPs excretion may be improbable.

Humans have both apocrine and eccrine sweat glands, with eccrine glands being the most abundant serving the principle function of thermoregulation during heat stress and exercise. The average human body has 2 to 4 million eccrine sweat glands distributed over the surface excluding axillae and genital regions (Sato et al., 1989). The eccrine sweat gland is a single tubular structure comprising a duct and a secretory coil. Fluid accumulates in the secretory coil via the active transport of ions across the basilar membrane of clear cells promoting an osmotic gradient into the cell from the vascular space followed by secretion into the lumen (Sato et al., 1989). Under comfortable conditions, ~0.5 L of water loss per day can be attributed to insensible perspiration from the skin at rest while exercise can result in sweat losses up to 2 L/h, and can be further exacerbated when exercising in hot conditions (Taylor and Machado-Moreira, 2013). Secreted sweat on the skin's surface contains primarily electrolytes such as sodium, chloride, and potassium, in addition to urea, amino acids, and trace amounts of fatty acids (Sato et al., 1989; Takemura et al., 1989). Since ancient times, excessive sweating has been thought to purify the body and release toxins from the blood, and more recent evidence provides some affirmation to these traditional practices which predate modern science.

POPs are a wide range of compounds that include dioxins, polychlorinated biphenyls (PCBs), organochlorine pesticides and perfluorinated acids. POPs have a high affinity to bind to lipids (e.g. lipophilic), thus they will preferentially accumulate in lipid-containing tissues and be primarily transported within the human body via lipid molecules. While excretion of hydrophilic compounds via perspiration has been documented (Cohn and Emmett, 1978; Genuis et al., 2011; Mitchell and Hamilton, 1949), the substantial release of POPs through sweat is questionable. Genuis et al. (Genuis et al., 2013) quantified perfluorinated compounds and PCBs in sweat and blood samples of men and women and reported that induced perspiration does not seem to favor the clearance of perfluorinated compounds, but appears to stimulate the elimination of some PCB congeners from the human body. Whether the elimination of POPs in sweat can possibly have a notable impact on reducing body burden warrants further investigation.

Alternatively, one can estimate the levels of POPs in sweat based on its lipid content. This can be done if one assumes that the amount of POPs per lipid basis in sweat is comparable to what is found in blood. For example, we have previously reported that the total POPs concentration derived from the sum of PCBs and organochlorine pesticides in individuals with obesity is approximately of 600 μg/kg lipids (Chevrier et al., 2000). Knowing that clean sweat, e.g. with no epidermal contamination, contained 0.08 μg/mL of lipids (Takemura et al., 1989), it is estimated that 4.8×10^{-8} μg of POPs would be contained per ml of clean sweat. An individual losing 1 L of sweat per day (double the mean rate of insensible perspiration) would eliminate approximately 4.8×10^{-5} μg of POPs. Based on the occurrence of non-dioxin-like PCBs (as represented by the PCBs congeners 28, 52, 101, 118, 138, 153 and 180) in food products consumed in The Netherlands that were collected in measurement programs carried out during 1998 and 1999, Baars et al. (Baars et al., 2004) reported that the estimated median lifelong-averaged intake of the measured PCBs was 5.6 ng per kilogram body weight per day. This would correspond to an estimated daily ingestion of 0.392 μg of PCBs for an individual of 70 kg. If one assumes an additional 1 L per day of sweat loss during physical activity, the total amount of POPs excretion via sweating would amount to 9.6×10^{-5} μg per day; corresponding to less than 0.024% of daily PCBs intake. In stark contrast, if previously reported quantity of PCBs measured in sweat by Genuis et al. (Genuis et al., 2013) are correct, the average individual would excrete over 25.5 μg per day of solely PCB_{52} through insensible perspiration; more than 65 times the mean daily PCBs intake. Together, based on our estimates, POPs excretion via sweat is negligible and can be easily compensated by the increased food intake commonly associated with regular physical activity (Mayer et al., 1956).

In sum, we fully agree with Lee et al. (Lee et al., 2017) that physical activity protects against the development of many cancers and improves prognosis among cancer survivors. The underlying mechanism by which physical activity operates its magic is probably not through an increase excretion of POPs via perspiration.

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APPENDIX K: Book chapter which comprises a portion of literature review

The biophysics of human heat exchange

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Abstract

This chapter describes the fundamental factors that influence heat exchange between the human body and its surrounding environment. The bulk of heat exchange takes place at the skin surface via sensible heat transfer (i.e. convection and radiation), and evaporation. With increasing ambient temperature, the gradient for sensible heat transfer declines, meaning that the human body becomes increasingly dependent on the evaporation of sweat for heat dissipation. If the combination of climate (air temperature, radiant temperature, humidity and air velocity) and clothing permit a sufficient level of heat dissipation to counterbalance the rate of internal heat production, elevations in core temperature are moderated (i.e. compensable heat stress). However, if heat production exceeds the upper capacity to lose heat from the skin surface due to high ambient temperatures, humidity, low wind speeds, or high evaporative resistance of clothing, a continuous increase in core temperature occurs (i.e. uncompensable heat stress).

Introduction

The ability to maintain body temperature within a narrow range during acute or chronic exposure to environmental extremes is paramount for optimal human performance, and ultimately, survival. Muscle contractions during different sporting activities can result in a greatly elevated internal heat production. The subsequent changes in body temperature are managed to an extent by physiologically modulating heat exchange between the skin surface and the surrounding environment via sensible (convection (C), radiation (R), and conduction (K)), and insensible (evaporation (E)) heat transfer. However, the net heat dissipation via these heat transfer avenues is also strongly determined by the physical characteristics of the thermal environment that the sport is performed in. To optimally assess the risk of thermal stress for an athlete performing a given sport in a particular environment, the biophysical processes that govern the dynamic balance between internal heat production and skin surface heat dissipation must therefore be fully considered.

Human heat balance

The fundamental law of human heat balance illustrates that internal metabolic heat production (M-W) must be balanced by an equal rate of net heat dissipation, i.e. combined sensible and insensible heat losses from the skin (sk) and respiratory tract (res) to the surrounding environment to ensure a rate of body storage (S) of zero (i.e. heat balance):

$$(M - W) = (\pm K_{sk} \pm C_{sk} \pm R_{sk}) + (C_{res} + E_{res}) + E_{sk} \pm S \qquad [\text{in } W \cdot m^{-2}] \qquad (1)$$

Metabolic Heat Production (M-W): is the difference between metabolic rate (M) and the external work performed (W). In its most basic form, M is the amount of energy released by hydrolyzing adenosine triphosphate (ATP) into adenosine diphosphate (ADP) and an inorganic phosphate

molecule. It follows that a proportion of the energy released from this process is then utilized to create W, however the human body is quite inefficient and about 75-95% of M does not ultimately contribute to W but instead is liberated internally as heat (17, 25, 55). Road cycling is one of the most efficient sporting activities (~30% of M is used for W (59)), so at an external work load of 240 W a metabolic rate of ~840 W is required, with ~600 W of this energy released as heat (Figure 1). Running and walking are among the least efficient activities, especially on a flat surface, where effectively no external work is performed and all metabolic energy is converted to heat (35, 50).

Carbohydrates and lipids are the two main substrates utilized by the body to produce ATP, and although ATP can be produced both aerobically and anaerobically within a cell, oxygen consumption is required to restore ATP pools. Thus, M can be estimated (44) by measuring the rate of oxygen consumption and carbon dioxide production using:

$$M = VO_2 \cdot \frac{\left[\left(\left(\frac{RER-0.7}{0.3}\right)\cdot e_c\right)+\left(\left(\frac{1.0-RER}{0.3}\right)\cdot e_f\right)\right]}{60} \cdot 1000 \qquad \text{[in W]} \qquad (2)$$

Where: VO_2 is the rate of oxygen consumption in $L \cdot min^{-1}$, RER is the ratio of carbon dioxide production to oxygen consumption, e_c is the caloric equivalent per liter of oxygen for the oxidation of carbohydrates (21.13 kJ), and e_f is the caloric equivalent per liter of oxygen for the oxidation of lipids (19.62 kJ). To normalize *M*-*W* in $W \cdot m^{-2}$ it must be divided by the body surface area (BSA) of the individual using the Dubois and Dubois equation (16):

$$BSA = 0.202 \times \text{mass}^{0.425} \times \text{height}^{0.725} \qquad \text{[in } m^2\text{]} \qquad (3)$$

Where: mass of the person is in kg, and the height of the person in m.

---- INSERT FIGURE 1 ----

Sensible Heat Transfer from the Skin (± K_{sk} ± C_{sk} ± R_{sk}): is the sum of conduction (K_{sk}), convection (C_{sk}), and radiation (R_{sk}). These three avenues of heat transfer abide by the second law of thermodynamics, whereby heat energy moves from an area of high concentration to low concentration (e.g. from high to low temperature). During active or passive heat stress, the prevailing temperature gradients for sensible heat transfer may be minimal or even negative, which leads to sensible heat gain through one or more avenue at ambient temperatures above skin temperature (i.e. 35 to 36°C) (Figure 1).

Conduction (K_{sk}): is the transfer of heat energy through direct contact between the skin and a solid object. From a whole-body heat balance perspective, particularly human heat stress conditions, K is generally assumed to be negligible, with the primary means for sensible heat transfer via convection and radiation. However, when a solid object is in direct contact with the skin (e.g. a cold metallic wall), conductive heat transfer can be calculated as:

$$K = kA\,(T_2 - T_1)/L \qquad [\text{in } W \cdot m^{-2}] \qquad (4)$$

Where: k is the estimated thermal conductivity of the object in contact with the skin, A is the total surface area of contact between the skin and solid (in m^2), (T_2-T_1) is the absolute temperature difference between the skin and the solid's external surface, and L is the thickness of the solid object in contact with the skin surface.

Radiation (R_{sk}): Heat exchange by radiation is the electromagnetic energy transfer between a relatively cool and warm body. Radiative heat loss from the skin for a nude person can be derived using:

$$R_{sk} = h_r\,(T_{sk} - T_r) \qquad [\text{in } W \cdot m^{-2}] \qquad (5)$$

Where: T_{sk} is mean skin temperature (in °C), T_r is mean radiant temperature (in °C), and h_r is the radiative heat transfer coefficient (in $W \cdot m^{-2} \cdot K^{-1}$), which is estimated using:

$$h_r = 4\varepsilon\sigma \frac{A_r}{A_D} [273.2 + \frac{T_{sk} + T_r}{2}]^3 \qquad [\text{in } W \cdot m^{-2} \cdot K^{-1}] \qquad (6)$$

Where: ε is the emissivity of the body surface (usually assumed to be 0.95), σ is the Stefan-Boltzmann constant (5.67×10^{-8} $W \cdot m^{-2} \cdot K^{-4}$), A_r/A_D is the effective radiative area of the body (m^2) which can be estimated as 0.70 or 0.73 for a seated or standing person (19), respectively, and $T_{sk} + T_r$ is the sum of mean skin temperature and mean radiant temperature. Mean radiant temperature is assumed to be equal to ambient air temperature when indoors without any substantial sources of radiation. However, in other environments, e.g. outdoor sun exposure, mean radiant temperature of the environment must be estimated using black globe temperature (T_g) measured with a standard 150 mm diameter black globe thermometer placed in a similar location as the exposed individual (e.g. in direct sunlight). T_g will vary depending on the time of day and year due to differences in the angle between the sun and the horizon. However, when interested in calculating radiative heat transfer for an individual wearing clothing, a black globe thermometer may overestimate the effect of a radiative source (particularly the sun) and should therefore be similar in color to the clothing worn by the individual. Lastly, air velocity (*v*) in m/s near the black globe thermometer must be measured as greater air flow will alter T_g for a given amount of radiant heat energy. According to ISO 7726:1998 (31) mean radiant temperature (T_r) can be derived as follows:

If v < 0.15 m/s:

$$T_r = [(T_g + 273)^4 + \frac{0.25 \cdot 10^8}{\varepsilon} \cdot \left[\frac{T_g + T_a}{d}\right]^{0.25} \cdot (T_g - T_a)]^{0.25} - 273 \qquad [\text{in °C}] \qquad (7)$$

Where: *d* is black globe diameter (in cm)

If v ≥ 0.15 m/s:

$$T_r = [(T_g + 273)^4 + \frac{1.1 \cdot 10^8 v^{0.6}}{0.44} \cdot (T_g - T_a)\ ]^{0.25} \quad - \quad 273 \qquad [\text{in °C}] \qquad (8)$$

Convection (C_{sk}): is the transfer of heat to a moving gas (air) or liquid (water), which is increased by the movement of the body in air or water or movement of air or water across the skin. It is directly proportional to the temperature difference between the skin surface and the ambient environment, and air velocity passing across the skin. A warm surface such as the skin can also produce natural convection when a person is still, where the boundary layer movement is a result of differing air densities arising from a temperature gradient (e.g. warm air rises). Alternatively, and more commonly, forced convection pushes air across the skin surface (e.g. a fan) or convection is self-generated as a person moves through an air mass. Convective heat transfer for a nude person can be estimated using (46):

$$C_{sk} = h_c\ (T_{sk} - T_a) \qquad [\text{in W}\cdot\text{m}^{-2}] \qquad (9)$$

Where: T_{sk} is mean skin temperature (˚C); T_a is ambient air temperature (˚C); and h_c is the convective heat transfer coefficient (in $W\cdot m^{-2}\cdot K^{-1}$). For natural convection in still conditions, this value can be assumed to be 3.1 $W\cdot m^{-2}\cdot K^{-1}$ (40). If air velocity is >0.2 m/s, but <4.0 m/s, the convective heat transfer coefficient can be estimated using:

$$h_c = 8.3v^{0.6} \qquad [\text{in W}\cdot\text{m}^{-2}\cdot\text{K}^{-1}] \qquad (10)$$

Where: *v* is the mean air velocity around the body in m/s. During physical activity, it may be more practical to consider the mean net air flow across the body surface rather than just the mean ambient air velocity as this accounts for the path of movement relative to wind direction. Indeed, it is evident that the magnitude of self-generated air flow can influence the convective heat transfer

coefficient. For example, independent of clothing and equipment, the higher heat strain for American football lineman compared to non-lineman has been attributed to the more static nature of their position specific activities (e.g. blocking vs. running routes) (14, 26). Alternatively, self-generated convection during outdoor cycling (>20 km/h) will in most cases be far greater than in laboratory settings (13). As such, specific equations have been derived for estimating the convective heat transfer coefficient during different modalities of human movement (Table 1).

---- INSERT TABLE 1 ----

All convective heat transfer coefficients presented have been developed for thermal stress at approximately sea level. The relationship between barometric pressure (P_b) and convective heat transfer can be integrated into equation 9 as follows (21):

$$C_{sk} = h_c\,(T_{sk} - T_a)\,(P_b/760)^{0.55} \qquad [\text{in } W\cdot m^{-2}] \qquad (11)$$

If clothing is worn, combined sensible heat transfer via convection and radiation ($C_{sk} + R_{sk}$) can be estimated using:

$$C_{sk} + R_{sk} = \frac{(T_{sk} - T_o)}{\left(R_{cl} + \frac{1}{h \cdot f_{cl}}\right)} \qquad [\text{in } W\cdot m^{-2}] \qquad (12)$$

Where: T_o is operative temperature (in °C):

$$T_o = \frac{(h_r T_r + h_c T_a)}{(h_r + h_c)} \qquad [\text{in } °C] \qquad (13)$$

And: h is the combined heat transfer coefficient (in $W\cdot m^{-2}\cdot K^{-1}$), i.e. $h_c + h_r$; and f_{cl} is the clothing area factor defined as the surface area of the clothed body divided by the surface area of the nude body and estimated using (37):

$$f_{cl} = 1 + \left[\frac{0.31 \cdot R_{cl}}{0.155}\right] \quad \text{[ND]} \quad (14)$$

Where: R_{cl} is the dry heat transfer resistance of clothing (in $m^2 \cdot °C^{-1} \cdot W^{-1}$), which can be obtained from normative tables (30, 37) such as the International Standardisation Organisation (ISO) 9920 standard.

Additionally, convective heat loss by water movement is important for example in swimmers. The convective heat loss is, in contradiction to convective heat loss by air movement, not a function of the water velocity (42). Due to water turbulence created during swimming in a swimming pool, the effective water velocity around a swimmer does not differ irrespective of swimming speed. As a result, convective heat exchange for swimmers is predominantly determined by water temperature, whereby heat is lost if water temperature is lower than skin temperature, and vice-versa. Due to a higher density, specific heat capacity, and thermal conductivity (34), convective heat loss is much greater in water than in air (42). Given exercise is typically performed on land, detailed equations for convective heat exchange in water is beyond the scope of this chapter. However, for a detailed description we refer readers to the article of Brandt and Pichowsky (6).

Respiratory Heat Exchange (C_{res} + E_{res}): Respiratory heat exchange occurs through the convective heat transfer (C_{res}) between inhaled air and the lungs, and evaporative heat loss from the respiratory tract (E_{res}) due to the saturation of air with water vapour when entering the lungs. Net respiratory heat exchange can be estimated using (2):

$$C_{res} + E_{res} = [0.0014M \bullet (34 - T_a)] + [0.0173M \bullet (5.87 - P_a)] \quad \text{[in } W \cdot m^{-2}\text{]} \quad (15)$$

Where: M is metabolic heat production in $W \cdot m^{-2}$, T_a is air temperature in °C, and P_a is the ambient water vapor pressure in kPa.

The rate of respiratory heat loss is dependent on the temperature and humidity of inspired air (36, 54) and minute ventilation (7, 41). As such, the amount of convective heat transfer through respiration during exercise in the heat compared to the cold is minimal due to the small temperature gradient between ambient and core temperature. Additionally, the amount of evaporative heat loss via respiration is dependent on the humidity gradient between the lungs and the air, and the rate of ventilation which is assumed to have a linear relationship with the rate of metabolic energy expenditure (up to 80% of maximum oxygen consumption; (41)).

Evaporation from skin surface (E_{sk}): The evaporation of sweat (or water) from the skin surface is the largest modifiable avenue of heat loss from the body. During heat stress, sweating becomes the predominant factor for determining whether heat balance is achieved, and when air temperature equals skin temperature and dry heat loss is eliminated, evaporation becomes the only avenue for dissipating metabolic heat at the skin surface (43). The latent heat lost for every gram of sweat that completely evaporates from the skin is 2.426 kJ (56). As such, evaporative heat loss can be estimated using body mass changes corrected for metabolic and respiratory mass losses, as well as any ingested fluids, but only under conditions that permit complete evaporation (3). Arguably the most accurate method for estimating evaporative heat loss is direct calorimetry, which measures the difference in absolute water vapor pressure between influent and effluent of an enclosed air space (51). However, once again the complete evaporation of all sweat from the skin is a necessity and is typically achieved in a calorimeter by ensuring a high and turbulent air mass flow (49).

Under combinations of climate and activity that yield incomplete sweat evaporation from the skin surface, evaporative efficiency (i.e. the proportion of secreted sweat that actually evaporates; (1)) can be roughly estimated. It is known that as the sweat saturation level of the skin reaches a maximum, evaporative efficiency rapidly declines (1, 10, 24). First described by Gagge (20), sweat

saturation levels can be expressed as a "skin wettedness" value (ω), which is physiologically defined as the fraction of the skin surface that is covered in sweat. It follows that reductions in evaporative efficiency have been reported when ω >0.50 during passive heat stress (11), and when ω >0.30 during upright cycling (1); meaning that while greater levels of skin wettedness permit greater rates of evaporation this comes at the expense of a disproportionately greater rate of sweating. Mathematically, the ω value required (for heat balance; ω_{req}) is defined as the ratio of the evaporative requirement to maintain heat balance (E_{req}) relative to the maximum evaporative capacity in the ambient environment (E_{max}):

$$\omega_{req} = {E_{req}}\Big/{E_{max}} \qquad \text{[ND]} \qquad (16)$$

By rearranging the conceptual heat balance equation (equation 1), and assuming a rate of body heat storage (S) of zero, E_{req} can be estimated as follows:

$$E_{req} = (M - W) - (\pm K_{sk} \pm C_{sk} \pm R_{sk}) - (C_{res} + E_{res}) \qquad \text{[in W·m}^{-2}\text{]} \qquad (17)$$

E_{max} is determined by the water vapour pressure gradient between the skin and the air, as well as air speed, clothing properties, and the maximum proportion of the skin that can be physiologically saturated with sweat (ω_{max}):

$$E_{max} = \omega_{max} \frac{(P_{sk,sat} - P_a)}{\left(R_{e,cl} + \frac{1}{h_e \cdot f_{cl}}\right)} \qquad \text{[in W·m}^{-2}\text{]} \qquad (18)$$

Where: ω_{max} is maximum skin wettedness, which can reach 1.00 for a fully heat acclimated person but only 0.72 in an untrained, non-heat acclimated individual (47); $P_{sk,sat}$ is the saturated water vapour pressure at skin temperature (in kPa); P_a is the water vapour pressure measured in ambient air (in kPa); $R_{e,cl}$ is the evaporative heat transfer resistance of clothing (in $m^2 \cdot kPa \cdot W^{-1}$); f_{cl} is the

clothing area factor (equation 14); and h_e is the evaporative heat transfer coefficient (in $W \cdot m^{-2} \cdot kPa^{-1}$).

Values for $P_{sk,sat}$ can be derived using Antoine's equation (52) as follows:

$$P_{sk} = \text{EXP}\left[18.956 - \frac{4030.18}{T_{sk}+235}\right] \quad \text{[in kPa]} \quad (19)$$

Values for the h_e can be estimated using h_c (from equation 10/Table 1) as follows:

$$h_e = 16.5 h_c \quad [\text{in } W \cdot m^{-2} \cdot kPa^{-1}] \quad (20)$$

Values for evaporative efficiency (E_{eff}) (i.e. as a fraction of secreted sweat that evaporates from the skin) can be subsequently estimated for a given level of ω_{req} using (32):

$$E_{eff} = 1 - \frac{{\omega_{req}}^2}{2} \quad \text{[ND]} \quad (21)$$

Evaporative efficiency can also be estimated by directly measuring the mass of dripped sweat trapped in an oil pan placed on scale directly underneath the participant. However, this technique had been primarily reported during passive heating (11) and is difficult to implement during exercise.

Evaporative heat loss from the skin surface (E_{sk}) can then be estimated using:

$$E_{sk} = (WBSL \times 2.426) \times E_{eff} \quad \text{[in kJ]} \quad (22)$$

Where: WBSL is whole-body sweat loss over a fixed exercise time (in g).

It is important to acknowledge that the approach described above is especially limited for individuals wearing layered clothing outfits. While trapped sweat can indeed still evaporate, the effective latent heat of vaporization of this sweat (which is usually assumed to be 2.426 $kJ \cdot g^{-1}$) has been shown to decline dramatically (by up to ~80%) depending the material properties and most

importantly the number of clothing layers (29). As such, E_{sk} from measured sweat losses, even if sweat trapped in clothing is accounted for, could be overestimated by more than 4-fold.

Heat Storage (S): occurs when an imbalance arises between metabolic heat production and the parallel rate of net heat dissipation via sensible and evaporative heat transfer. Typically, at rest in a temperate environment, humans are in heat balance (i.e. S=0) as heat loss from sensible heat exchange via convection and radiation match resting metabolic rate without any requirement for evaporation other than passively through respiration. However, elevated rates of heat production following the onset of exercise under nearly all environmental conditions lead to a positive rate of heat storage. On the other hand, cold exposure without sufficient clothing insulation can cause high rates of convective and radiative heat loss that exceed metabolic heat production leading to a heat imbalance and thus a negative rate of heat storage. Cumulatively over time, sustained rates of positive or negative heat storage result in changes in internal (i.e. core) body temperature, which if left unchecked can become detrimental to human performance and ultimately health.

The change in heat storage required to alter core temperature is dependent on biophysical factors. Firstly, the body mass of an individual represents their heat sink, meaning that changes in core temperature for an absolute amount of heat stored in the body are negatively correlated, i.e. a smaller rise in core temperature is observed with a larger body mass for a fixed heat storage (12, 48). Secondly, large differences in the specific heat of the tissues of the body (C_p) caused by marked differences in body composition can also alter core temperature despite a similar heat storage. A C_p of 3.47 $kJ \cdot kg^{-1} \cdot {}^{o}C^{-1}$ is assumed for the average person (23). However, owing to the different C_p of fat tissue (2.97 $kJ \cdot kg^{-1} \cdot {}^{\circ}C^{-1}$) and lean mass (3.64 $kJ \cdot kg^{-1} \cdot {}^{\circ}C^{-1}$) overall C_p can vary depending on adiposity. While small differences in C_p do not seem to meaningfully influence core temperature, it has been recently demonstrated that a ~20% difference in body fat

percentage is sufficient to independently yield ~0.2-0.3°C greater rises in core temperature during moderate exercise at a fixed metabolic heat production of 6 W per kilogram of total body mass in healthy males (mean body fat % of 10.8% versus 32.0%) in a 28°C environment (15).

Temporal changes in human heat balance: Reflex physiological mechanisms as described in Chapter 1 aid the maintenance of body temperature within prescribed limits for human health by modifying heat balance. Autonomic increases in vascular conductance of the skin mediated by a cutaneous vasodilatation, and eccrine sweating, are observed in proportion to elevations in skin and/or core temperature during exercise and/or with heat exposure. Similarly, in the cold, a vasoconstriction response and shivering thermogenesis occur in proportion to reductions in skin and/or core temperature (27, 28, 58).

While at rest, mean T_{sk} in a temperate, and thermally comfortable environment is typically 33 to 34˚C (5, 46)**.** During heat stress, an initial vasodilatation causes an increase in T_{sk}, which alters the temperature difference between the skin surface and the ambient environment and thus increases sensible heat loss (or decreases sensible heat gain if $T_a > T_{sk}$) via convection (Equation 9) and radiation (Equation 5) (43). If net heat loss via convection and radiation (and the small heat losses via respiration) are not sufficient to balance the rate of internal heat production via metabolism (Equation 2), eccrine sweating must be initiated to enhance evaporative heat loss from the skin. Once sweat is secreted from eccrine sweat glands and reaches the skin surface, the area of skin directly under the sweat is considered to be 100% saturated with water vapour (22). As such, the gradient between the partial pressure of water vapour at the skin surface (P_{sk}) and in ambient air (P_a), and therefore the rate of evaporative heat loss, is increased by sweating. As sweat gland output increases, skin wettedness (ω) increases until reaching a maximum theoretical value of 1.00 when the entire surface area of the body that is available for evaporation

(typically equal to total body surface area in healthy humans) is completely covered in sweat. This level of ω is only possible in fully heat acclimated individuals (32) and has been recently shown to be as low as 0.72 in an untrained, non-heat acclimated individual, and 0.84 in trained but non-heat acclimated people (47). The ability to saturate ~15-25% more of the skin surface following heat acclimation permits an extension of the range of compensable conditions for a given ambient temperature and humidity (Figure 2). Whole-body sweat rate is regulated to ensure that, and if possible, a steady-state core temperature is attained (57). It follows that for thermal equilibrium to be possible a rate of heat storage of zero must be achieved. As such whole-body sweat rate is effectively controlled to ensure heat balance, or more specifically the evaporative heat requirement for heat balance (E_{req}) (Equation 17) (22). The relationship between whole-body sweat rate and E_{req} becomes non-linear however, once decrements in evaporative efficiency (Equation 21) are observed; i.e. when E_{req} is approximately greater than 50% of E_{max} (Equation 18).

---- INSERT FIGURE 2 ----

As skin surface sweating is autonomically controlled via a feedback loop using afferent signals from thermoreceptors throughout the body (9), sweating cannot commence without a "load error", i.e. a rise in internal temperature (8, 27), which in almost all circumstances requires heat storage. As a result, the time course of the activation of physiologically-mediated changes in skin surface heat dissipation is longer relative to the almost immediate increase in heat production following the onset of exercise leading to a transient heat imbalance. The duration of this imbalance is determined by i) the rate at which sweating and skin blood flow increase relative to the rise in core and skin temperature; and ii) the maximum physiological capacity to increase sweat production and skin blood flow. The longer this imbalance between heat production and net heat dissipation

lasts, the greater S will be for a particular individual, and the greater the rise in internal tissue temperatures.

Compensable and Uncompensable heat stress: The risk associated with heat stress or hyperthermia, in terms of the magnitude of rise in core temperature, is greatly dependent on the physiological compensability of the individual in a given environment. While body temperature will eventually plateau if heat balance is attainable (compensable), it will continue to rise without a plateau occurring if heat balance is not possible (uncompensable). Uncompensable heat stress can occur because i) metabolic heat production is too high, and/or ii) the physiological capacity to sweat has been reached, and/or iii) the environment/clothing prevents a sufficiently high rate of heat dissipation from the skin. In the context of the previously described heat balance components, whether a given heat exposure is compensable or not is determined by, a) the amount of evaporation required for heat balance (E_{req}); and 2) the maximal evaporative capacity of environment (E_{max}): i.e. if $E_{req} \leq E_{max}$ = *Compensable*; if $E_{req} > E_{max}$ = *Uncompensable*.

The E_{req} and E_{max} for a given exposure are determined by both environmental conditions and physiological characteristics. A lower E_{req} is observed as i) T_a and T_r become lower; ii) *v* becomes greater apart from when $T_a > T_{sk}$; iii) M-W is lower; and iv) T_{sk} is higher. On the other hand, a higher E_{max} is observed as i) P_a becomes lower and thus drier; ii) *v* becomes greater; iii) body surface area of the person is greater; and iv) $R_{e,cl}$ of clothing worn is lower. Therefore, the cooler, windier, and drier an environment is, the more likely it will lead to compensable heat stress, especially if levels of physical activity are low and/or clothing with a low evaporative resistance is worn. Nevertheless, numerous combinations of activities and climates can yield uncompensable heat stress. Even activities with a low metabolic heat production can result in uncompensable heat stress if the climate is sufficiently hot, humid, and still. Similarly, activities with high rates of

metabolic heat production can result in uncompensable heat stress even in relatively temperate climates. In sum, for a fixed set of environmental characteristics, the more skin temperature can be increased through elevations in skin blood flow, and the greater the skin wettedness that can be achieved, the more likely an individual will a) avoid uncompensable heat stress and a continued increase in core temperature; and b) limit the magnitude of heat storage and therefore the increase in core temperature during a compensable heat stress exposure.

Cold Stress: Although the current chapter focuses primarily on heat stress, it will conclude with a brief comment on the biophysical processes associated with cold stress as they follow identical principles. In the cold, high temperature gradients between the cold ambient air to the warmer skin cause extensive sensible heat loss, primarily via convection and radiation. A reduction in skin blood flow via sympathetic vasoconstriction causes a concomitant decrease in T_{sk} (33), and subsequently reduces the temperature gradient between the skin surface and the ambient environment and therefore blunts sensible heat loss for a given air temperature and air velocity. Restricting blood flow to the skin and maintaining blood flow to the body core ensures that the heat produced via metabolism remains close to the deep visceral organs and the brain. As a result, a substantial temperature gradient develops between the body core and peripheral tissues. If skin blood flow does not sufficiently limit dry heat loss and a negative rate of body heat storage persists, shivering thermogenesis will be instigated to increase the rate of metabolic heat production via the asynchronous firing of muscle fibres to produce heat without external work. Heat production during maximal shivering can reach up to 5-6 times resting metabolic rate (18). Primary input for the magnitude of shivering thermogenesis appears to come from deep body thermoreceptors (i.e. spinal cord, intestines and brain), whereas the onset threshold for shivering is modified by skin temperature (4, 53). While shivering thermogenesis is an effective means of compensating for a

negative rate of body heat storage, shivering has been shown to interfere with the performance of fine motor tasks (38, 39).

Summary: This chapter describes the fundamental factors that influence heat exchange between the human body and its surrounding environment. The bulk of heat exchange takes place at the skin surface via sensible heat transfer (i.e. convection and radiation), and evaporation. With increasing ambient temperature, the gradient for sensible heat transfer declines, meaning that the human body becomes increasingly dependent on the evaporation of sweat for heat dissipation. If the combination of climate (air temperature, radiant temperature, humidity and air velocity) and clothing permit a sufficient level of heat dissipation to counterbalance the rate of internal heat production, elevations in core temperature are moderated (i.e. compensable heat stress). However, if heat production exceeds the upper capacity to lose heat from the skin surface due to high ambient temperatures, humidity, low wind speeds, or high evaporative resistance of clothing, a continuous increase in core temperature occurs (i.e. uncompensable heat stress).

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Table 1. Estimations of the convective heat transfer coefficient (h_c) for common modalities of exercise.

Exercise Modality	Equation/ Constant h_c ($W \cdot m^{-2} \cdot K^{-1}$)	Comments
Stationary cycle ergometer (50 RPM)	5.4	Ambient air flow <0.2 m/s (45)
stationary cycle ergometer (60 RPM)	6.0	Ambient air flow <0.2 m/s (45)
Outdoor cycling	$h_c = 8.4 v_{speed}^{0.84}$	v_{speed}: cycling velocity (m/s) (13)
Walking/Running	$h_c = 8.3 v_{loc}^{0.531}$	v_{loc}: speed of locomotion (m/s) (45)
Treadmill exercise	$h_c = 8.3 v_{loc}^{0.391}$	v_{loc}: speed of locomotion (m/s) (45)

FIGURES

Figure 1. An example of partitional heat exchange for an exercising individual on an upright ergometer. E_{req}: evaporative requirements for heat balance; C: convection; R: radiation; Res: respiratory heat loss.

Figure 2. The upper limits of compensability for an exercising individual at 600 W of heat production who is unacclimated (white area) or fully heat acclimated (light grey area). As depicted, the ability to attain a greater maximum skin wettedness following complete heat acclimation permits the maintenance of heat balance in more humid environments (for a given ambient temperature) in comparison to unacclimated.

Figure 1

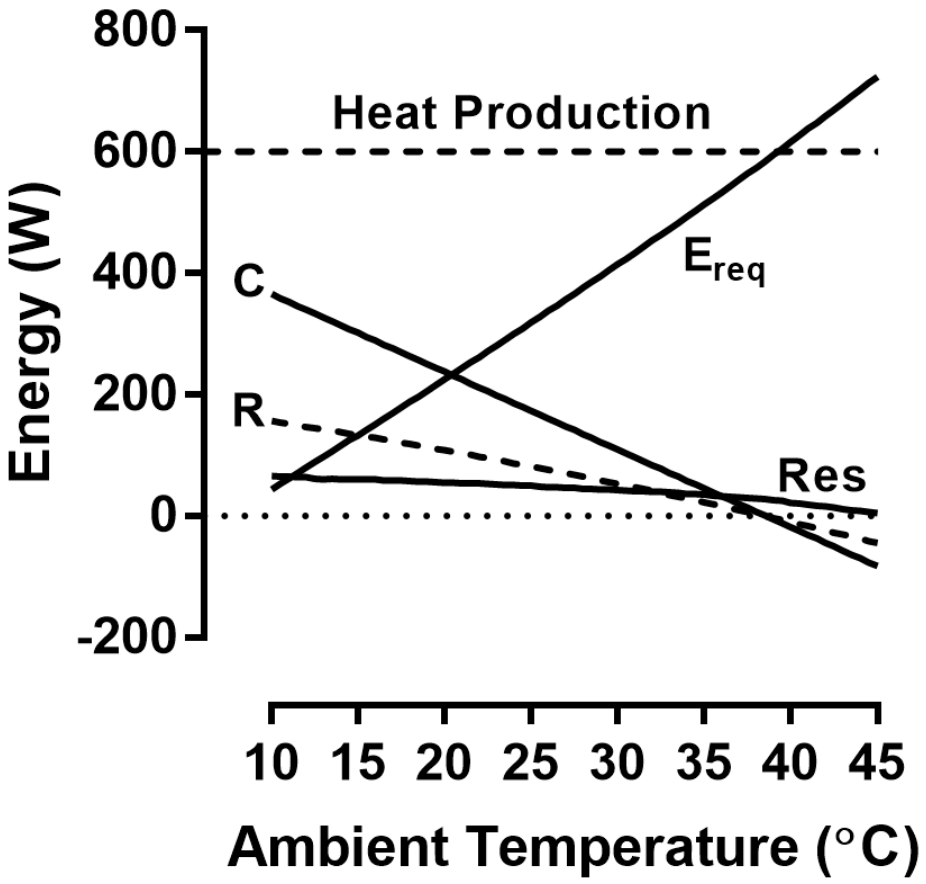
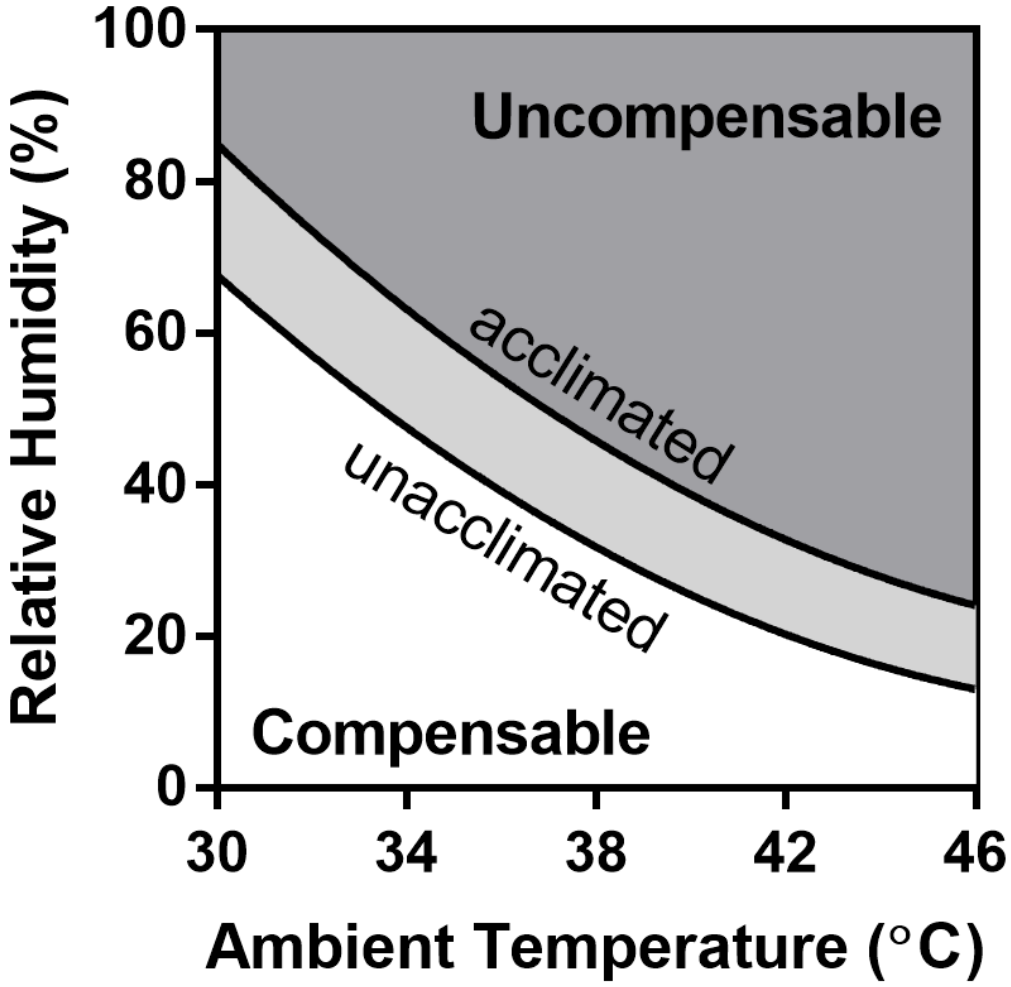

800
600
400
200
0
-200
Energy (W)
Heat Production
C
R
E_{req}
Res
10 15 20 25 30 35 40 45
Ambient Temperature (°C)

Figure 2


Relative Humidity (%)
100
80
60
40
20
0
Uncompensable
acclimated
unacclimated
Compensable
30
34
38
42
46
Ambient Temperature (°C)

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Publication:	Medicine & Science in Sports & Exercise
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