The contribution of body morphology to individual variability in the thermoregulatory responses to exercise, and the effect of altered skin blood flow on heat loss potential

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Thesis submitted to the
Faculty of Graduate and Postdoctoral Studies
in partial fulfillment of the requirements
for the Doctorate in Philosophy degree in Human Kinetics

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THESIS ABSTRACT

Three studies were performed to examine biophysical sources of individual variability in the thermoregulatory responses to exercise, and the influence of skin blood flow on heat loss potential during severe heat stress. Study 1 investigated whether unbiased comparisons of changes in rectal temperature (ΔT_{re}) should be compared at a fixed absolute rate of heat production (H_{prod}; W) or a fixed H_{prod} per unit mass (W/kg), and whether local sweat rates (LSR) should be compared at a fixed evaporative requirement for heat balance (E_{req}; W) or a fixed E_{req} per unit of surface area (W/m^2), between independent groups of unequal body mass and body surface area (BSA). Study 2 examined whether individual variation in ΔT_{re}, whole-body sweat loss (WBSL), and steady-state LSR is best explained by biophysical factors related to H_{prod}, $E_{req,}$ and body size, and if factors related to aerobic fitness (VO_{2max}) and body fatness correlate with the residual variance in these responses. Study 3 tested whether alterations in skin blood flow shift the critical vapour pressure (P_{crit}) above which core temperature could no longer be regulated in hot/humid conditions, indicating altered heat loss potential from the skin. In study 1, exercise at fixed absolute H_{prod} and E_{req} resulted in greater ΔT_{re} and LSR in smaller individuals (smaller mass and BSA), but exercise at set H_{prod} in W/kg and E_{req} in W/m^2 resulted in no differences in ΔT_{re} and LSR, respectively, regardless of body size and $\%VO_{2max}$. In study 2, 50-71% of the individual variation in ΔT_{re}, whole-body sweat loss (WBSL), and steady-state LSR was explained by H_{prod} (W/kg), absolute E_{req} (W) and E_{req} (W/m^2) respectively, while body fat percentage and $\%VO_{2max}$ contributed merely 1-4% to the total variability. In study 3, despite a ~20% lower skin blood flow, P_{crit} was unaffected by a large reduction in skin blood flow following iso-smotic dehydration, with no differences in core and skin temperatures and sweating observed. Collectively, these findings suggest that between-group comparisons and

modelling of thermoregulatory responses must first consider biophysical factors related to metabolic heat production and body size, rather than factors related to VO_{2max} and body fatness. Furthermore, lower levels of skin blood flow may not impair maximum heat dissipation from the skin to the external environment during severe passive heat stress as previously thought.

ACKNOWLEDGEMENTS

Firstly, I must express my gratitude to the volunteers who graciously participated in my thesis studies. The many visits, prolonged exercise, and/or extreme heat exposures were often challenging and uncomfortable, so I thank them for their effort and co-operation.

To Ollie Jay: I thank you greatly for your guidance, support, and mentorship over the last 5 years. I reflect on the work we did over this time with great pride. I can also look forward to my next career steps with great confidence knowing that the training and opportunities I received from you as a PhD student were truly exceptional. I would also like to thank Drs. Bob Kenefick and François Haman for serving as thesis supervisory committee members, and providing important feedback on the proposed projects.

I had the immense pleasure of working with many great students and in the Thermal Ergonomics Laboratory. Nate Morris, Nick Ravanelli, and Geoff Coombs deserve special mention for their intellectual contributions to my thesis projects, but also for making my day-to-day experience in the lab incredibly enjoyable with just the right balance of scientific curiosity and extra-curricular shenanigans.

I would also like to thank our neighbours in the Behavioural and Metabolic Research Unit. Pascal Imbeault and Éric Doucet served as my co-supervisors at various points of my thesis, hosted us in the lab for many years, and were invaluable sources of knowledge and insight. I must especially thank Pascal for guiding me through the final stages of my thesis. Also, I want to thank Marie-Ève Riou and Jess McNeil for their friendship and camaraderie, as well as Isabelle LaForest and Ann Beninato for their assistance with many of our projects.

I had the extraordinary opportunity to visit Dr. Craig Crandall's Thermal and Vascular Physiology Laboratory at the Institute for Exercise and Environmental Medicine in Dallas, Texas

for 6 months to conduct my final PhD thesis study. The IEEM is an incredible learning environment for young scientists, and I am very appreciative to Craig for hosting me during this time. I am also very grateful to Naomi Kennedy, Amy Adams, and Dan Gagnon for their assistance throughout the study (and tolerance to such terrible humidity in the chamber), and to Jena Langlois, Zac Schlader, Paula Poh, and Steven Romero for their contributions at various stages of the project.

I must also acknowledge the various agencies that provided scholarship support throughout my PhD. External scholarships were provided by the Natural Sciences and Engineering Research Council (NSERC) of Canada and the Ontario Graduate Scholarship. The Faculty of Graduate and Postdoctoral Studies (FGPS) sponsored my visit to the IEEM through a student mobility bursary. Travel bursaries were supplied by the FGPS and Faculty of Health Sciences to attend and present at various scientific conferences.

To my wife, Candace, and daughter, Alison: thank you for your patience as I inched closer to this goal. I promise the next stop will be warmer. I love you both ☺.

PREFACE

The work presented herein is my own, and I take full responsibility for its contents. All thesis studies in Chapter 3 were co-authored by Dr. Ollie Jay, and study 3 was co-authored by Drs. Craig Crandall and Dan Gagnon. Study 1 was published in the *Journal of Applied Physiology*, and highlighted in an invited editorial by Dr. Samuel Cheuvront. At the time of thesis submission, Study 2 had been accepted for publication by the *Journal of Applied Physiology*. Ethical approval was required for all studies, and certificates of ethical approval from the University of Ottawa Health Sciences and Science Research Ethics Board for studies 1 and 2, and the University of Texas Southwestern Medical Center Institutional Review Board for study 3, are included in Appendix A. Final versions of study 1 and the accompanying editorial can be found in Appendices B and D, respectively.

In addition to my thesis studies, five non-thesis works are included that were published during the course of my PhD: (i) a contribution to a Point:Counterpoint debate on selective brain cooling in the *Journal of Applied Physiology* (Appendix E), (ii) our argument against an influence of aerobic fitness on core temperature during exercise in *Exercise and Sport Sciences Reviews* (Appendix F), (iii) a biophysical model of compensatory hyperhidrosis following sympathectomy in the *American Journal of Physiology Regulatory, Integrative and Comparative Physiology* (Appendix G), (iv) an experimental study examining the independent effect of aerobic fitness on forehead local sweat rate in *Experimental Physiology* (Appendix H), and (v) our study on the rate of heat storage and fatigue during cycling in the *European Journal of Applied Physiology* (Appendix I). Co-authors on these non-thesis articles include Dr. Ollie Jay (Appendix E-I), Nathan Morris (Appendix F), Anthony Bain (Appendix H), Nicholas Ravanelli (Appendix I), Yannick Molgat-Seon (Appendix I), and Dr. Tony Carlsen (Appendix I).

Since the *Journal of Applied Physiology* and the *American Journal of Physiology Regulatory, Integrative and Comparative Physiology* are journals of the American Physiological Society, permission for republication of these articles in a thesis is not required (see Appendix J). Republication permissions were required for the articles published in *Experimental Physiology* and the *European Journal of Applied Physiology* only, and these can be found in Appendix J.

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THESIS DISCUSSION

LIST OF ABBREVIATIONS & SYMBOLS

Term	Description	Units
ATP	Adenosine triphosphate	[–]
BF%	Body fat percentage	[%]
BSA	Body surface area	[m^2]
BSA:mass	Body surface area-to-mass ratio	[cm^2/kg]
BSA_r/BSA	Effective radiant surface area	[ND]
BV	Blood volume	[–]
C	Rate of convective heat exchange	[W]
C_p	Specific heat capacity	[$J \cdot g^{-1} \cdot °C^{-1}$]
C_{res}	Respiratory heat exchange via convection	[W]
d	Black globe diameter	[m]
DXA	Dual-energy x-ray absorptiometry	[–]
E_{max}	Maximum capacity for evaporation to the environment	[W]
E_{req}	Rate of evaporation required for heat balance	[W]
E_{res}	Rate of evaporative heat loss from the respiratory tract	[W]
E_{sk}	Rate of evaporative heat loss from the skin	[W]
e_c	Energetic equivalent of carbohydrate	[kJ/L O_2]
e_f	Energetic equivalent of fat	[kJ/L O_2]
EE	Energy equivalent	[Wh]
ERF	Effective radiant field	[W/m^2]
f_{cl}	Area clothing factor	[ND]
H_{loss}	Rate of total heat loss	[W]
H_{prod}	Rate of metabolic heat production	[W, W/m^2, W/kg]
h	Combined heat transfer coefficient	[$W \cdot m^{-2} \cdot K^{-1}$]
h_c	Convective heat transfer coefficient	[$W \cdot m^{-2} \cdot K^{-1}$]
h_e	Evaporative heat transfer coefficient	[$W \cdot m^{-2} \cdot kPa^{-1}$]
h_r	Radiant heat transfer coefficient	[$W \cdot m^{-2} \cdot K^{-1}$]
I_{cl}	Intrinsic clothing insulation	[Clo, $m^2 \cdot °C \cdot W^{-1}$]
K	Rate of conductive heat exchange	[W]
k	Thermal conductivity	[$W \cdot m^{-1} \cdot K^{-1}$]
Leg LM	Lean mass of the legs	[kg]
LBM	Lean body mass	[kg]
LDF	Laser-Doppler flux	[PU]

LDF_{mean}	Mean laser-Doppler flux	[PU]
LR	Lewis relation coefficient	[K/kPa]
LSR	Local sweat rate	[$mg \cdot cm^{-2} \cdot min^{-1}$]
LSR_{mean}	Mean local sweat rate	[$mg \cdot cm^{-2} \cdot min^{-1}$]
LSR_{req}	Local sweat rate required for heat balance	[$mg \cdot cm^{-2} \cdot min^{-1}$]
LSR_{ss}	Steady-state local sweat rate	[$mg \cdot cm^{-2} \cdot min^{-1}$]
M	Rate of metabolic energy expenditure	[W]
MAP	Mean arterial pressure	[mmHg]
P_a	Ambient vapour pressure	[kPa]
P_{crit}	Critical ambient vapour pressure	[kPa]
P_{osm}	Plasma osmolality	[mOsm/kg H_2O]
$P_{s,sk}$	Vapour pressure of the saturated skin	[kPa]
PV	Plasma volume	[–]
R	Rate of radiant heat exchange	[W]
R_{cl}	Resistance to dry heat exchange	[$m^2 \cdot °C \cdot W^{-1}$]
$R_{e,cl}$	Resistance to evaporation due to clothing	[$m^2 \cdot kPa \cdot W^{-1}$]
RER	Respiratory exchange ratio	[ND]
RH	Ambient relative humidity	[%]
S	Rate of body heat storage	[W]
SkBF	Skin blood flow	[–]
T	Temperature	[°C]
T_a	Ambient temperature	[°C]
T_b	Mean body temperature	[°C]
T_c	Core temperature	[°C]
T_{cl}	Clothing surface temperature	[°C]
T_{es}	Oesophageal temperature	[°C]
T_g	Black-globe temperature	[°C]
T_o	Operative temperature	[°C]
T_r	Mean radiant temperature	[°C]
T_{re}	Rectal temperature	[°C]
T_{sk}	Mean skin temperature	[°C]
TBM	Total body mass	[kg]
USG	Urine specific gravity	[ND]
v	Air velocity	[m/s]
VCO_2	Rate of carbon dioxide production	[L/min]

VO_2	Rate of oxygen uptake	[L/min]
VO_{2max}, VO_{2peak}	Maximum/peak rate of oxygen uptake	[L/min, $ml \cdot kg^{-1} \cdot min^{-1}$]
$\%VO_{2max}$, $\%VO_{2peak}$	Relative exercise intensity	[%]
W	External work rate	[W]
WBSL	Whole-body sweat loss	[g]
$WBSL_{req}$	Whole-body sweat loss required for heat balance	[g]
WBSR	Whole-body sweat rate	[g/min]
x	Distance	[m]

Greek symbol	Description	Units
Δ	Change in value	[–]
ε	Area-weighted emissivity of the skin	[ND]
σ	Stefan-Boltzmann constant	$[W \cdot m^{-2} \cdot K^{-4}]$
ω	skin wettedness	[ND]
ω_{max}	maximum skin wettedness	[ND]
ω_{req}	skin wettedness required for heat balance	[ND]

CHAPTER 1: INTRODUCTION

Thermoregulatory responses to work (e.g. physical activity) are characterized by a high degree of individual variability that may be explained by physiological/physical factors such as age (89, 182), sex (58, 59), and body composition (36, 77, 78). From a methodological point of view, in order to isolate the true independent influences of such factors on changes in core temperature, thermoregulatory sweating, and skin blood flow, it is of primary importance to first identify the influence of all biophysical factors that can vary greatly between individuals, including the rate of metabolic heat production, body mass, body surface area (BSA), and body composition. Such information would allow researchers to standardize exercise intensity appropriately and avoid the introduction of inherent bias to their experimental design when performing independent-groups comparisons. This is particularly important for researchers investigating potential differences in thermoregulatory function between healthy control groups and special/clinical populations, such as those with multiple sclerosis (33), obesity (78, 115), spinal cord injuries (181) and burn-related injuries (125, 163).

Although core temperature (60, 131, 154), thermoregulatory sweating (60, 87, 182), and skin blood flow (50) responses have been traditionally assessed at a relative exercise intensity (i.e., percentage of peak oxygen uptake, $\%VO_{2max}$), most studies have ignored differences in heat production that invariably arise when comparing groups heterogeneous for VO_{2max} and/or morphological characteristics that could modify these thermoregulatory responses (3). For example, changes in core temperature during exercise in compensable conditions are determined primarily by the rate of heat production within individuals or groups (9, 118, 139) or between groups matched for body mass (92). Also, the manipulation of $\%VO_{2max}$ at a fixed rate of heat production does not seem to alter the core temperature response (70, 152). Since body mass

reflects the internal heat sink, observed differences in the change in core temperature at a fixed absolute intensity (i.e., absolute rate of heat production) may be explained by differences in body mass alone (55, 74, 118). Additionally, recent evidence has also demonstrated that whole-body sweat rate is strongly associated with the evaporative requirements for heat balance (E_{req}; W) regardless of body size (56). However, since physiological control of thermoregulatory sweating is often examined using local sweat rates expressed relative to the measurement surface area, dissimilar local sweat rate values at a fixed absolute E_{req} (i.e., similar whole-body sweat rate) may be explained by differences in BSA *per se*. It follows that prescribing exercise intensities that achieve the same heat production per unit of total body mass (W/kg) and E_{req} per unit of BSA (W/m^2) may normalize the effects of body mass and BSA on changes in core temperature and local sweat rate, respectively, yet this remains to be experimentally proven. Furthermore, how well these biophysical parameters, as well as those related to body composition and VO_{2max}, explain individual variability in changes in core temperature, whole-body sweat rate, and local sweat rate, requires further evaluation.

Attenuated skin blood flow during thermal stress is thought to profoundly impact the capacity for heat dissipation from the body surface to the external environment, placing certain populations (e.g. the elderly, skin graft recipients, and those with hypertension, diabetes, or heart failure) at greater risk for thermal injury during severe heat stress (21, 30, 34, 84). However, skin blood flow is routinely investigated in encapsulated conditions (e.g., water-perfused suit) at a fixed and often supra-physiological skin temperature, which does not permit a true assessment of heat loss potential. Also, in non-encapsulated conditions, greater changes in core temperature with diminished skin blood flow are not always met by a lower mean skin temperature or reduced sweat production (47, 140), which would be expected if heat loss potential were truly

affected. Nevertheless, local physical reductions in skin blood flow via arterial occlusion and noradrenaline infusion attenuate local sweat rate (41, 122, 193). Therefore, a high skin blood flow may be necessary to maintain sweat production (and thus evaporation) and ensure environmental compensability during severe heat stress.

1.1 Rationale and statement of the problem

To isolate the independent influence of any physiological factor on the core temperature and sweating responses to exercise, the independent roles of all biophysical factors must first be identified. Due to the putative association between VO_{2max} and thermoregulatory function, traditional exercise protocols have administered fixed relative exercise intensities (i.e., $\%VO_{2max}$) to compare thermoregulatory responses. However, among individuals that differ in VO_{2max}, this approach invariably leads to large differences in the absolute rate of heat production and E_{req}, which are primarily responsible for the change in core temperature and sweat rate, respectively, among individuals matched for body size in compensable conditions. Since differences in body morphology also affect core temperature and sweating responses, the prescription of an exercise intensity accounting for heat production and body mass (W/kg) for core temperature comparisons, as well as E_{req} and BSA (W/m^2) for local sweat rate comparisons, may be the best solutions for independent-groups experimental designs. If so, it would also be expected that these biophysical factors predominate in the description of individual variability of core temperature and sweating responses over factors traditionally associated with the modulation of thermoregulatory responses such as aerobic fitness (VO_{2max}) and body fatness.

Cutaneous vasodilatation and the attendant rise in skin blood flow facilitate heat transfer from the core to the skin surface. Numerous studies have suggested that alterations to skin blood

flow affect heat dissipation from the skin to the surrounding environment, yet large reductions in skin blood flow do not seem to be reliably accompanied by lower mean skin temperatures. Thus, meaningfully lower dry heat loss via convection/conduction with a diminished skin blood flow does not seem likely. Similarly, whole-body sweating does not appear to be reduced alongside lower rates of skin blood flow during exercise at the same E_{req}. Therefore, whether heat loss potential is indeed compromised by alterations in skin blood flow requires further investigation.

The studies outlined below are designed to (i) identify how exercise intensity should be prescribed to perform unbiased comparisons of core temperature and sweat rate (whole-body and local) among independent groups (such as clinical populations) who cannot be matched for body mass and BSA, respectively, (ii) determine how well factors related to heat production, body morphology, VO_{2max}, and body fatness contribute to the explained individual variation in core temperature and sweating responses, and (iii) to investigate whether differences in skin blood flow contribute to changes in heat loss potential during exercise.

1.2 Objectives

The proposed thesis aims to answer the following questions:

1) In compensable conditions, should changes in core temperature be compared between independent groups at the same absolute rate of heat production or the rate of heat production per unit body mass (W/kg) independently of body mass and relative exercise intensity (i.e. $\%VO_{2max}$)?
2) In compensable conditions, should local sweat rate be compared between independent groups at the same absolute rate of heat production (and thus E_{req}) or at the same rate of heat production (and thus E_{req}) per unit BSA (W/m^2), regardless of BSA?

3) Are heat production (W/kg), E_{req} (W), and E_{req} (W/m^2) the primary determinants of changes in core temperature, whole-body sweat losses, and steady-state local sweat rates, respectively, during exercise in compensable conditions, and do factors related to VO_{2max} and body fatness explain any of the residual variance in these thermoregulatory responses?
4) Do manipulations of skin blood flow shift the critical environmental limits for physiological compensability, indicating an altered heat loss potential?

1.3 Hypotheses

1) In compensable conditions, the change in core temperature will be greater in otherwise similar individuals of low (~65 kg) compared to high (~90 kg) body mass during exercise at a fixed absolute rate of heat production (W), but no different at a fixed rate of heat production per unit body mass (W/kg), irrespective of $\%VO_{2max}$.
2) Local sweat rate (measured per unit surface area) will be greater in individuals of small (~1.8 m^2) compared to large (~2.1 m^2) BSA at a fixed absolute workload, but no different at a fixed rate of heat production per unit BSA (W/m^2).
3) Heat production (W/kg), E_{req} (W), and E_{req} (W/m^2) will be the primary determinants of changes in core temperature, whole-body sweat losses, and steady-state local sweat rates, respectively, while parameters related to VO_{2max} and body fatness will contribute marginally (if at all) to the total variability in these responses.
4) Greater skin blood flow will not raise the critical vapour pressure for core temperature, but an attenuated skin blood flow response will lower the critical vapour pressure for core temperature, indicating diminished heat loss potential.

1.4 Implications

From a methodological perspective, these studies will provide new approaches to comparing core temperature and thermoregulatory sweating responses between independent groups. This is of particular importance for researchers wishing to perform unbiased comparisons between normal and clinical populations (e.g., multiple sclerosis patients, spinal cord injury victims, sympathectomy patients, skin graft recipients) in which matching subjects for body mass and BSA may be difficult or even impossible. Additionally, identifying the relative contributions of various biophysical and physiological factors to core temperature and sweating may improve thermoregulatory modelling efforts. Finally, clarifying the relationship between skin blood flow and heat loss potential will have practical implications in determining exposure limits for individuals with well-established reductions in skin blood flow.

1.5 Limitations and delimitations

The application of these findings will be limited to healthy males, aged 18-39 with VO_{2max} values above 30 $ml \cdot kg^{-1} \cdot min^{-1}$, body mass of 60-115 kg, and BSA of 1.6-2.4 m^2. Therefore, these findings cannot be directly applied to children, the elderly, individuals with diseases affecting thermoregulatory function, and/or individuals of extreme morphological characteristics.

CHAPTER 2: REVIEW OF THE LITERATURE

2.1 Energy exchange and human heat balance

The principal function of the human thermoregulatory system is to maintain thermal homeostasis. Changes in heat storage, and subsequently core temperature, occur due to an imbalance between the rates of endogenous heat production and net heat loss from the skin and respiratory tract to the environment, and may be summarized arithmetically using the conceptual heat balance equation (195):

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

Where: S is the rate of body heat storage; M is the rate of metabolic energy expenditure; W is the external work rate; dry heat losses are denoted by K, R, and C, representing the rates of heat loss via conduction, radiation, and convection, respectively; C_{res} and E_{res} are the rates of convective and evaporative heat loss from the respiratory tract, respectively; and E_{sk} is the rate of evaporative heat loss from the skin. If heat production exceeds net heat loss (i.e., $S > 0$), core temperature rises; if heat production is balanced by net heat losses (i.e., $S = 0$), core temperature remains unchanged (i.e., in a steady state). All components are in watts (W); however, heat exchange parameters are often expressed per square metre of total BSA (W/m^2). Often, BSA is estimated using the DuBois and DuBois equation based on body mass (in kilograms) and standing height (in metres) (37):

$$BSA = 0.202 \cdot (mass)^{0.425} \cdot (height)^{0.725} \text{ [m}^2\text{]} \quad \text{(Eq. 2)}$$

Metabolic heat production

Metabolic energy expenditure represents the free energy released by the transfer of chemical energy from stored macromolecules (carbohydrate, fat, amino acids) to adenosine

triphosphate (ATP), which supplies energy for a range of cellular activities such as biosynthesis, transport, and muscular contractions. The rate of metabolic energy expenditure (M) can be estimated from the rate of oxygen uptake (VO_2) and the non-dimensional respiratory exchange ratio (RER):

$$M = VO_2 \cdot \frac{\left(\left(\frac{RER - 0.7}{0.3}\right)e_c\right)+\left(\left(\frac{1.0 - RER}{0.3}\right)e_f\right)}{(60)} \cdot 1000\ [W] \qquad \text{(Eq. 3)}$$

$$RER = \frac{VCO_2}{VO_2}\ [ND] \qquad \text{(Eq. 4)}$$

Where: e_c and e_f are the energy equivalents in kilojoules per litre of O_2 consumed for carbohydrate (21.13 kJ/L O_2) and fat (19.62 kJ/L O_2), respectively; and VCO_2 is the rate of carbon dioxide production in litres per minute (L/min). The International System of Units adopted watts as the measurement unit for rates of energy conversion, but metabolic rate is also commonly expressed in kilocalories per hour (1 kcal/h = 1.163 W) or kilojoules per minute (1 kJ/min = 16.67 W). The rate of metabolic heat production is the difference between the rate of metabolic energy expenditure and the external work rate. At a given external work rate, the rate of heat production is determined by the efficiency with which chemical energy is converted to mechanical work (i.e., force over a given distance). Mechanical efficiency may be described in a number of ways, and varies between modes of exercise. Gross efficiency, for example, represents the fraction of total metabolic energy expenditure that is used to perform mechanical work. Cycling exercise has a gross efficiency between ~10-20%, in other words, heat production accounts for 80-90% of the total free energy liberated via substrate oxidation (26, 51). Alternatively, net efficiency is the external work rate relative to the difference between the metabolic rate during exercise and at rest, and therefore reflects the change in metabolic rate

from baseline associated with a particular work rate. Net efficiency values for cycling are in the range of 18-24% (51). Furthermore, work efficiency during cycling is the ratio of external work rate to the difference between the metabolic cost of a particular work rate and the metabolic cost of unloaded pedalling. Values for work efficiency approach 30% (51, 190).

Respiratory heat losses

Inspired ambient air is warmed and humidified through dry and latent heat exchange with the surface of the respiratory tract, and some of this heat exits the lungs upon exhalation. The rate of dry (C_{res}) and evaporative (E_{res}) respiratory heat exchange may be estimated by (53):

$$C_{res} = 0.0014 \cdot (H_{prod}) \cdot (34 - T_a) \text{ [W]} \quad \text{(Eq. 5)}$$

$$E_{res} = 0.0173 \cdot (H_{prod}) \cdot (5.87 - P_a) \text{ [W]} \quad \text{(Eq. 6)}$$

Where: H_{prod} is the absolute rate of heat production in watts (i.e., M – W). Although many animals rely heavily on respiratory heat loss to regulate core temperature, it contributes relatively little to total heat losses in exercising humans except in very cool, dry environments (17).

Conduction

The intermolecular transfer of heat along a thermal gradient and across the boundary of a system is termed conduction. According to Fourier's Law:

$$K = -k \cdot \Delta T/x \cdot BSA \text{ [W]} \quad \text{(Eq. 7)}$$

Where: k is thermal conductivity in watts per metre per degree Celsius ($W \cdot m^{-1} \cdot °C^{-1}$) and $\Delta T/x$ is the thermal gradient per metre (°C/m). Due to minimal contact between the skin and solid surfaces during many physical activities (e.g., running, cycling), conductive heat exchange is

often considered negligible in humans. However, one must account for conduction if large skin areas are in contact with a surface of a different temperature (e.g., prone and supine postures).

Radiation

The exchange of heat via thermal radiation occurs between two bodies of different surface temperatures. In human heat balance, radiation may be described in terms of heat flux from the skin to the environment and the effective radiant field (ERF), which is determined by radiant heat exchange with all bodies emitting/absorbing radiation that differ in temperature from the environment. The ERF relates the ambient temperature (T_a) to mean radiant temperature, which is the temperature of an isothermal black enclosure within which a body would exchange the same amount of thermal radiation as in a real environment (53). Mean radiant temperature (T_r) can be measured via globe temperature (T_g) using a black-globe thermometer according to ISO 7726 (91):

$$T_r = \left[\left(T_g+273.15\right)^4 + \frac{1.1\cdot10^8\cdot v^{0.6}}{\varepsilon\cdot d^{0.4}}\cdot\left(T_g - T_a\right)\right]^{0.25} - 273.15\ [°C] \qquad \text{(Eq. 8)}$$

Where: 273.15 is the conversion factor between Kelvin degrees (K) and degrees Celsius (°C); T_g and T_a are in K; v is air velocity in metres per second (m/s); ε is the non-dimensional emissivity of the globe (0.95), which is defined as the ratio of radiation emitted from an object's surface relative to that of a black body (i.e., ε = 1) at the same temperature; and d is the globe diameter, which is 0.15 m for a standard globe. Total radiant heat exchange (R) from a nude body is quantified using the following equations:

$$R = h_r\cdot(T_{sk} - T_a)\cdot BSA - ERF\ [W] \qquad \text{(Eq. 9)}$$

$$ERF = h_r\cdot(T_r - T_a)\cdot BSA\ [W] \qquad \text{(Eq. 10)}$$

$$h_r = \varepsilon\cdot4\sigma\cdot(BSA_r/BSA)\cdot[(T_{sk} + T_r)/2 + 273.15]^3\ [W\cdot m^{-2}\cdot K^{-1}] \qquad \text{(Eq. 11)}$$

Where: h_r is the radiant heat transfer coefficient; ε is the emissivity of the skin, assumed to be 0.95 (ND); σ is the Stefan-Boltzmann constant ($5.67 \cdot 10^{-8}$ $W \cdot m^{-2} \cdot K^{-4}$); BSA_r/BSA is the effective radiant surface area (ND), which depends on body position and relative body size (71, 109); T_{sk} is the mean skin temperature (°C). From the clothed skin surface, radiation may be calculated as:

$$R = f_{cl} \cdot h_r \cdot (T_{cl} - T_r) \cdot BSA \text{ [W]} \quad \text{(Eq. 12)}$$

Where: T_{cl} is clothing temperature (K), and f_{cl} is the non-dimensional clothing area factor, which represents the area of the clothed body relative to BSA. The value of f_{cl} depends on the intrinsic clothing insulation (I_{cl}), which is expressed in Clo units.

$$f_{cl} = 1 + 0.31 \cdot I_{cl} \text{ [ND]} \quad \text{(Eq. 13)}$$

A value of 1 Clo reflects the thermal insulation required to keep an individual with a metabolic rate of 1 met comfortable at 21°C (approximately 0.155 $m^2 \cdot °C \cdot W^{-1}$).

Convection

Convective heat transfer occurs along a temperature gradient from an object's surface to a surrounding fluid medium by means of intermolecular interactions (i.e., conduction) and bulk transport of the fluid across the surface in accordance with Newton's Law of Cooling. Convective heat loss is calculated for nude (Eq. 14) and clothed (Eq. 15) individuals as:

$$C = h_c \cdot (T_{sk} - T_a) \cdot BSA \text{ [W]} \quad \text{(Eq. 14)}$$

$$C = f_{cl} \cdot h_c \cdot (T_{cl} - T_a) \cdot BSA \text{ [W]} \quad \text{(Eq. 15)}$$

Where: $T_{sk} - T_a$ is the skin-air temperature gradient through the boundary layer (K); $T_{cl} - T_a$ is the clothing-air temperature gradient (K). The convective heat transfer coefficient, h_c, is calculated for a seated individual facing an air velocity (v) of 0.2-4.0 m/s as:

$$h_c = 8.3 \cdot v^{0.6} \, [W \cdot m^{-2} \cdot K^{-1}] \quad \text{(Eq. 16)}$$

At air velocities less than 0.2 m/s, h_c has a value of 3.16 $W \cdot m^{-2} \cdot K^{-1}$ (128, 143). Numerous factors affect h_c, including the mechanism of convection (natural and/or forced), the pattern of air flow (laminar and/or turbulent), ambient temperature, and body geometry (53, 109). Natural convection occurs as buoyancy forces drive warmed air away from the skin, and is therefore affected primarily by air density. Forced convection (e.g., wind, motor-driven fan, physical displacement through an air mass) augments air flow over the skin, and is influenced primarily by air velocity. Typical values for h_c have been determined for various activities based on fixed air velocities (54).

Evaporation

Vaporization of a liquid from its surface layer into its gaseous phase is termed evaporation. At the skin surface, the phase change of 1 gram of sweat from liquid to vapour requires 2,426 J of heat drawn from the skin (the latent heat of vaporization) (187). Next, vaporized sweat moves along its concentration gradient across the boundary layer to the external environment. Since the driving force for this process is the skin-air vapour pressure gradient, evaporation is expressed as:

$$E_{sk} = \omega \cdot h_e \cdot (P_{s,sk} - P_a) \cdot BSA \, [W] \quad \text{(Eq. 17)}$$

$$h_e = h_c \cdot LR \, [W \cdot m^{-2} \cdot kPa^{-1}] \quad \text{(Eq. 18)}$$

Where: ω is the fraction of the skin surface covered in sweat (skin wettedness, see below); h_e is the evaporative heat transfer coefficient in watts per square metre per kilopascal of vapour pressure ($W \cdot m^{-2} \cdot kPa^{-1}$), which is the product of the convective heat transfer coefficient and the Lewis relation coefficient (LR, 16.5 K/kPa); and $P_{s,sk} - P_a$ is the vapour pressure difference

between the saturated skin and the ambient air (kPa). Since values for skin and ambient vapour pressures are proportional to skin and ambient temperatures, respectively, the rate of evaporative heat loss can be elevated by raising skin temperature. Additionally, greater air velocity facilitates evaporative heat loss through convection (1, 22). The relationship between evaporation and convection is defined by the Lewis relation coefficient, which links convective heat loss to mass transfer (53).

In conditions of fixed air velocity, ambient humidity, and mean skin temperature, the theoretical maximum capacity for evaporative heat loss to the environment (E_{max}) occurs with complete wetting of the skin (i.e., $\omega = 1$):

$$E_{max} = h_e \cdot (P_{s,sk} - P_a) \cdot BSA \text{ [W]} \quad \text{(Eq. 19)}$$

To describe submaximal rates of evaporative heat loss in relation to E_{max}, Gagge introduced the concept of skin wettedness (52): if E_{sk} represents the actual rate of evaporation, and E_{max} represents maximal evaporation, E_{sk}/E_{max} is the fraction of BSA covered in sweat that would result in E_{sk} at a given mean skin temperature. Skin wettedness may also be described in terms of the skin wettedness required for heat balance (ω_{req}), which is the ratio of the rate of evaporation required for heat balance (E_{req}) and E_{max}:

$$\omega_{req} = E_{req}/E_{max} \text{ [ND]} \quad \text{(Eq. 20)}$$

By rearranging Eq. 1, E_{req} is calculated as:

$$E_{req} = M - W - (K + R + C + C_{res} + E_{res}) \text{ [W]} \quad \text{(Eq. 21)}$$

If $\omega_{req} \leq 1$, the rate of evaporative heat loss may be sufficient to restore heat balance, and the conditions are termed ‘compensable’. In contrast, an ‘uncompensable’ environment is defined by a $\omega_{req} > 1$. In most uncompensable conditions, the inability to maintain heat balance is due to environmental limitations on the ability to dissipate sufficient heat (e.g., very high ambient

temperature or humidity), resulting in persistent heat storage. However, conditions may be physiologically uncompensable despite a $\omega_{req} < 1$. For example, at high rates of metabolic heat production in hot/dry or windy conditions, the rate of evaporative heat loss may be high, but a limited sweat production can lead to uncompensable heat stress due to the inability to fully wet the skin (10). Additionally, maximum skin wettedness (the maximum fraction of BSA that can participate in evaporation, ω_{max}) is limited to a value of ~0.85 in non-heat acclimated individuals (18). Consequently, the actual value of E_{max} will be reduced, thereby lowering the threshold for compensability to a ω_{req} value of 0.85.

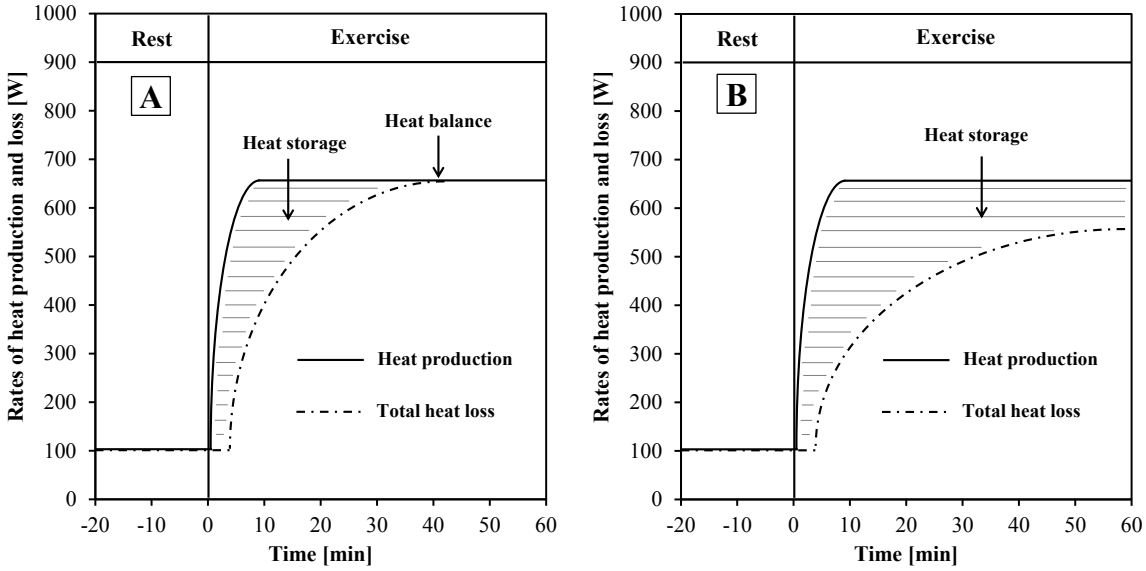


Figure 1. Patterns of change in heat production and loss during exercise in compensable and uncompensable conditions

At rest, the rate of metabolic heat production is balanced by the rate of total heat loss, resulting in net heat storage of zero. At the commencement of exercise, metabolic heat production rises rapidly (*solid line*), reaching a steady state within ~5 minutes. Due to the delay in the onset of thermoeffector responses, total heat loss (*dashed line*) does not immediately balance heat production, resulting in net heat storage (*hatched area*). The accumulation of heat within body tissues initiates cutaneous vasodilatation and sweating to increase total heat dissipation. For a given rate of heat production, heat balance can be attained over a wide range of environmental conditions known as the 'prescriptive zone' (A). Outside of the prescriptive zone, heat imbalance persists due to limited heat dissipation capacity (B). Such conditions are uncompensable, as the rate of evaporative heat loss required for heat balance is greater than the maximum capacity for evaporative heat loss to the environment.

2.2 Human temperature regulation

The principal function of human thermoregulation is effectively to maintain heat balance at levels that preserve cellular function (e.g., enzymatic reactions) and integrity (e.g., membrane fluidity) during periods of thermal stress such as physical activity and environmental heat exposure. Physical activity results in greater demand for ATP to perform mechanical work, leading to a rise in heat production from ~100 W at rest to over 1000 W during periods of sustained high-intensity exercise in aerobically fit individuals (62). The rapid and exponential rise in heat production is not met immediately by greater heat dissipation to the environment, resulting in net heat storage (Figure 1). This imbalance raises core temperature until the onset threshold for thermoeffector responses has been reached, leading to a slow exponential rise in total heat loss. For a given rate of heat production, heat balance will be achieved over a wide range of environmental conditions that define the 'prescriptive zone' (117). Outside the prescriptive zone, the rate of heat dissipation is limited and heat balance is unattainable, resulting in a continuously rising core temperature.

The rise in deep tissue and skin temperatures that are associated with internal heat storage during exercise and/or heat exposure is sensed by warm-sensitive peripheral thermoreceptors in the skin, blood vessels, and viscera (79) that relay afferent information via unmyelinated C-fibres to the central nervous system (80). Central thermoreceptors in the spinal cord, brain stem, and hypothalamus also sense changes in temperature (79). Nuclei of the pre-optic region and anterior hypothalamus integrate thermal afferents and subsequently initiate thermoeffector responses to restore heat balance (46, 124, 137). Efferent signalling through sympathetic pathways to the cutaneous vasculature and sweat glands promotes heat loss through greater skin blood flow

(secondary to cutaneous vasodilatation) and sweat evaporation, respectively. These effectors represent the 'active' or 'controlling' part of the thermoregulatory system (143, 189).

Active thermoregulatory control

The physiological processes involved in thermoregulation are initiated by changes in core and skin temperature (8, 95, 138, 147, 194, 197, 198), but can be modified by various factors associated with neural drive (central modifiers) and with local conditions (peripheral modifiers). Non-thermoregulatory reflexes contribute to active thermoregulatory control (108, 111, 165), but these factors are beyond the scope of this review. The rapidity of reaching a steady-state core temperature (i.e., heat balance) is dependent upon the operational parameters of temperature regulation that are defined by (i) the onset threshold core or mean body temperature, (ii) the gain of the response per 1°C change in core or mean body temperature (thermosensitivity), and (iii) the response maximum (62). The use of mean body temperature (T_b) as a forcing function of thermoeffector responses accounts for the relative contributions of core (T_c) and mean skin temperature (T_{sk}) to the changes in a given response, and can be estimated as:

$$T_b = x \cdot T_c + (1-x) \cdot T_{sk} \ [°C] \quad \text{(Eq. 22)}$$

Where: x and $1-x$ are sum-to-one coefficients for core and skin temperatures, respectively. Typical values for x in warm/hot climates are between 0.8 and 0.9 (72, 153, 167, 173, 180).

Physiological differences in vasomotor and sudomotor control can be characterized by changes in these control properties (Figure 2). For example, higher mean skin temperatures lower (94, 133, 188) and plasma hyperosmolality delays (49) the onset threshold core temperature for cutaneous vasodilatation and sweating through central mechanisms. Peripheral modification of cutaneous vasodilatation (127) and sweat rate (6, 133, 135) by high local skin

temperature alters thermosensitivity, resulting in greater responsiveness for a given change in core temperature. Additional modifying factors for cutaneous vasodilatation include, but are not limited to, circadian rhythm (177), heat acclimation (136, 145), and aerobic training (136, 145), which shift the onset for cutaneous vasodilatation to a lower absolute core temperature threshold, but have little influence on thermosensitivity. Similarly, heat acclimation has been shown to shift the onset threshold of sweating to a lower absolute core temperature and may slightly improve thermosensitivity (116, 136, 168). While this onset threshold shift is likely due to a similar reduction in resting core temperature (12, 92), greater thermosensitivity may be due to alterations in the size and sensitivity of sweat glands following repeated bouts of exercise and/or heat exposure (14, 15, 155, 159). Maximum skin blood flow during passive heating can approach 8.0 L/min (148), but only reaches ~60% of peak resting values during exercise (11, 93). This plateau occurs despite a rising core temperature due to a limit on active vasodilator activity imposed by exercise (100). Maximum whole-body sweat rates in excess of 2 L/h have been reported during intense exercise (184), and may be influenced by age (13), the degree of heat acclimation (19), and/or aerobic training (15).

Cutaneous vasodilatation

Heat conductance between the core and skin occurs predominantly by convection in the circulatory system, which is enabled by a high specific heat capacity of blood (141), the ability to redistribute cardiac output (150, 151), and the capacity to raise skin blood flow through cutaneous vasodilatation. In most conditions (i.e., core temperature exceeds skin temperature), this latter trait serves to increase heat flux to the skin, and thereby expand the temperature and vapour pressure gradients between the skin and air to facilitate heat loss (see Eq. 7, 10, 11).

Estimates of skin blood flow range from 250-500 ml/min during normothermic rest, up to 8 L/min during severe hyperthermia (148, 149).

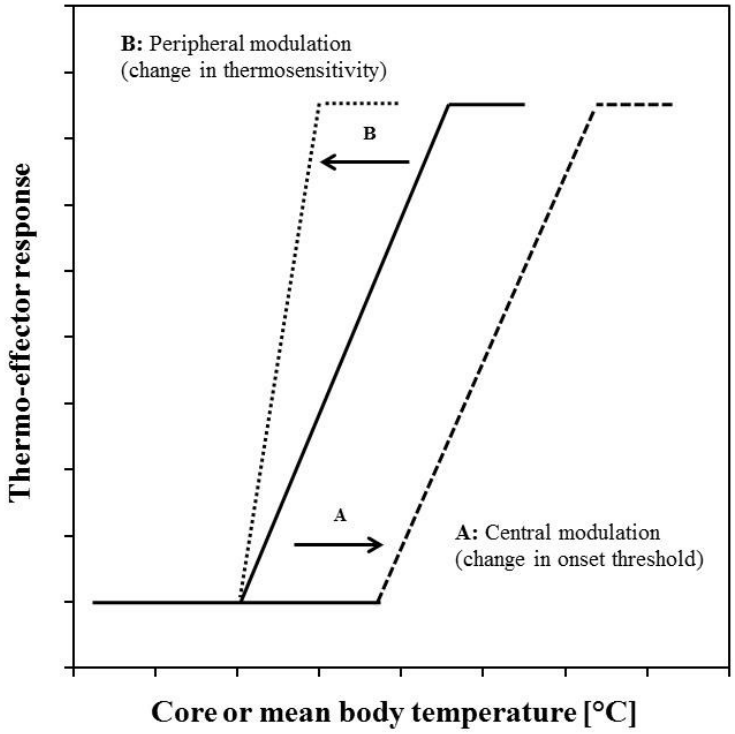


Figure 2. Schematic of thermo-effector control
Thermoregulatory control is characterized primarily by the onset threshold core or mean body temperature, the thermosensitivity, and the maximum rate of the thermos-effector response. A typical pattern of response is indicated by the solid line. Factors influencing the central modulation of temperature regulation, including mean skin temperature and plasma osmolality, exert their effects on the onset threshold as indicated by the dashed line (A). Factors influencing the peripheral modulation of temperature regulation, such as local skin temperature, exert their effects on thermosensitivity, indicated by the dotted line (B).

In non-glabrous (hairy) skin that covers most of the skin surface area, cutaneous vessel diameter is under neural control by two branches of the sympathetic nervous system: noradrenergic vasoconstriction and cholinergic vasodilatation (96). At the onset of exercise, active vasoconstriction within the cutaneous vasculature occurs due to non-thermoregulatory factors associated with exercise, such as the maintenance of blood pressure (123). As core temperature rises (during rest and exercise), skin blood flow increases due to the withdrawal of basal vascular tone (147), which likely occurs via inhibition of noradrenergic vasoconstriction by

nitric oxide (166), and by cholinergic active vasodilatation (38, 67, 147), which is responsible for up to 95% of total skin blood flow (93, 99). This rise in skin blood flow continues up to a core temperature of ~38.0-38.5°C (11); however, the rise in skin blood flow during exercise reaches only 50-60% of its maximum value (96). Although the precise mechanism of active vasodilatation is not known, infusion of atropine (a muscarinic receptor antagonist) cannot completely abolish active vasodilatation (147), suggesting acetylcholine, an unidentified co-transmitter (101, 102), and nitric oxide release (96, 99) all contribute to cutaneous vasodilatation. Local heating can also affect skin blood flow independently of the active vasodilatory pathway (101). A high local skin temperature (39-40°C) induces a biphasic rise in skin blood flow via initial reflex vasodilatation followed by local nitric oxide release (127).

Eccrine sweating

The thermoeffector response with the highest capacity for heat loss to the environment during exercise and/or environmental heat stress is sweat evaporation. Indeed, under conditions of high metabolic heat production or those in which air temperature exceeds skin temperature, sweat evaporation is the principal avenue of heat loss. The secretion of sweat begins shortly after the onset of exercise within all skin regions, but demonstrates large inter- and intra-regional variability (25, 75, 81, 120, 121, 171, 186). The highest local sweat rates are typically observed on the forehead, followed by the medial aspects of the torso, the lower leg, thigh, and arm (25, 171). Thermoregulatory sweating originates from the 1.6-4.0 million eccrine sweat glands located in the dermal layer of the skin and distributed throughout the non-glabrous skin areas (158). The highest density of active eccrine sweat glands exists on the volar surfaces of the hands and feet, followed by the forehead, limbs, and torso (110, 157, 183). There is also considerable

regional variability in the onset sequence and sweat rate across body surfaces that are best explained by differences in sweat gland output rather than heat-activated sweat gland density (4, 81, 90).

Stimulation of an eccrine sweat gland occurs primarily through the release of acetylcholine from sympathetic post-ganglionic unmyelinated C fibres and its subsequent binding to muscarinic receptors located around the secretory coil (and to a lesser extent, the duct) of the sweat gland (103, 167). Upon stimulation, fluid from the interstitial space supplied by blood plasma follows sodium, chloride, and potassium movement through 'clear' cells and into the glandular lumen, forming 'precursor sweat' (183). As this isotonic solution is transported through the duct towards the skin, ions are reabsorbed, resulting in the secretion of an aqueous hypotonic fluid onto the skin surface (156). Through internal convection/conduction, heat transfer to the skin expands the skin-air vapour pressure gradient, and the subsequent evaporation of sweat carries with it a large amount of heat due to its high latent heat of vaporization.

The passive system

The biophysical properties of the body under active control represent the 'passive' or 'controlled' system (143, 179). Models of the passive system typically divide the human body into segments (head, trunk, extremities) and compartments (skin, muscle, blood, viscera), each with its own mass and thermal properties affecting heat flux between tissues, to the skin, and to the environment (43, 44, 178, 179). These properties determine total body mass and BSA—physical traits that should alter human heat exchange (3). Nevertheless, researchers have rarely accounted for these properties when performing comparisons between groups of different body mass and BSA. Failure to account for body morphology may result in spurious conclusions

regarding the impact of various physiological factors on temperature regulation. This possibility is discussed below.

2.3 Influence of body morphology on the thermoregulatory responses to exercise

Factors such as sex (87), age (83, 89, 182), aerobic fitness (60, 131, 154), multiple sclerosis (20, 33), and spinal cord injury (160, 181) have been suggested to alter the change in core temperature and thermoregulatory sweat rate during exercise. From a biophysical perspective, the change in core temperature during exercise should be determined by the difference between heat production and total heat dissipation (i.e., heat storage), body mass (i.e., the internal heat sink), and body composition (i.e., the specific heat capacity of tissue). Similarly, whole-body sweat rate should be determined by E_{req} and sweating efficiency, with local sweat rate (measured per unit surface area) further modified by differences in BSA (i.e., the interface between the body and the environment). Since many studies have failed to account for heat production and body morphology, it is unclear whether the different changes in core temperature and sweat rates reported in many studies actually reflect the independent influence of the physiological factor under investigation. By characterizing the independent effect of each of these biophysical factors, researchers will be able to perform unbiased experiments to assess true physiological differences between groups or special populations. For the most part, this is currently not the case.

To compare changes in core temperature between groups distinguished by a single physiological factor, researchers have often used relative exercise intensities ($\%VO_{2max}$). This protocol is based primarily on a study by Saltin and Hermansen (154) that reported similar end-exercise absolute core temperatures at 25%, 50%, and 75%, independently of fitness status, and

concluded that core temperature is regulated according to $\%VO_{2max}$. These findings led to the widely-held belief that aerobic fitness *per se* profoundly influences exercise thermoregulation; therefore, between-groups comparisons of core temperature must account for variability in aerobic fitness by prescribing exercise intensity at a fixed $\%VO_{2max}$. However, closer scrutiny of these data reveals numerous problems with this interpretation. Firstly, since heat production is largely determined by absolute VO_2 (see Eq. 2), comparisons between independent groups heterogeneous for VO_{2max} working at the same $\%VO_{2max}$ will lead to large differences in metabolic rate, the rate of heat production, and the thermolytic requirements for heat balance (i.e., E_{req}). Consequently, a wide range of core temperature (50, 57, 92, 131, 154), sweating (57, 61, 87, 92, 131, 154), and skin blood flow (50, 83, 182) responses would be expected. Secondly, since changes in core temperature reflect heat storage, it is more appropriate to measure and report changes in core temperature rather than the absolute end-exercise core temperature when assessing the physiological effect of some factor (e.g., aerobic fitness) on heat balance. In the study of Saltin and Hermansen (154), the range of core temperature changes was ~1.0°C at 25% and 50% VO_{2max}, and more than 2.0°C at 75% VO_{2max}. The greater changes in core temperature from rest, but similar end-exercise absolute core temperatures in aerobically fit individuals is explained by a combination of lower pre-exercise resting values in aerobically fit individuals secondary to a greater blood volume and internal conduction between deep and more peripheral tissues, and higher rates of heat production at a given relative exercise intensity (92, 131). The findings of Saltin and Hermansen (154) therefore do not support an independent effect of VO_{2max} on changes in core temperature.

More recently, Jay *et al.* (92) used a heat balance approach to assess the influence of VO_{2max} on changes in core temperature and sweating during exercise in compensable conditions

and the utility of administering a relative exercise intensity to compare these responses between groups. Fundamentally, among individuals matched for body mass, exercise eliciting the same rate of heat production (in watts) should result in similar changes in core temperature as long as there is no physiological alteration to sweat rate or mean skin temperature that would alter heat dissipation. In the study of Jay *et al.* (92), mass-matched groups of high VO_{2max} (~60 $ml \cdot kg^{-1} \cdot min^{-1}$) and low VO_{2max} (~40 $ml \cdot kg^{-1} \cdot min^{-1}$) exercised at (i) a fixed rate of heat production (540 W; E_{req} of 175 W/m^2) but vastly different $\%VO_{2max}$, and (ii) 60% of VO_{2max}, which elicited a higher absolute rate of heat production and E_{req} in high-VO_{2max} individuals. At 540 W, nearly identical changes in rectal temperature, whole-body sweat loss, local sweat rate, and mean skin temperature were observed in both groups (Figure 3), while exercise at 60% VO_{2max} resulted in significantly greater changes in core temperature, whole-body sweat loss, and local sweat rate, but similar mean skin temperatures, in the high-VO_{2max} group (Figure 3). The findings of this study suggest that (i) VO_{2max} has no role in determining the thermoregulatory responses to exercise in compensable conditions, and (ii) the rate of metabolic heat production and body mass are the primary factors affecting changes in core temperature, not $\%VO_{2max}$.

The results of Jay *et al*. (92) potentially suggest that changes in core temperature are determined by absolute heat production, and whole-body sweat losses and local sweat rate are determined by E_{req} in accordance with previous studies (5, 66, 119, 164). However, exercise eliciting the same absolute heat production and E_{req} would not likely result in the same changes in core temperature and sweating, respectively, between groups that differ in body morphology, specifically body mass and BSA (24, 69, 73, 74, 76, 146). To overcome the difficulty of matching subjects for these characteristics, particularly in clinical populations, Jay *et al*. proposed that exercise should be administered to elicit (i) equivalent rates of heat production per

unit body mass (W/kg) to compare changes in core temperature among participants that differ in mass, (ii) equivalent rates of heat production per unit BSA (W/m^2) to compare local sweat rate among participants that differ in BSA, and (iii) equivalent rates of absolute heat production (W) to compare whole-body sweat losses (92). The following sections will review the evidence in support of these proposals.

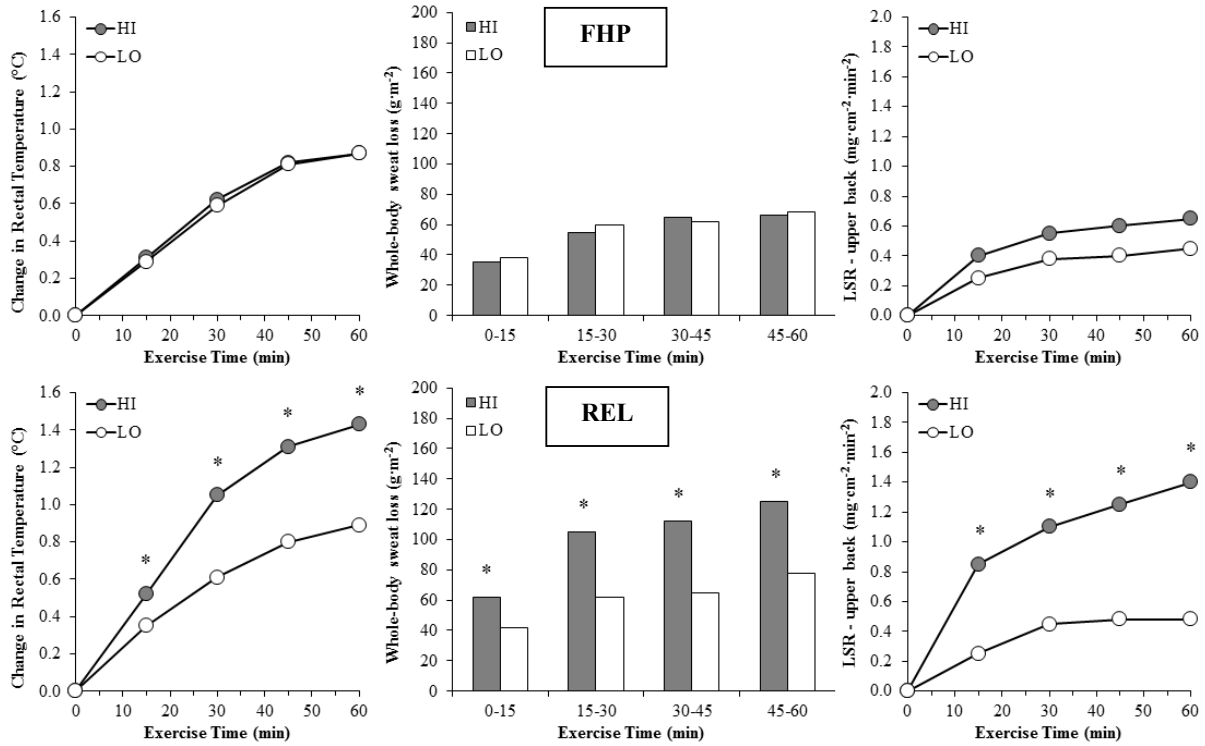
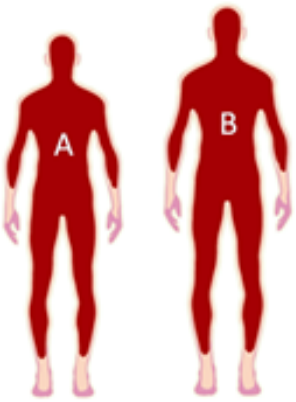


Figure 3. Summary of results from Jay *et al.* (2011)
Changes in rectal temperature, whole-body sweat loss, and local sweat rate (LSR – upper back) during exercise at a fixed absolute heat production of 540 W (FHP, *top panel*) or a relative exercise intensity of 60% VO_{2max} (REL, *bottom panel*) in groups of high (HI) and low (LO) aerobic fitness (VO_{2max}) matched for body mass and body surface area. Exercise at 60% VO_{2max} results in greater heat production and E_{req}, leading to greater changes in core temperature and whole-body sweat losses; however, exercise eliciting the same rate of heat production and E_{req} between groups resulted in no differences in these responses. No differences in mean skin temperature were observed between groups in FHP or REL. These results suggest high VO_{2max} does not enhance heat dissipation in compensable conditions. Redrawn from (92).

Body mass and core temperature

Since total body mass represents the internal heat sink, it stands to reason that differences in body mass can independently influence the core temperature response for a given change in body heat content (e.g., in kilojoules) and therefore the same absolute heat production and heat loss. A conceptual example is shown in Figure 4 in which we evaluate changes in core temperature between two individuals of very different body mass (but similar body tissue composition) during exercise. With the same change in body heat content (200 kJ), individuals 'A' (60 kg) and 'B' (100 kg) demonstrate very different changes in core temperature ('A': 0.96°C, 'B': 0.58°C) by virtue of the much greater body mass of individual 'B', that is, the same absolute amount of heat is stored within a greater total mass, resulting in a smaller change in core temperature. However, if individual 'B' stored 333 kJ of heat compared to the 200 kJ of heat stored by individual 'A', the change in core temperature would be theoretically be the same between them. Accordingly, numerous studies have reported large differences or high variability in the change in core temperature following exercise at a fixed absolute rate of heat production that may be explained by differences in body mass alone. For example, Lind (118) reported rectal temperatures that varied by as much as 1.5°C at a fixed metabolic rate of ~350 W during treadmill walking. Similarly, end-exercise rectal temperature varied by ~1.7°C after 1 h of cycling at an absolute workload of 60 W among subjects weighing 49.8 to 102.1 kg, and demonstrated a significant negative correlation with body mass (74). Moreover, Gagnon *et al*. (55) found that rectal and oesophageal temperatures were ~0.3°C and ~0.4°C greater, respectively, in females compared to males at an absolute heat production of 500 W, which can be explained by the lower body mass of female subjects. It is clear from these findings that the change in core temperature during exercise is altered by differences in body mass despite similar

absolute rates of heat production. Therefore, to properly isolate the influence of some physiological factor on changes in core temperature, comparisons between groups likely need to account for both heat production and body mass. If different changes in core temperature are observed despite fixing the rate of heat production and body mass, only then may it be concluded that a true physiological impairment of heat dissipation has indeed occurred. However, while standardizing exercise intensity to elicit a fixed absolute rate of heat production is relatively easy (e.g., a fixed VO_2 verified with indirect calorimetry), matching independent groups for body mass may be laborious, impractical, or even impossible, with clinical/special populations.



	(1)	(2)	(3)
Body mass (kg)	A = 60 kg	B = 100 kg	B = 100 kg
$\int H_{prod} - H_{loss}$ (kJ)	200	200	333
C_p (kJ·kg^{-1}·°C^{-1})	3.47	3.47	3.47
T_c (°C)	0.96	0.58	0.96

Figure 4. Theoretical example outlining the interaction between heat production, body mass, and changes in core temperature
Total body mass can alter the change in core temperature (ΔT_c) for a given change in body heat content, which is the net difference between rates of heat production and heat loss ($\int H_{prod} - H_{loss}$). To demonstrate this effect of body mass, the change in core temperature is estimated for a 60-kg individual ('A') and a 100-kg individual ('B') for a given change in body heat content (assuming the same body tissue composition, that is, average specific heat capacity of tissue, C_p). With a change in body heat content of 200 kJ, individual 'A' demonstrates a greater change in core temperature compared to individual 'B' by virtue of greater total body mass in 'B' (columns 1-2). To attain the same change in core temperature in individuals 'A' and 'B', the change in whole-body heat content must much greater in individual 'B' (column 3).

A potential solution to the issue of matching subjects for body mass may be to administer an exercise intensity that elicits similar rate of heat production in W/kg (29, 92). Although this has not been tested directly, support for this approach may be found in studies comparing core temperature responses between independent groups at fixed $\%VO_{2max}$ that coincidentally resulted in similar heat production in W/kg. Fritzsche and Coyle (50) reported similar changes in oesophageal temperature (~1.0°C) among trained and untrained subjects exercising at 50% and 70% VO_{2max}, respectively, which corresponded to ~9.0 W/kg in both groups. Similarly, Mora-Rodriguez *et al*. (131) found identical changes in rectal temperature (~0.6°C) among aerobically trained and untrained subjects exercising at 40% and 60% VO_{2max}, respectively, which elicited 8.2 W/kg in both groups (Figure 5). It should be noted that in both studies, body mass was 8-10 kg greater in the untrained group. Additionally, among groups matched for body mass, Shvartz *et al*. (169) reported similar VO_2 (~0.6 L/min) and changes in rectal temperature (~1.0°C) among trained, untrained, and unfit individuals during bench-stepping exercise before and after a period of heat acclimation and aerobic training. Since external workload remained constant, exercise elicited similar rates of heat production per unit mass (~4.2 W/kg) in that study. These findings are in agreement with those of Jay *et al*. (92), and suggest exercise should be prescribed to elicit similar rates of heat production in W/kg of total body mass to compare core temperature between groups heterogeneous for body mass, irrespective of the associated $\%VO_{2max}$.

Body surface area and local sweat rate

As with core temperature responses, conclusions regarding the determinants of thermoregulatory sweat rate during exercise may be equally confounded by differences in biophysical factors. Differences in whole-body and local sweat rates have been associated with

physiological factors such as sex (87, 172) and age (89, 182); however, exercise in these studies was performed at a $\%VO_{2max}$, resulting in differences in workload, heat production, and E_{req}. Numerous studies have shown an association between whole-body sweat rate and absolute workload (69, 154, 161), as well as the absolute rate of metabolic heat production (32, 35, 138). More recently, Gagnon *et al*. (56) identified absolute E_{req} (i.e., in watts) as the primary determinant of whole-body sweat rate, explaining 93% of the variance in steady-state whole-body sweat rate during exercise across a range of ambient conditions and rates of heat production. Therefore, previous studies that have concluded that physiological differences in sweat rate exist between groups may simply reflect differences in absolute E_{req} secondary to differences in absolute heat production.

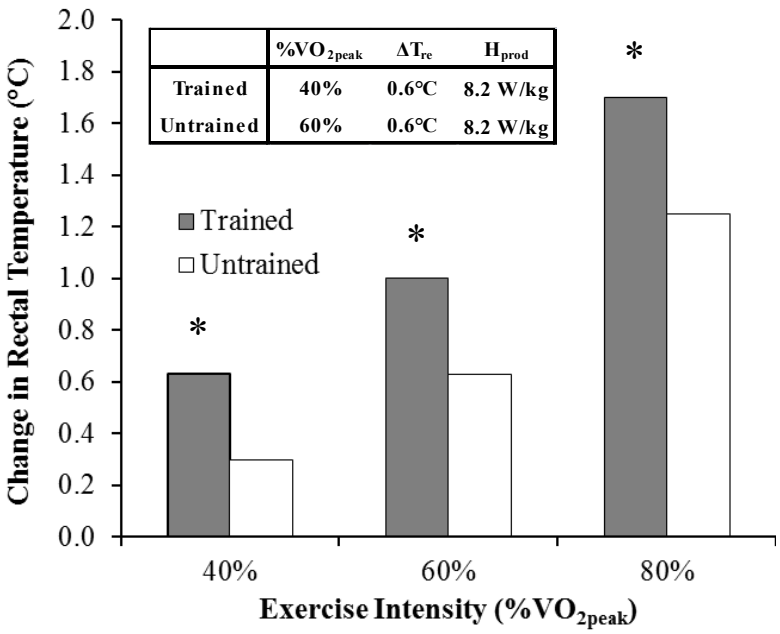


Figure 5. Summary of results from Mora-Rodriguez *et al.* (2010)
Changes in rectal temperature between aerobically trained (60 ± 6 $ml \cdot kg^{-1} \cdot min^{-1}$) and untrained (44 ± 3 $ml \cdot kg^{-1} \cdot min^{-1}$) subjects at three relative exercise intensities: 40%, 60%, and 80% VO_{2max}. Trained subjects had a greater rate of metabolic heat production in W/kg at all relative intensities. However, as shown in the table, trained subjects at 40% VO_{2max} and untrained subjects at 60% VO_{2max}, indicated by the red line, had the same rate of heat production (8.2 W/kg), concomitant with similar changes in rectal temperature (~0.6°C), indicated by the red line. Redrawn from (131).

While the findings of Gagnon *et al*. (56) suggest that independent-groups comparisons of absolute whole-body sweat rate (in g/min) should be performed at the same absolute E_{req}, differences in body morphology may affect the rate of local sweat production despite similarities in absolute E_{req}. To demonstrate the potential biophysical effects of BSA on local sweat rates, we consider the example of two individuals, one of low BSA ('A': 1.8 m^2) and one of high BSA ('B': 2.1 m^2), exercising in conditions of negligible dry and respiratory heat losses and 100% sweating efficiency (Table 1). Exercise at a workload of 85 W results in similar rates of absolute heat production and E_{req} in both individuals. But while both individuals should have similar absolute whole-body sweat rates due to similar absolute E_{req} values, individual 'A' would theoretically require a greater average local sweat rate as a greater amount of sweat per unit BSA must be produced to achieve the same absolute rate of evaporation as individual 'B'. Similarly, at a higher workload (e.g., 130 W), absolute heat production and E_{req} are the same, but the amount of sweat produced per unit BSA must be higher for individual 'A'. However, if exercise is prescribed to elicit the same heat production in W/m^2, this would yield similar E_{req} per unit BSA (i.e., in W/m^2), but very different absolute E_{req} values, between individuals 'A' and 'B', resulting theoretically in similar average local sweat rates but different absolute whole-body sweat rates. For example, exercise eliciting a heat production of 250 W/m^2 would result in similar E_{req} (W/m^2) for individuals 'A' and 'B', leading to similar average local sweat rates despite a lower absolute workload for individual 'A'. Also, whole-body sweat loss would be lower for individual 'A' because of a lower absolute E_{req}. It follows that even higher rates of heat production (e.g., 350 W/m^2) by both individuals, yielding similar E_{req} (in W/m^2), will result in a similar average local sweat rate despite a difference in absolute E_{req}, which would again lead to differences in whole-body sweat rate. This analysis is in agreement with the findings of Gagnon

et al. (56) regarding absolute whole-body sweat rates in conditions that permit 100% sweating efficiency. As such, prescribing exercise to elicit similar rates of heat production (and E_{req}) in W/m^2 may be the most appropriate method to perform unbiased comparisons of mean local sweat rates among individuals heterogeneous for BSA or between independent experimental groups that differ greatly in BSA.

Table 1. Influence of body surface area on mean local sweat rate
A theoretical analysis of the determinants of the mean local sweat rate (LSR_{req}) and whole-body sweat loss ($WBSL_{req}$) required for heat balance among individuals of high or low body surface area (BSA) during exercise at absolute workloads (85 W, 130 W) and at two levels of heat production per unit BSA (250 W/m^2, 350 W/m^2). Corresponding evaporative requirements (E_{req}) are also shown. In conditions of 100% sweating efficiency, a similar absolute H_{prod} and thus E_{req} should lead to similar WBSL (56), but different LSR due to differences in BSA. Normalizing the effect of BSA by prescribing a fixed H_{prod} (and thus E_{req}) in W/m^2 should lead to similar mean LSR regardless of body size. In this case, absolute H_{prod} and E_{req} will be greater in larger individuals, resulting in greater WBSL.

Fixed External Workload (W)							
BSA	Workload	H_{prod}		E_{req}		LSR_{req}	$WBSL_{req}$
[m^2]	[W]	[W]	[W/m^2]	[W]	[W/m^2]	[$mg \cdot cm^{-2} \cdot min^{-1}$]	[g]
2.1	**85**	387	184	355	169	0.42	527
1.8	**85**	387	215	355	197	0.49	527
2.1	**130**	592	282	543	259	0.64	806
1.8	**130**	592	329	543	302	0.75	806
Fixed Heat Production (W/m^2)							
BSA	Workload	H_{prod}		E_{req}		LSR_{req}	$WBSL_{req}$
[m^2]	[W]	[W]	[W/m^2]	[W]	[W/m^2]	[$mg \cdot cm^{-2} \cdot min^{-1}$]	[g]
2.1	113	525	**250**	481	229	0.57	714
1.8	96	450	**250**	413	229	0.57	612
2.1	158	735	**350**	674	321	0.88	1111
1.8	135	630	**350**	578	321	0.88	952

The workloads required to elicit the target rates of heat production were estimated assuming a gross efficiency of 18% for upright cycling. Calculations were based on 34°C, 20% RH, and 1.0 m/s air velocity ambient conditions; a 34°C mean skin temperature; and negligible evaporative resistance due to clothing.

2.4 Alterations to skin blood flow: effect on heat dissipation?

As discussed in section 2.2, the rise in skin blood flow attending cutaneous vasodilatation is one of two effector responses of the human thermoregulatory system. Adjustments in skin blood flow maintain adequate heat conductance from the core to the skin, raising skin temperature and the partial pressure of water vapour on the skin to facilitate an increase in dry and evaporative heat losses, respectively. Interventions that enhance skin blood flow (e.g., aerobic training, heat acclimation) are thought to enhance heat dissipation (170), while conditions that reduce skin blood flow (e.g., dehydration, ageing, disease) reportedly lower heat dissipation and cause elevations in core temperature (21, 84, 129). However, such responses are often observed during whole-body passive heating to a target change in core temperature in an encapsulated environment. Even in non-encapsulated conditions, reduced skin blood flow is often observed in the absence of any difference in whole-body sweat loss and mean skin temperature. Therefore, whether large increases or decreases in skin blood flow modify the capacity for heat dissipation is presently unclear.

Although the effects of a high VO_{2max} (50, 175) and heat acclimation (39, 191, 196) on heat dissipation through elevations in skin blood flow are equivocal, acute hypervolemia can effectively raise skin blood flow. For example, the infusion of transfused blood (47) and saline (31, 140) has been shown to quickly increase skin blood flow relative to non-infusion control conditions. Yet whether a relative hypervolemia actually enhances heat dissipation due to an elevated skin blood flow is unclear. During exercise, Nose *et al*. (140) used saline infusion to significantly raise skin blood flow compared to no infusion in thermoneutral (22°C) and warm (30°C) conditions, but no differences in mean skin temperature and sweat rate within each environment, and only a slight difference in the change in oesophageal temperature, were evident

after 55 min of exercise. Moreover, reinfusion of withdrawn blood resulted in similar changes in oesophageal temperature and skin temperature during exercise despite a higher thermosensitivity of the forearm blood flow response (47). While these studies suggest that hypervolemia effectively raises skin blood flow, such alterations do not appear to augment heat dissipation.

Nevertheless, the importance of maintaining a high rate of skin blood flow may only be apparent in comparison to conditions that result in a diminished skin blood flow. For example, diuretic administration and high sweat losses during prolonged exercise has been shown to lower skin blood flow (63–65, 88, 129, 130) and alter skin blood flow control (49, 134) compared to euhydrated and normovolemic conditions, resulting in higher changes in core temperature at a given rate of metabolic heat production. While it has been argued that a lower skin blood flow *per se* is responsible for subsequent elevations in core temperature (129), such large reductions in skin blood flow are not met by profound alterations in mean skin temperature, suggesting no change in the rate of dry heat loss. Furthermore, while some studies have reported a concomitant or subsequent decline in whole-body sweat losses (40, 48, 63, 85), other studies have reported similar whole-body sweat rates despite a fall in skin blood flow (64, 65, 129, 130). Without any differences in whole-body sweat rate and mean skin temperature, greater changes in core temperature at the same rate of heat production (and E_{req}) and under the same environmental conditions may be explained by the effects of a declining skin blood flow only if (i) the production or distribution of sweat were altered in such a way that modified evaporative efficiency, that is, more sweat dripped off the body and therefore less sweat evaporated from the skin, or (ii) heat flux throughout the body were altered, leading to a rising core temperature. The former possibility is supported by evidence that suggests a functional relationship between skin blood flow and thermoregulatory sweating responses, as lowering skin blood flow through

arterial occlusion (23, 41, 82, 113, 144) or noradrenaline infusion (193) during passive heating attenuates the rise local sweat rate. Therefore, for a given E_{req}, maintenance of skin blood flow could ensure adequate sweat production and an even sweat distribution across the skin – the advantage of which would be an improved evaporative efficiency under conditions in which dripping might otherwise occur with a lower skin blood flow (i.e., high metabolic heat production, high ambient temperature and humidity, or low air velocity). Further investigation is required to determine the consequences of altered skin blood flow on sweat production, sweat distribution, evaporative efficiency, and whole-body heat loss potential.

CHAPTER 3: METHODS AND RESULTS

3.1 Thesis article #1

This article was accepted for publication on 4 February 2014 by the *Journal of Applied Physiology*, and has been formatted accordingly. The final published version can be found in Appendix B, additional figures can be found in Appendix C, an accompanying editorial may be found in Appendix D, and a podcast interview regarding the study findings from 6 May 2014 can be accessed at http://jappl.podbean.com/.

Selecting the correct exercise intensity for unbiased comparisons of thermoregulatory responses between groups of different mass and surface area

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Running Title: Core temperature, local sweating, and exercise intensity

Author contributions: M.N.C. and O.J. conceived and designed experiments; M.N.C. performed experiments; M.N.C analyzed data; M.N.C. and O.J. interpreted data; M.N.C. drafted manuscript; M.N.C. and O.J. edited/revised manuscript; M.N.C and O.J. approved final draft of manuscript.

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ABSTRACT

We assessed whether comparisons of thermoregulatory responses between groups unmatched for body mass and surface area (BSA) should be performed using a metabolic heat production (H_{prod}) in W or W/kg for changes in rectal temperature (ΔT_{re}), and an evaporative heat balance requirement (E_{req}) in W or W/m^2 for local sweat rates (LSR). Two groups with vastly different mass and BSA (Large, LG: 91.5 ± 6.8 kg, 2.12 ± 0.09 m^2, n=8; Small, SM: 67.6 ± 5.6 kg, 1.80 ± 0.09 m^2, n=8; $P < 0.001$), but matched for heat acclimation status, sex, age, and with the same onset threshold esophageal temperatures (LG: +0.37 ± 0.12ºC; SM: +0.41 ± 0.17ºC; $P = 0.364$) and thermosensitivities (LG: 1.02 ± 0.54, SM: 1.00 ± 0.38 mg·cm^{-2}·min^{-1}·ºC^{-1}; $P = 0.918$) for sweating, cycled for 60 min in 25°C at different levels of H_{prod} (500 W, 600 W, 6.5 W/kg, 9.0 W/kg) and E_{req} (340 W, 400 W, 165 W/m^2, 190 W/m^2). ΔT_{re} was different between groups at a H_{prod} of 500 W (LG: 0.52 ± 0.15°C, SM: 0.92 ± 0.24ºC; $P < 0.001$) and 600 W (LG: 0.78 ± 0.19°C, SM: 1.14 ± 0.24ºC; $P = 0.007$), but not different at 6.5 W/kg (LG: 0.79 ± 0.21°C, SM: 0.85 ± 0.14ºC; $P = 0.433$) and 9.0 W/kg (LG: 1.02 ± 0.22°C, SM: 1.14 ± 0.24ºC; $P = 0.303$). Furthermore, ΔT_{re} was not different at 9.0 W/kg in a 35ºC environment (LG: 1.12 ± 0.30°C, SM: 1.14 ± 0.25°C) as at 25ºC ($P > 0.230$). End-exercise LSR was different at E_{req} of 400 W (LG: 0.41 ± 0.18, SM: 0.57 ± 0.13 mg·cm^{-2}·min^{-1}; $P = 0.043$) with a trend toward higher LSR in SM at 340 W (LG: 0.28 ± 0.06, SM: 0.37 ± 0.15 mg·cm^{-2}·min^{-1}; $P = 0.057$), but similar at 165 W/m^2 (LG: 0.28 ± 0.06, SM: 0.28 ± 0.12 mg·cm^{-2}·min^{-1}; $P = 0.988$) and 190 W/m^2 (LG: 0.41 ± 0.18, SM: 0.37 ± 0.15 mg·cm^{-2}·min^{-1}; $P = 0.902$). In conclusion, when comparing groups unmatched for mass and BSA, future experiments can avoid systematic differences in ΔT_{re} and LSR by using a fixed H_{prod} in W/kg and E_{req} in W/m^2, respectively.

Key Words: core temperature, local sweat rate, body mass, body surface area, thermoregulation

INTRODUCTION

Studies of human thermoregulation often employ a between-groups experimental design to isolate the independent effect of a particular physiological factor – e.g. age (5, 24, 50), sex (18, 25), aerobic fitness (19, 39), disease (29, 30), injury (21) – on the core temperature and sudomotor responses to exercise. The exercise intensity prescribed to facilitate these comparisons is fundamentally important since the introduction of any inherent bias to an experimental design may lead researchers to incorrectly attribute different changes in core temperature and/or sweating between groups to the physiological factor under examination.

For decades, many exercise and thermal physiologists have interpreted the seminal work of Saltin and Hermansen (44) to mean that a fixed relative exercise intensity (a percentage of the maximum rate of oxygen uptake, $\%VO_{2max}$) should be administered to compare thermoregulatory responses between independent groups due to the prevailing notion that VO_{2max} is a primary contributor influences the change in core temperature and sweating during exercise (13, 19, 20, 39). However, we recently reported that two groups matched for body mass and body surface area (BSA), but differing greatly in VO_{2max}, exhibit no differences in the changes in core temperature and whole-body sweat loss during exercise at the same absolute rate of metabolic heat production (540 W) in a physiologically compensable environment despite large differences in relative intensity (58% vs. 40% of VO_{2max}) (27). It is now also clear that protocols utilizing $\%VO_{2max}$ can lead to systematically different changes in core temperature and sweating between groups that may otherwise respond similarly from a physiological perspective, due to differences in heat production (H_{prod}) and the evaporation required for heat balance (E_{req}) (16, 27). However, since the participants in our previous study were matched for body mass (27), it is still unknown whether an absolute H_{prod} (in watts) should be used to prescribe exercise intensity

for between-group experimental designs, or if H_{prod} should be normalized for body mass (W/kg) if groups are unmatched for this physical trait. The practical importance of this question is emphasized by the fact that matching groups for body mass may in some cases be impossible for researchers investigating the consequences of potential thermoregulatory dysfunction in special populations such as multiple sclerosis patients (10), the obese (23, 33), spinal cord injury victims (21, 49), sympathectomy patients (8), and skin-graft recipients (36, 47).

From a biophysical perspective, changes in core temperature are determined by the cumulative imbalance between H_{prod} and net heat loss to the environment (i.e. body heat storage), body mass (i.e. internal heat sink), and body composition (i.e. specific heat capacity of body tissue). Previous studies have shown that large variations in body mass lead to diverse core temperature responses during exercise at the same absolute work rate or H_{prod} (15, 22, 35, 43). It therefore stands to reason that normalizing H_{prod} for body mass should lead to similar changes in core temperature between groups of dissimilar body mass unless heat loss changes as a function of the physiological parameter under investigation (e.g. age, sex, etc).

Using direct calorimetry and therefore under conditions permitting full evaporation, Gagnon et al. (16) recently demonstrated that whole-body sweat rate (WBSR) in g/min is determined by the absolute rate of evaporation required for heat balance (E_{req}) in W, irrespective of $\%VO_{2max}$, core temperature, BSA, and body mass. However, local sweat rate (LSR) is typically measured in $mg \cdot cm^{-2} \cdot min^{-1}$ over a fixed surface area with either a ventilated capsule (18, 25, 50) or absorbent patch (3, 7, 11, 48); therefore, a higher mean LSR would be expected at a fixed absolute E_{req} (and therefore WBSR) in individuals with a lower BSA because the same absolute amount of sweat would have to secreted over a smaller area. The prescription of an exercise intensity that elicits the same absolute E_{req} may therefore lead to a systematically

different LSR between independent groups unmatched for BSA, yet an intensity eliciting the same E_{req} per unit BSA (in W/m^2) may remove this inherent bias (11, 18).

The purpose of this study was to derive the optimal methods for comparing changes in rectal temperature (ΔT_{re}) and local sweat rates (LSR) between groups unmatched for body mass and BSA so that any inherent bias due to biophysical factors is removed. To this end, we compared responses between groups vastly different in body mass (~90 kg vs. ~65 kg) and BSA (~2.10 m^2 vs. 1.80 m^2) but matched for age, sex, and heat acclimation status, and with identical operational parameters for sudomotor control (i.e., onset threshold and thermosensitivity). Values for ΔT_{re} were compared using fixed levels of i) absolute H_{prod} (in W), and ii) H_{prod} per unit total body mass (in W/kg). Values for mean LSR were compared using fixed levels of i) absolute E_{req} (in W), and ii) E_{req} per unit BSA (in W/m^2). It was hypothesized that 1) H_{prod} in W would yield a greater ΔT_{re} in the small body mass group due to a greater W/kg, but H_{prod} in W/kg would lead to a similar ΔT_{re} between groups despite differences in body mass, and 2) E_{req} in W would yield similar WBSR between large and small BSA groups, but mean LSR would be greater in the small BSA group due to a greater E_{req} in W/m^2; however, E_{req} in W/m^2 would lead to similar mean LSR between groups despite differences in BSA.

METHODS

Ethical approval

Approval of the experimental protocol was obtained from the University of Ottawa Health Sciences and Science Research Ethics Board (File No. H12-11-05). All procedures conformed to the principles set forth in the Declaration of Helsinki. Volunteers were fully informed of the experimental protocol and potential risks before providing written informed

consent. Also, a Physical Activity Readiness Questionnaire (PAR-Q) and an American Heart Association/American College of Sports Medicine Health/Fitness Facility Pre-participation Screening Questionnaire were completed prior to participation.

Participants

Using a power calculation (G*power v3.1.5) with conventional β (0.1) and α (0.05) values, a minimum sample size of 12 participants (six per group) was required based on a mean ΔT_{re} of 0.35°C and a standard deviation of 0.15°C following 60 min of exercise at a fixed H_{prod} of 500 W between independent groups with a 17.7-kg difference in body mass (15). Sixteen males of large (LG: n=8) or small (SM: n=8) body mass and BSA volunteered for this study. Groups were matched for age, but not aerobic fitness, to ensure differences in $\%VO_{2max}$ at each W/kg, and thereby isolate whether systematic differences in ΔT_{re} are avoided by prescribing a fixed W/kg between groups unmatched for body mass. All participants were non-smokers, reported no history of cardiovascular, respiratory, neurological, or metabolic disease, and were not taking any medications at the time of participation.

Preliminary session

Each participant visited the laboratory for a preliminary session that included an explanation of the experimental protocol, anthropometric measurements, and an exercise test. Height was measured using a wall-mounted stadiometer (HR-200, Tanita, Arlington Heights, IL, USA), and body mass was measured using a digital scale (BWB-800, Tanita, Arlington Heights, IL, USA). These values were used subsequently to estimate BSA (12). Body composition was

measured via dual-energy x-ray absorptiometry (DXA; GE-LUNAR Prodigy module, GE Medical Systems, Madison, WI, USA).

The exercise test was performed in a climate-controlled room set to 22°C on a semi-recumbent cycle ergometer (Lode Corival, Groningen, Netherlands) in two phases. The first phase was performed to determine the relationship between external work rate and steady-state VO_2 (and thus H_{prod}) for each participant over the full range of H_{prod} targeted in the experimental trials. This procedure permitted greater accuracy in achieving each target H_{prod} from the onset of exercise (see appendix for step-by-step instructions for prescribing exercise intensity to achieve target H_{prod}). Participants completed four 5-min submaximal stages, which began at 80 W (SM) or 100 W (LG) and increased by 20 W/stage. Expired gases were analyzed throughout exercise via indirect calorimetry using a metabolic cart (Vmax Encore, CareFusion, Yorba Linda, CA, USA), which was calibrated for gas analysis and flow measurements prior to every trial. Following a 10-min rest period, the second phase of exercise included an incremental exercise test to exhaustion to determine VO_{2max}. This protocol commenced at an external work rate of 80 W and increased by 20 W/min until volitional exhaustion in accordance with guidelines from the Canadian Society for Exercise Physiology (9).

Heat acclimation

Prior to experimentation, each participant performed seven consecutive days of low-intensity cycling at 35°C and 35% relative humidity (RH) for 90 min/day to improve exercise tolerance and to minimize potential variance in the operational parameters of sudomotor activity (i.e., onset threshold and thermosensitivity) that could possibly explain differences in LSR between groups (45).

Experimental design

Experimental trials were separated by 2-3 days, and were performed in a randomized, counterbalanced order at the same time of day to eliminate any systematic differences between groups due to circadian variation. Participants were asked to abstain from alcohol and caffeine, avoid strenuous exercise in the 12 h prior to each experimental session, and consume a light meal and 500 ml of water ~2 h before arriving at the laboratory. Upon arrival, each participant provided a urine sample, which was immediately analyzed for urine specific gravity (USG) to ensure pre-exercise hydration status was similar between groups. A USG cut-off value of 1.025 was enforced, as values below this threshold have been suggested to indicate normal hydration (28). Participants inserted the rectal thermocouple, changed into a standardized pair of cotton running shorts, and then an initial body mass measurement was taken to determine the rate of heat production for each W/kg trial. Next, the participants put on a pair of cotton socks and running shoes, and sat on the ergometer while they were instrumented. Following 30 min of baseline data collection while seated on the ergometer, participants then performed 60 min of semi-recumbent cycling in one of four experimental conditions: three trials in neutral ambient conditions (25.1 ± 0.5°C, 36.8 ± 12.7% RH, and 1.2 ± 0.1 m/s air velocity) at exercise intensities eliciting 500 W, 6.5 W/kg, or 9.0 W/kg of heat production, and one trial in the heat (34.7 ± 1.7°C, 34.1 ± 8.7% RH, and 1.1 ± 0.3 m/s air velocity) at 9.0 W/kg. This latter trial was performed to determine whether similar ΔT_{re} would be observed within each group in different, but compensable, ambient conditions that remained within the 'prescriptive zone' (34). Two LG subjects could not complete the protocol in the heat, and were therefore not included. Air flow was provided by three 46-cm mechanical fans stacked vertically and positioned 1.25 m in front of the ergometer. By virtue of the targeted differences in body mass between LG and SM groups,

comparisons of ΔT_{re} at H_{prod} of 600 W were also possible from data collected in the 6.5 W/kg and 9.0 W/kg trials in the LG and SM groups, respectively. Due to differences in BSA between LG and SM, LSR comparisons were possible at E_{req} of 165 W/m^2 and 190 W/m^2. Specifically, exercise at 500 W in LG and 6.5 W/kg in SM corresponded to an E_{req} of 165 W/m^2, while exercise at 6.5 W/kg for LG and 500 W for SM corresponded to an E_{req} of 190 W/m^2, in both groups. Cycling cadence was maintained at 80 revolutions per minute in all trials. Core temperature, skin temperature, and LSR on the upper back and forearm were measured continually (see below). Body mass measurements were taken in triplicate while clothed and fully instrumented immediately prior to exercise (i.e.as a baseline for WBSL estimations) and every 15 min throughout exercise, which required a 2-min break from cycling.

Instrumentation

Core temperatures were measured using general-purpose pediatric thermocouple probes (Mon-a-therm, Mallinckrodt Medical, St. Louis, MO, USA). Rectal temperature (T_{re}) was measured at a depth of 12 cm beyond the anal sphincter. Esophageal temperature (T_{es}) was measured at a maximum depth of ~40 cm (37) for the first 15 min of exercise to determine the sudomotor onset threshold and thermosensitivity (see below). Both T_{re} and T_{es} are expressed as changes from baseline (i.e., ΔT_{re} and ΔT_{es}). Skin temperature was measured at eight sites with thermistors integrated into 2.5-cm^2 heat flux sensors (Concept Engineering, Old Saybrook, CT, USA). These sensors were affixed to the skin using double-sided adhesive discs (3M Health Care, Neuss, Germany) and surgical tape (Transpore, 3M, London, ON, Canada). Mean skin temperature (T_{sk}) was calculated using weighting coefficients according to ISO 9886 (26): forehead, 0.07; shoulder, 0.07; triceps, 0.07; chest, 0.175; scapula, 0.175, hand, 0.05; thigh, 0.19;

and calf, 0.20. Values for T_{sk} are reported as an average over the 60 min of exercise. Core and skin temperatures were recorded with a data acquisition system (NI cDAQ-9172, National Instruments, Austin, TX, USA) and LabView software (v 7.0, National Instruments, Austin, TX, USA), sampled at 0.2 Hz.

Estimations of WBSR were made from changes in body mass every 15 min. Body mass was measured in triplicate using a platform scale accurate to the nearest ± 2 g (Combics 2, Sartorius, Mississauga, ON, Canada) and corrected for metabolic mass loss and vapor losses from the respiratory tract (38). Values for WBSR are reported for each 15-min time period in grams per minute (g/min). Cumulative whole-body sweat loss (WBSL) for the 60-min exercise period is also reported in grams.

Local sweat rate was measured using ventilated capsules (4.1 cm^2) placed on the forearm ~5 cm distal to the antecubital fossa and the upper back ~5 cm above the scapular spine over the trapezium, and secured with adhesive (Collodion HV, Mavidon Medical, Lake Worth, FL, USA) and surgical tape. The flow of anhydrous air through each capsule was regulated at 1.80 L/min (FMA-A2307, Omega Engineering, Stamford, CT, USA). The vapor concentration of effluent air was measured at 0.2 Hz using factory-calibrated capacitance hygrometers (HMT333, Vaisala, Vantaa, Finland). Local sweat rate is reported as the product of the vapor concentration and the flow rate, normalized to the skin surface area covered by the capsule, and expressed in milligrams per square centimeter per minute ($mg \cdot cm^{-2} \cdot min^{-1}$). The sudomotor onset threshold and thermosensitivity were determined via segmented regression using 1-min averages for the mean LSR response and ΔT_{es} (6).

Heat balance parameters

Heat balance parameters were estimated via partitional calorimetry, and are presented as the mean value within each experimental condition. All heat exchange parameters were calculated in W/m^2, but are presented in W, W/m^2, or W/kg where appropriate. Due to a minimal clothing ensemble, dry insulation and evaporative resistance of clothing were considered negligible.

The rate of metabolic energy expenditure (M) was estimated as:

$$M = VO_2 \cdot \frac{\left(\left(\frac{RER - 0.7}{0.3}\right)\cdot e_c\right)+\left(\left(\frac{1.0 - RER}{0.3}\right)\cdot e_f\right)}{60 \cdot BSA} \cdot 1000\ [W/m^2] \quad (1)$$

Where: RER is the respiratory exchange ratio; e_c and e_f represent the energy equivalent of carbohydrate (21.13 kJ) and fat (19.69 kJ), respectively, per liter of O_2 consumed (L/min). Actual VO_2, RER, and M values for each trial can be found in Appendix C. H_{prod} was determined as the difference between M and the external work rate (W):

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

Heat loss via radiation (R) was calculated as:

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

Where: T_a denotes ambient temperature (°C), and h_r is the radiant heat transfer coefficient:

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

Where: ε is the emissivity of the skin (0.95); σ is the Stefan-Boltzmann constant ($5.67 \cdot 10^{-8}$ $W \cdot m^2 \cdot K^{-4}$); BSA_r/BSA is the effective radiant surface area (ND), equal to 0.70 (31); and T_r is the mean radiant temperature, assumed to be equivalent to T_a (°C). Convective heat exchange from the skin, C, was calculated as:

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

where h_c is the convective heat transfer coefficient for a seated individual facing an air velocity (v) between 0.2 and 4.0 m/s (41):

$$h_c = 8.3 \cdot v^{0.6} \ [W \cdot m^{-2} \cdot K^{-1}] \quad (6)$$

Respiratory heat losses through evaporation (E_{res}) and convection (C_{res}) were determined by:

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

Where: P_a is the ambient vapor pressure (kPa). The evaporation required for heat balance (E_{req}) was calculated as:

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

Statistical analysis

Mean participant characteristics were compared using independent-samples t-tests. Data for ΔT_{re} and LSR were analyzed as 5-min averages ending at 0 (i.e. the final 5 min of baseline), 15, 30, 45, and 60 min of exercise. For each H_{prod}, two-way mixed model ANOVA with the repeated factor of time (five levels: baseline, 15, 30, 45, 60 min) and the non-repeated factor of body mass (two levels: LG and SM) were performed to compare $\Delta T_{re,}$ WBSR, and LSR with a Bonferroni correction for multiple comparisons (i.e., at each time point). Independent-samples t-tests were used for single comparisons of heat balance parameters, $\%VO_{2max}$, 60-min ΔT_{re}, T_{sk}, and cumulative WBSL, as well as sudomotor onset threshold and thermosensitivity. All statistical analyses were performed with GraphPad Prism (v6.0, GraphPad Software, La Jolla, CA, USA). All data are expressed as means ± SD. P values ≤ 0.05 were considered statistically significant.

RESULTS

Participant characteristics

Mean participant characteristics are presented in Table 1. No differences in age ($P = 1.000$) existed between groups. Body mass ($P < 0.001$), height ($P = 0.017$), BSA ($P < 0.001$), and body fat percentage ($P < 0.001$) were greater in LG, while relative VO_{2max} (expressed in $ml \cdot kg^{-1} \cdot min^{-1}$) was higher in SM ($P = 0.019$). Pre-experimental USG was similar between groups in each trial, with mean values of 1.019 ± 0.006 and 1.015 ± 0.008 in LG and SM, respectively.

Rectal temperature

In the fixed absolute heat production trials of 500 W and 600 W (Fig. 1), end-exercise ΔT_{re} after 60 min was significantly greater in SM at both 500 W (LG: 0.52 ± 0.15°C, SM: 0.92 ± 0.24°C; $P < 0.001$) and 600 W (LG: 0.78 ± 0.19°C, SM: 1.14 ± 0.24°C; $P = 0.007$). Differences in ΔT_{re} were observed between groups from 30 min of exercise onwards in both trials. Due to differences in body mass, the corresponding W/kg was greater in SM at both 500 W ($P < 0.001$) and 600 W ($P < 0.001$). Furthermore, the relative exercise intensity ($\%VO_{2max}$) was higher in SM at 500 W ($P = 0.038$) and tended to be higher at 600 W ($P = 0.053$).

In contrast, when comparing SM and LG groups at the same fixed H_{prod} per unit mass trials of 6.5 W/kg and 9.0 W/kg (Fig. 1), end-exercise ΔT_{re} after 60 min was not different between groups at both 6.5 W/kg (SM: 0.85 ± 0.14°C, LG: 0.79 ± 0.21°C; $P = 0.433$) and 9.0 W/kg (SM: 1.14 ± 0.24°C, LG: 1.02 ± 0.22°C; $P = 0.303$). Furthermore, no differences in ΔT_{re} were observed between SM and LG at any time at 6.5 W/kg ($P = 0.129$) or 9.0 W/kg ($P = 0.635$). While there were no differences in ΔT_{re}, the corresponding absolute H_{prod} in W were higher in

LG due to their greater mass at both 6.5 W/kg ($P < 0.001$) and 9.0 W/kg ($P < 0.001$). The $\%VO_{2max}$ was also greater in LG at 6.5 W/kg ($P = 0.019$) and 9.0 W/kg ($P = 0.002$).

When exercise at 9.0 W/kg was repeated in a hotter environment (35°C), a similar ΔT_{re} was observed over time relative to a neutral environment (25ºC) within both the LG ($P = 0.398$) and SM ($P = 0.646$) groups (Fig. 2).

Whole-body and local sweat rates

Absolute E_{req} was ~340 W for both LG and SM at a fixed H_{prod} of 500 W ($P = 0.330$) and absolute E_{req} was ~400 W for both LG and SM at a fixed H_{prod} of 600 W ($P = 0.453$). In parallel, similar WBSR values were observed between groups in both trials (Fig. 3), resulting in cumulative WBSL values at an E_{req} of 340 W (LG: 383 ± 108 g, SM: 380 ± 52 g; $P = 0.956$) and 400 W (LG: 473 ± 156 g, SM: 493 ± 65 g; $P = 0.734$) that were not different between groups. At 6.5 W/kg and 9.0 W/kg, WBSR was greater in the LG group in parallel to a higher absolute E_{req} in the LG group in both conditions (Fig. 3), leading to greater cumulative WBSL in the LG compared to the SM group at 6.5 W/kg (LG: 473 ± 156 g, SM: 298 ± 35 g; $P = 0.008$) and 9.0 W/kg (LG: 774 ± 210 g, SM: 493 ± 65 g; $P = 0.003$). Although H_{prod} and ΔT_{re} were similar between groups, absolute E_{req} was higher in the heat for both LG (35°C: 792 ± 83 W, 25°C: 575 ± 73 W; $P < 0.001$) and SM groups (35°C: 585 ± 60 W, 25°C: 391 ± 44 W; $P < 0.001$). Accordingly, cumulative WBSL was greater in the heat for LG (35°C: 1067 ± 218 g, 25°C: 774 ± 210 g; $P < 0.001$) and SM (35°C: 817 ± 159 g, 25°C: 493 ± 65 g; $P < 0.001$) groups.

Despite similar WBSR and WBSL values, LSR was greater in the SM group when absolute E_{req} was 340 W ($P = 0.007$) and 400 W ($P = 0.032$) (Fig. 4). These greater LSR values in the SM group at the same absolute E_{req} corresponded with a greater E_{req} in W/m^2 in the SM

group in both cases (Fig. 4). In contrast, when comparing LG and SM groups at the same E_{req} values in W/m^2, no differences in LSR were evident throughout exercise at an E_{req} of 165 W/m^2 or 190 W/m^2, despite very different absolute E_{req} values in W in both conditions (Fig. 4). After 60 min of exercise, LSR was similar between groups at an E_{req} of 165 W/m^2 (LG: 0.28 ± 0.06 mg·cm^{-2}·min^{-1}, SM: 0.28 ± 0.12 mg·cm^{-2}·min^{-1}; P = 0.988) and 190 W/m^2 (LG: 0.41 ± 0.18 mg·cm^{-2}·min^{-1}, SM: 0.37 ± 0.15 mg·cm^{-2}·min^{-1}; P = 0.902).

Onset threshold and thermosensitivity

The mean LSR response relative to ΔT_{es} is shown in Fig. 5, and the onset threshold ΔT_{es} and thermosensitivity of the mean LSR response are presented in Table 2. In support of our aim to ensure that no differences in the physiological control parameters for sudomotor activity existed between the SM and LG group, neither the onset threshold ΔT_{es} ($P \geq 0.360$) nor thermosensitivity ($P \geq 0.351$) of the mean LSR response was different between groups during any of the experimental trials.

Mean skin temperature

Values for T_{sk} were not different between groups at H_{prod} of 500 W (LG: 31.31 ± 0.52°C, SM: 31.30 ± 0.48°C; P = 0.965), 600 W (LG: 31.39 ± 0.45°C, SM: 31.54 ± 0.40°C; P = 0.493), and 6.5 W/kg (LG: 31.39 ± 0.45°C, SM: 31.02 ± 0.50°C; P = 0.139). A higher T_{sk} was observed in LG at 9.0 W/kg in 25°C (LG: 32.10 ± 0.40°C, SM: 31.54 ± 0.40°C; P = 0.016). Similar T_{sk} were also observed at each E_{req} of 165 W/m^2 (LG: 31.31 ± 0.52°C, SM: 31.02 ± 0.50°C; P = 0.275) and 190 W/m^2 (LG: 31.39 ± 0.45°C, SM: 31.30 ± 0.48°C; P = 0.692).

DISCUSSION

The present study clearly demonstrates that a large difference in body mass systematically alters ΔT_{re} during exercise at a fixed H_{prod} (in W; Fig. 1) between independent groups that are otherwise matched for age, sex, heat acclimation status, and physiologically identical in terms of their control parameters for sudomotor activity (i.e., onset threshold and thermosensitivity; Fig. 5, Table 2). However, when an exercise intensity eliciting a fixed H_{prod} per unit mass is prescribed (W/kg; Fig. 1-2), the systematic difference in ΔT_{re} is eliminated despite differences in body mass, absolute H_{prod} (in W) and relative exercise intensity ($\%VO_{2max}$). The present study also demonstrates that despite an almost identical WBSR (in g/min) between groups differing greatly in BSA during exercise at a fixed absolute E_{req} (in W; Fig. 3) – as would be expected given the recent findings of Gagnon et al. (16) – local sweat rate (LSR) measured with a ventilated sweat capsule (in $mg \cdot cm^{-2} \cdot min^{-1}$) is systematically greater in the group with a smaller BSA (Fig. 4). However, when an exercise intensity eliciting a fixed E_{req} per unit surface area (in W/m^2) is prescribed, changes in LSR throughout 60 min of exercise are the same (Fig. 4), despite different BSA and absolute E_{req} in W. These findings demonstrate that future studies aiming to isolate the independent influence of a particular physiological factor (e.g. age, sex, injury, autonomic diseases) on thermoregulatory responses by comparing ΔT_{re} and LSR between experimental and control groups unmatched for body mass and BSA, should use a fixed heat production in W/kg for ΔT_{re} comparisons and a fixed E_{req} in W/m^2 for LSR comparisons. It follows that if different ΔT_{re} or LSR responses are subsequently observed, they can be confidently attributed to the physiological factor under examination and are not a consequence of an inherent bias arising from the prescription of exercise intensity, such as with the $\%VO_{2max}$ approach (27).

Core temperature

From a biophysical perspective, different changes in core temperature will arise from differences in heat storage (cumulative differences between heat production and heat dissipation throughout exercise), body composition, or body mass. In the present study, the greater ΔT_{re} observed in the SM group at the same absolute rates of heat production (Fig. 1) is directly explained by the influence of body mass per se, and not by any differences in heat dissipation or body composition. Firstly, while factors such as age (32), sex (17), and heat acclimation status (42) are known to alter thermoeffector responses, sudomotor control, and heat dissipation, all of these factors were controlled in the present study. Secondly, at a heat production of both 500 W and 600 W, no differences in T_{sk} and therefore dry heat loss were evident between groups, resulting in a similar absolute E_{req} and therefore the same WBSR (Fig. 3) and presumably evaporation. Although a high body fat percentage may alter core temperature changes due to a lower average specific heat capacity of adipose tissue (1), a nearly two-fold difference (11.9% vs. 22.2%) in body fat percentage does not alter ΔT_{re} in mass-matched participants exercising at the same absolute heat production (27). As such, it is unlikely that the difference in body fat percentage between LG and SM (Table 1) contributed to the observed difference in ΔT_{re}. While it may be possible that much larger differences in body fat percentage alter changes in core temperature, the independent influence of high vs. low adiposity (i.e., while controlling for heat production and body mass) has not yet been evaluated and merits further investigation.

By prescribing the same heat production in W/kg, the influence of body mass is effectively normalized, resulting in similar ΔT_{re} between two groups despite a 23.9-kg difference in body mass (Fig. 1). A retrospective assessment of data from previous studies examining core temperature responses over a range of relative intensities (i.e., $\%VO_{2max}$) in groups unmatched

for aerobic fitness and body mass also supports the use of the W/kg method for eliminating systematic differences in ΔT_{re}. For example, aerobically-trained individuals exercising at 50% VO_{2max} demonstrated a similar rate of heat production (~9.0 W/kg) and ΔT_{es} (~0.8°C) as aerobically-untrained individuals exercising at 70% VO_{2max}, despite an 8.2-kg difference in body mass between groups (13). Similarly, a closer look at the data of Mora-Rodriguez et al. (39) reveals a ΔT_{re} of ~0.6°C in trained and untrained groups of dissimilar mass (10-kg difference) cycling at 40% and 60% VO_{2max}, respectively, which actually corresponded to a heat production of ~8.2 W/kg in both groups. As noted by Jay et al. (27), it follows that different changes in core temperature attributed to some physiological effect [e.g. age (24, 50), aerobic fitness (19, 39, 44), burn injury (36)] may be explained simply by differences in W/kg of as little as 1.8 W/kg (Fig 1). Therefore, a re-evaluation of some of these potential physiological alterations to heat balance may be warranted. To further demonstrate the validity of the W/kg approach, an additional trial was performed at 9.0 W/kg in a hotter environment (35°C) but within the classical prescriptive zone (34). For both the LG and SM groups, ΔT_{re} was not different compared to 25ºC (Fig. 2), with a compensatory rise in sweating and evaporative heat loss in association with the higher E_{req} (34, 40).

The present data provide further evidence that a $\%VO_{2max}$ approach is not appropriate for comparing changes in core temperature between individuals and groups of different relative VO_{2max} and body size (27). The LG group had a lower VO_{2max} than the SM group (Table 1), and while exercise at 500 W and 600 W resulted in a higher $\%VO_{2max}$ and a greater ΔT_{re} in SM in both cases (Fig. 1), exercise at 6.5 W/kg and 9.0 W/kg resulted in a significantly greater $\%VO_{2max}$ in LG, but no differences in ΔT_{re} (Fig.1). Furthermore, although it may be argued that there was a slightly greater end-exercise ΔT_{re} in the SM group at 6.5 W/kg and 9.0 W/kg,

$\%VO_{2max}$ was in fact lower in the SM group, which according to conventional wisdom should have led to a lower, not a higher, change in core temperature. Nevertheless, two points regarding the prescription of $\%VO_{2max}$ should be noted. Firstly, the prescription of $\%VO_{2max}$ may be used without concern in a within-subjects (repeated measures) experimental design to compare changes in core temperature provided that the rate of heat production is not altered between conditions. Secondly, it is possible that despite differences in VO_{2max} and body mass between groups, combinations of these factors may yield similar core temperature changes during exercise at a fixed $\%VO_{2max}$. However, by maintaining a fixed H_{prod} in W/kg, the present approach ensures an unbiased comparison at all combinations of VO_{2max} and body mass. This may be especially useful in studies comparing core temperature responses during weight-bearing exercise (e.g. walking and running), during which heat production varies with body mass, and a high inter-individual variability in movement economy at a given speed is often observed. Future studies should evaluate the present approach for between-groups comparisons during treadmill exercise.

Sweating

Gagnon et al. (16) recently demonstrated that absolute E_{req} (in W) is the principal determinant of WBSR (in g/min) irrespective of $\%VO_{2max}$. Accordingly, WBSR was similar between the SM and LG groups at an E_{req} of 340 W (H_{prod}: 500 W) and 400 W (H_{prod}: 600 W) despite greater $\%VO_{2max}$ in the SM group, while differences in body mass led to greater absolute E_{req} and WBSR in the LG group at 6.5 W/kg and 9.0 W/kg (Fig. 3). However, at an absolute E_{req} of 340 and 400 W, greater mean LSR values (in $mg \cdot cm^{-2} \cdot min^{-1}$) were observed in the SM group (Fig. 4), demonstrating that the conclusions of Gagnon et al. (16) do not necessarily hold for

measurements of local sudomotor activity in individuals of different morphological characteristics. Although it has been suggested that LSR is determined by the absolute external work rate (46), there were no differences in work rate between groups at either fixed absolute E_{req} value (Fig. 4). Therefore, the differences in LSR between groups at the same absolute E_{req} are attributed to the influence of body size alone. Considering that LSR is measured across a fixed surface area, it is most logical that this influence is related to BSA, that is, at a given absolute E_{req}, the same absolute rate of sweat production (in g/min) must be secreted over a smaller surface area in the SM group; therefore, the mean rate of sweating per unit area (in $mg \cdot cm^{-2} \cdot min^{-1}$) should be greater with a smaller BSA. For the purpose of comparing LSR responses between groups unmatched for BSA, this systematic difference in LSR due to differences in BSA at a fixed absolute E_{req} can theoretically be removed by prescribing the same E_{req} per unit of BSA (in W/m^2). In the present study, this notion is strongly supported by the similar mean LSR values during exercise at E_{req} values of 165 W/m^2 and 190 W/m^2 (Fig. 4) despite differences in absolute E_{req} and BSA. By removing this systematic difference in LSR due to differences in BSA between groups, researchers can isolate the independent influence of physiological factors on local sudomotor activity since any difference will be due to the factor under investigation as opposed to inherent bias associated with the exercise intensity prescribed.

Perspectives

Although previous research has clearly highlighted the importance of changes in core and skin temperature for sudomotor control (4), the present study emphasizes the large influence of biophysical factors on ΔT_{re}, WBSR, and LSR among individuals of different morphological characteristics (Table 1) that demonstrate no difference in the physiological control of sudomotor

activity (Fig. 5, Table 2). In participants unmatched for mass and BSA, separate experimental approaches are necessary to isolate the influence of other factors that are different between participants on ΔT_{re}, WBSR and LSR. For example, WBSR should be compared between groups using a fixed absolute E_{req} in W (16), whereas a fixed heat production in W/kg is most appropriate for comparing core temperature changes between groups. The latter, however, would not be valid for simultaneous comparisons of WBSR between groups of dissimilar mass because absolute E_{req} (in W) would be different. Likewise, LSR can only be compared using a fixed E_{req} in W/m^2, so if groups are of dissimilar mass, WBSR could not be independently compared, whereas changes in core temperature could only be compared if groups had similar BSA-to-mass ratios, since a fixed W/m^2 would simultaneously yield the same W/kg between groups.

Finally, the present findings may only be applicable in compensable conditions. In an uncompensable environment (i.e. E_{req} exceeds the maximum potential for evaporation, E_{max}) differences in BSA-to-mass ratio will raise E_{req} (in W/m^2) in larger individuals for a given H_{prod} in W/kg, while E_{max} is unchanged. The greater difference between E_{req} and E_{max} in larger individuals should theoretically result in a higher rate of heat storage; however, this remains to be experimentally proven.

Conclusion

In conclusion, to prevent the introduction of systematic bias to an experimental design related to differences in H_{prod} and body morphology, the present data suggest that exercise should be prescribed to elicit the same H_{prod} in W/kg to compare changes in core temperature and the same E_{req} in W/m^2 to compare LSR responses. These approaches may be particularly useful for researchers investigating thermoregulatory responses between healthy/control and special

populations that may potentially demonstrate impaired heat dissipation secondary to alterations in thermoeffector function, such as diseases that lead to autonomic dysfunction (e.g. multiple sclerosis) or injuries that dennervate sweat glands (e.g. spinal cord injury).

ACKNOWLEDGEMENTS

This study was performed by M.N. Cramer in partial fulfillment of the degree Doctor of Philosophy from the University of Ottawa. The authors thank the volunteers for their participation, Zuzana Novak for her assistance with data collection, Dr. Éric Doucet for use of the DXA scanner, and Ms. Isabelle LaForest for performing DXA scans.

FUNDING

This research was supported by a Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant (#386143-2010, O. Jay). M.N. Cramer is supported by a University of Ottawa Excellence Scholarship and a NSERC Postgraduate Scholarship (PGS-D).

DISCLOSURES

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

APPENDIX

Prescribing exercise intensity to elicit a fixed heat production (H_{prod})

Step 1: During a pre-experimental visit, height and body mass must first be measured if prescribing H_{prod} in W/m^2 or W/kg. Body surface area can be estimated using equation of DuBois and DuBois (12).

Step 2: Prior to testing, identify the target absolute H_{prod} (in W) to be used. For example, if a fixed H_{prod} of 7.0 W/kg is required and the individual is 75 kg, the target absolute H_{prod} is: 7.0 × 75 = 525 W

Step 3: The exercise intensity required to elicit each target absolute H_{prod} may be estimated from the relationship between the rate of oxygen consumption (VO_2) and external work rate. To establish this relationship, have each participant perform a submaximal incremental exercise test that includes a range of work rates that will elicit the experimental target absolute H_{prod}. The work rates in this test may be estimated based on pilot testing, previous research, or in the case of cycling, assumed gross efficiency values. For example: if H_{prod} values of 400 W and 600 W will be targeted, assuming a gross efficiency of 17% (14), work rates of ~80 W and ~125 W would be expected, respectively. Therefore, during the preliminary test, the initial work rate may be set to 80 W and increased by 20 W/stage for four stages (i.e. up to 140 W) to include all estimated target work rates. The duration of each stage should be sufficient to attain steady-state VO_2 values (i.e. 3 to 5 min). Metabolic data (i.e. VO_2 and RER) should be collected throughout this test.

Step 4: Take the final 1-min (i.e. steady-state) VO_2 value of each stage, and using conventional equations (i.e. equation 1 in the present manuscript), calculate M and then subtract W to obtain H_{prod} for each stage. As the H_{prod}-work rate relationship is linear at submaximal intensities (2), the work rate required to elicit each target absolute H_{prod} may be estimated using the equation of a straight line ($y = mx + b$). It is also important to note the corresponding VO_2 value for each required work rate.

Step 5: During experimentation, set the initial work rate as that predicted to elicit the target absolute H_{prod}. The actual H_{prod} should be verified using real-time VO_2 measurements; slight work rate adjustments may be necessary to ensure a constant H_{prod} throughout exercise. To this end, it is crucial that VO_2 is monitored closely.

Prescribing exercise intensity to elicit a fixed evaporative heat balance requirement (E_{req})

Since E_{req} is primarily determined by H_{prod} (see Equation 8 in the present manuscript), prescribing work rates that elicit a fixed H_{prod} in W or H_{prod} in W/m^2 will result in fixed E_{req} in W or E_{req} in W/m^2, respectively, provided that the experimental environmental conditions (ambient temperature, air velocity) are constant. To calculate the actual E_{req}, dry and respiratory heat exchange must be calculated using mean skin temperature, air velocity and ambient temperature measurements (see Equations 3 to 7 in the present manuscript).

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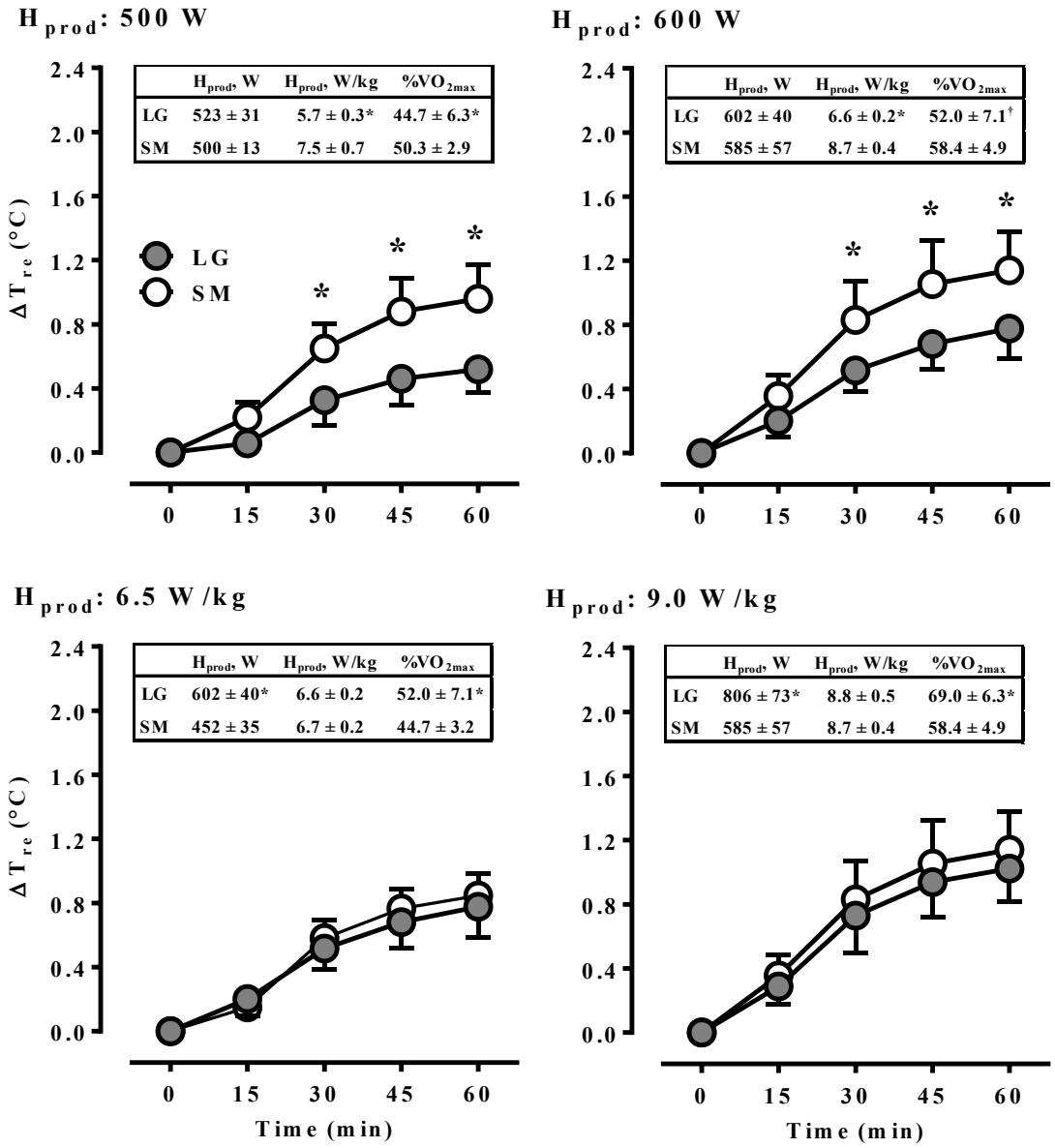
FIGURE 1



	H_{prod}, W	H_{prod}, W/kg	$\%VO_{2max}$
LG	523 ± 31	5.7 ± 0.3*	44.7 ± 6.3*
SM	500 ± 13	7.5 ± 0.7	50.3 ± 2.9

	H_{prod}, W	H_{prod}, W/kg	$\%VO_{2max}$
LG	602 ± 40	6.6 ± 0.2*	52.0 ± 7.1†
SM	585 ± 57	8.7 ± 0.4	58.4 ± 4.9

	H_{prod}, W	H_{prod}, W/kg	$\%VO_{2max}$
LG	602 ± 40*	6.6 ± 0.2	52.0 ± 7.1*
SM	452 ± 35	6.7 ± 0.2	44.7 ± 3.2

	H_{prod}, W	H_{prod}, W/kg	$\%VO_{2max}$
LG	806 ± 73*	8.8 ± 0.5	69.0 ± 6.3*
SM	585 ± 57	8.7 ± 0.4	58.4 ± 4.9

Figure 1. Changes in rectal temperature (ΔT_{re}) in large (LG) and small (SM) group during exercise at fixed rates of heat production (H_{prod}) in watts (500 W and 600 W) and watts per unit of total body mass (6.5 W/kg and 9.0 W/kg). Error bars indicate SD. Tables indicate mean ± SD for H_{prod} and relative exercise intensity ($\%VO_{2max}$).* indicates significant difference between LG and SM ($P \leq 0.05$). † $P = 0.053$.

FIGURE 2

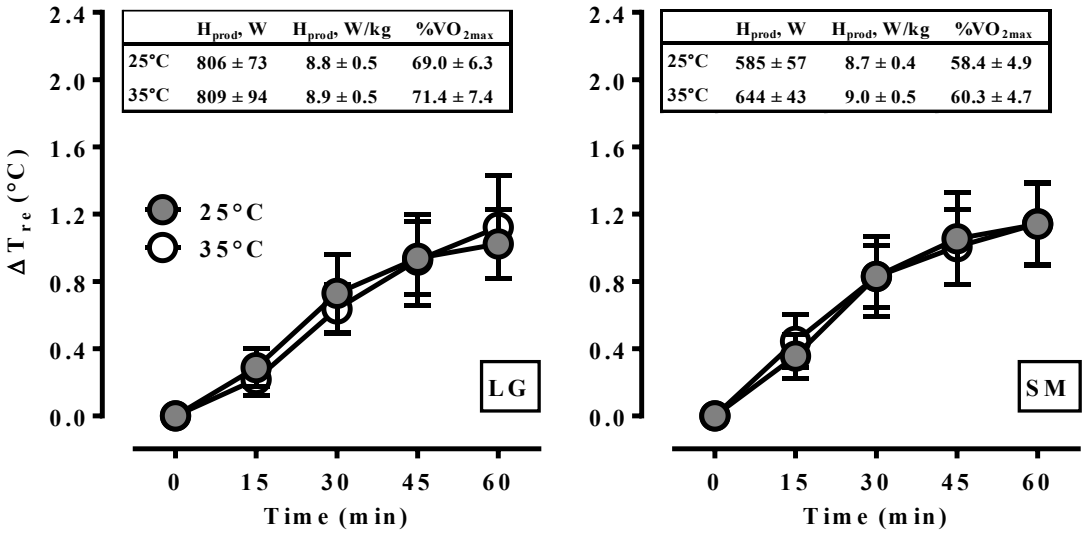


Figure 2. Changes in rectal temperature (ΔT_{re}) during exercise at 9.0 W/kg in 25°C and 35°C between large (LG, n=6; *left*) and small (SM, n=8; *right*) group. Error bars indicate SD. Tables indicate mean ± SD for heat production (H_{prod}) and relative exercise intensity ($\%VO_{2max}$).

FIGURE 3

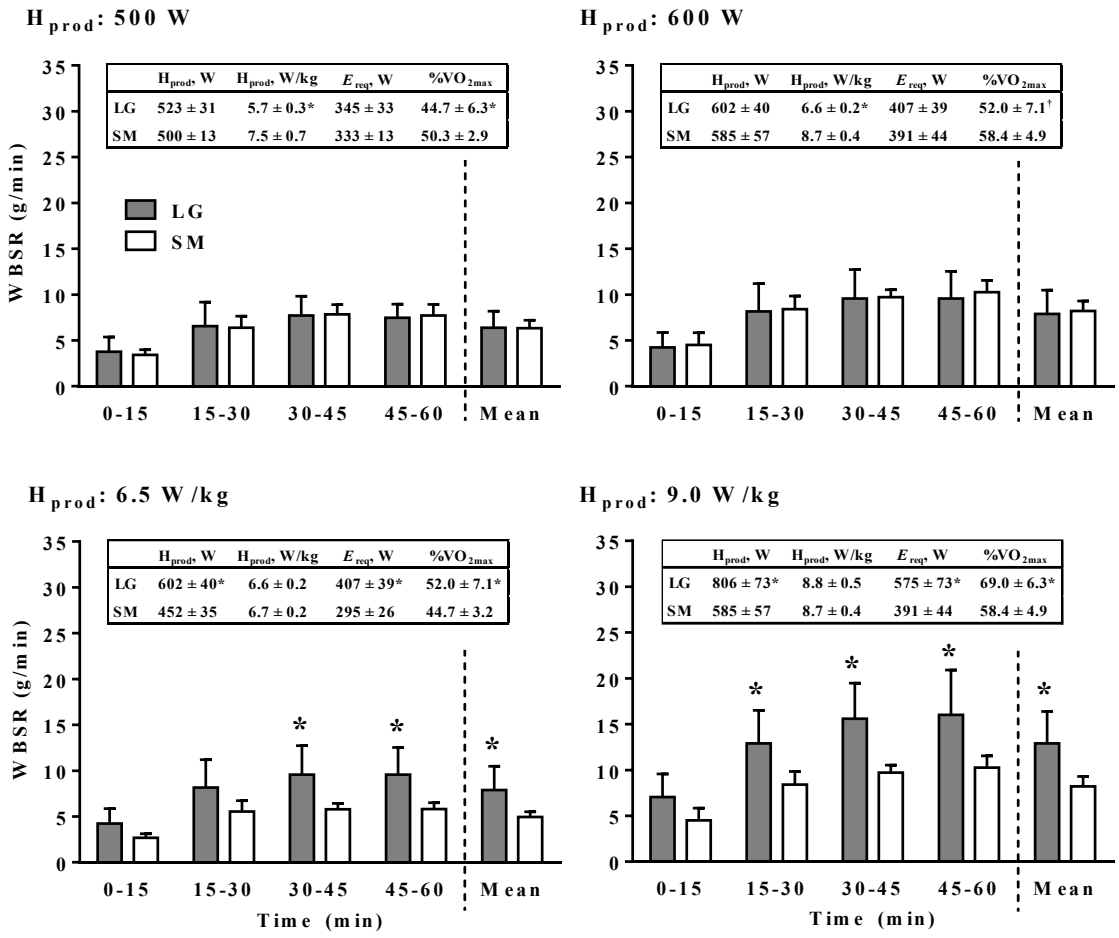


Figure 3. Whole-body sweat rate (WBSR) at fixed rates of heat production (H_{prod}) in watts (500 W and 600 W) and watts per unit of total body mass (6.5 W/kg and 9.0 W/kg) in large (LG) and small (SM) groups. Error bars indicate SD. Tables indicate mean ± SD for H_{prod} in watts (W) and watts per unit of total body mass (W/kg), absolute E_{req} (W), and relative exercise intensity ($\%VO_{2max}$) for each condition. * indicates significant difference between LG and SM ($P \leq 0.05$); † $P = 0.053$.

FIGURE 4

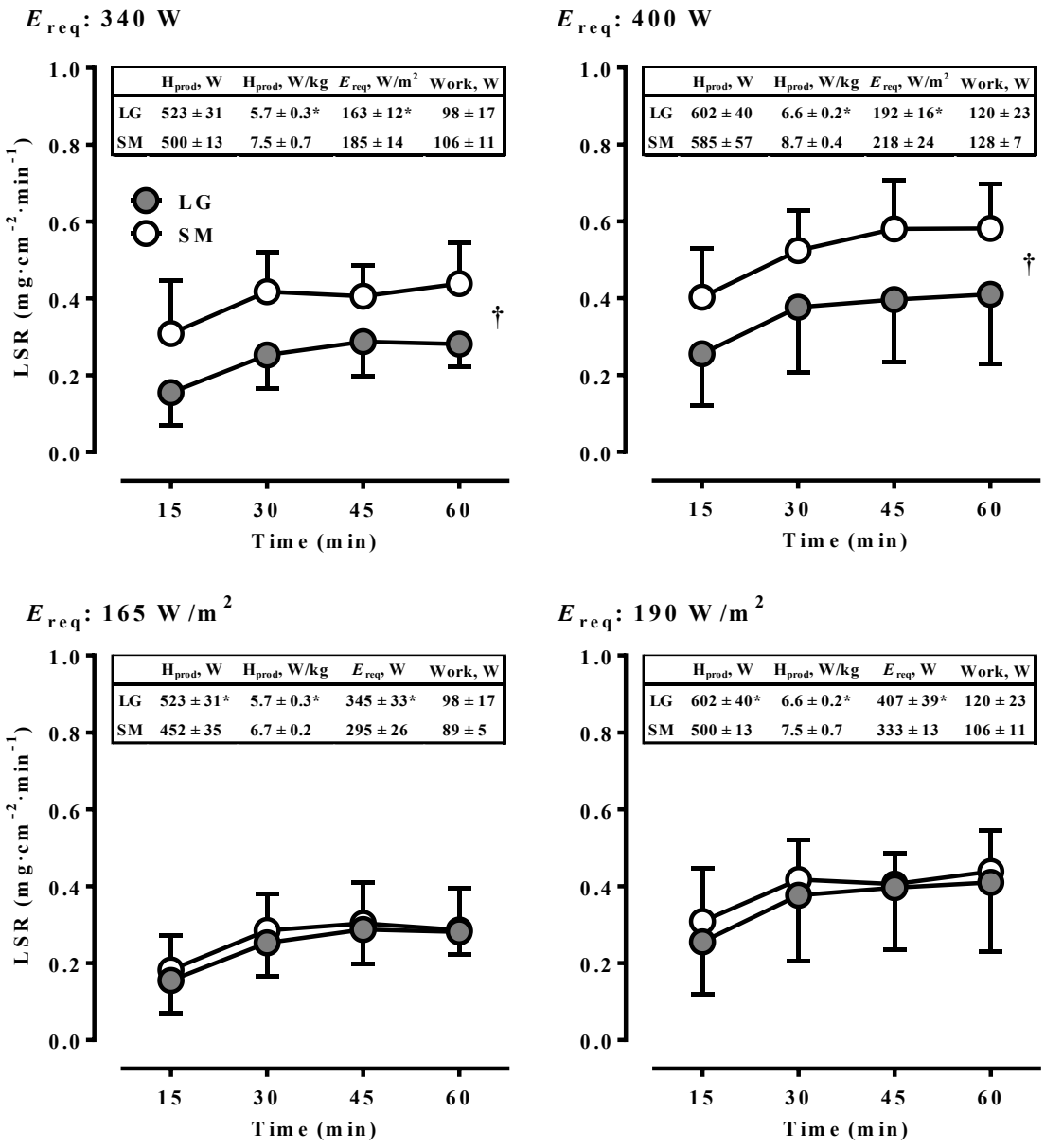


Figure 4. Mean local sweat rate (LSR) at rates of evaporation required for heat balance (E_{req}) of 340 W, 400 W, 165 W/m^2, and 190 W/m^2 in large (LG) and small (SM) group. Error bars indicate SD. Tables indicate mean ± SD for heat production (H_{prod}) in watts (W) and watts per unit of total body mass (W/kg), the corresponding E_{req} in W or W/m^2, and work rate for each E_{req}. * indicates significant difference between LG and SM; † indicates significant main effect of body size ($P \leq 0.05$).

Figure 5

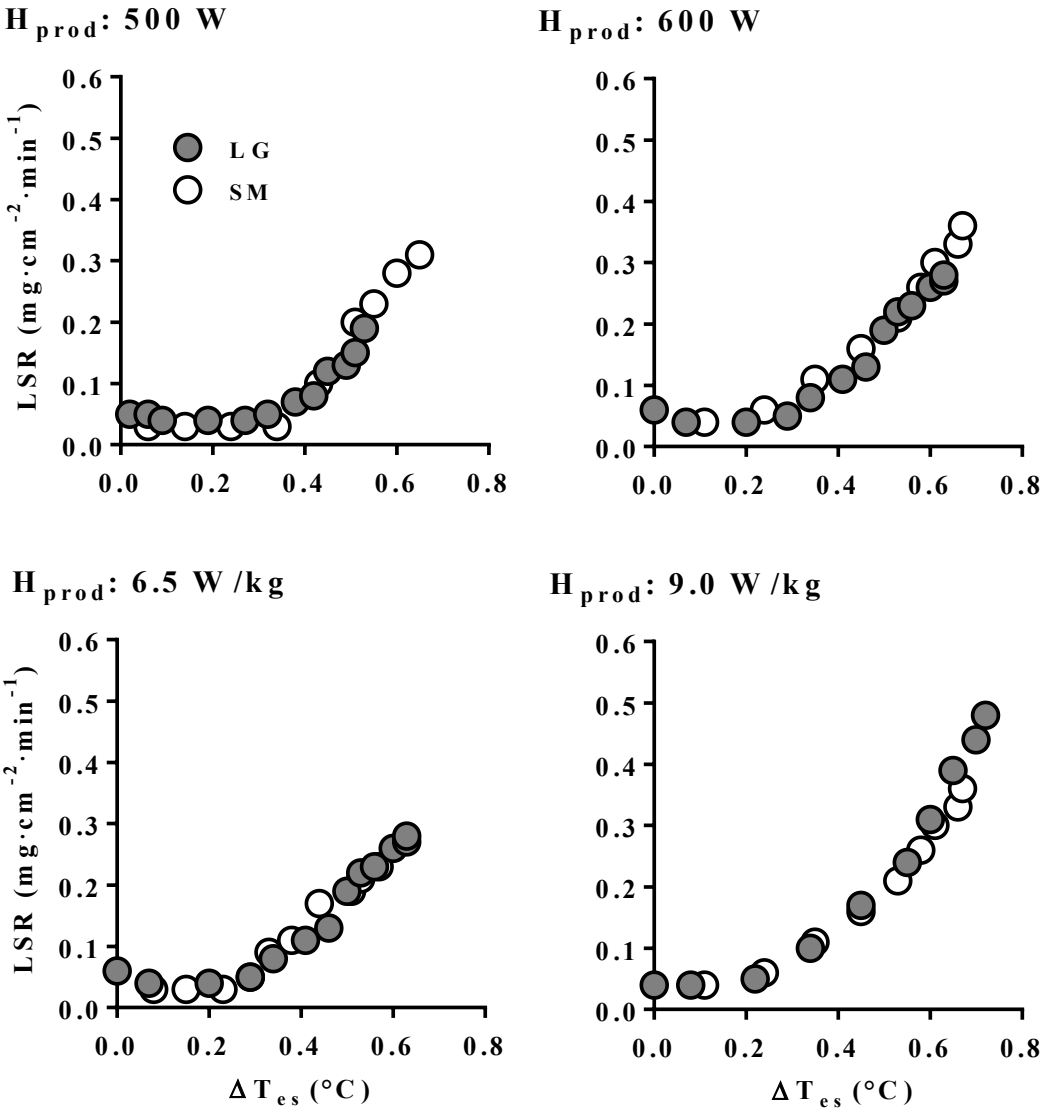


Figure 5. Mean local sweat rate in large (LG) and small (SM) group, expressed relative to the change in esophageal temperature (ΔT_{es}), during the first 15 min of exercise at intensities eliciting 500 W, 600 W, 6.5 W/kg, and 9.0 W/kg of heat production. Error bars have been excluded for clarity.

Table 1. Mean participant characteristics

	Age, y	Mass, kg	Height, m	BSA, m^2	Body fat, %	VO_{2max}, $ml \cdot kg^{-1} \cdot min^{-1}$
LG	24.4 ± 4.2	91.5 ± 6.8*	1.81 ± 0.05*	2.12 ± 0.09*	22.0 ± 5.2*	44.8 ± 6.2*
SM	24.2 ± 4.8	67.6 ± 5.6	1.73 ± 0.06	1.80 ± 0.09	12.5 ± 2.6	52.9 ± 4.2

LG, large body size group; SM, small body size group; BSA, body surface area; VO_{2max}, maximum rate of oxygen uptake. Values are means ± SD. *Significantly different from SM group ($P < 0.05$).

Table 2. Onset threshold and thermosensitivity of the mean local sweat rate response

	500 W		600 W		6.5 W/kg		9.0 W/kg	
	LG	SM	LG	SM	LG	SM	LG	SM
Onset threshold (°C)								
	0.35 ± 0.16	0.41 ± 0.17	0.40 ± 0.10	0.44 ± 0.21	0.40 ± 0.10	0.38 ± 0.16	0.35 ± 0.11	0.44 ± 0.21
Thermosensitivity ($mg \cdot cm^{-2} \cdot min^{-1} \cdot °C^{-1}$)								
	0.79 ± 0.32	1.07 ± 0.43	0.99 ± 0.33	1.02 ± 0.29	0.99 ± 0.33	0.91 ± 0.46	1.21 ± 0.76	1.02 ± 0.29

LG, large body size group; SM, small body size group. Values are means ± SD.

3.2 Thesis article #2

This article was accepted for publication on 27 August 2015 by the *Journal of Applied Physiology*, and has been formatted accordingly.

Explained variance in the thermoregulatory response to exercise: The independent roles of biophysical and fitness/fatness-related factors

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Running title: Descriptors of core temperature and sweating variation during exercise

Key words: body morphology; core temperature; evaporation; heat balance; sweating

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ABSTRACT

Individual variation in the thermoregulatory responses to exercise is notoriously large. Although aerobic fitness (VO_{2max}) and body fatness are traditionally considered important predictors of individual core temperature and sweating responses, recent evidence indicates potentially important and independent roles for biophysical factors. Using stepwise regression we examined the proportion of individual variability in rectal temperature changes (ΔT_{re}), whole-body sweat loss (WBSL), and steady-state local sweat rate (LSR_{ss}) independently described by i) biophysical factors associated with metabolic heat production (H_{prod}) and evaporative heat balance requirements (E_{req}) relative to body size, and ii) factors independently related to VO_{2max} and body fatness. In a total of 69 trials, twenty-eight males of wide-ranging morphological traits and VO_{2max} values cycled at workloads corresponding to a range of absolute H_{prod} (410-898 W) and relative intensities (32.2-82.0% VO_{2max}) for 60 min in 24.8±0.7°C, 33.4±12.2%RH. H_{prod} (in W/kg of total body mass) alone described ~50% of the variability in ΔT_{re} (adjusted R^2=0.496; P<0.001), while surface area-to-mass ratio and body fat percentage (BF%) explained an additional 4.3% and 2.3% of variability, respectively. For WBSL, E_{req} (in W) alone explained ~71% of variance (adjusted R^2=0.713, P<0.001), and the inclusion of BF% explained an additional 1.3%. Similarly, E_{req} (in W/m^2) correlated significantly with LSR_{ss} (adjusted R^2=0.603, P<0.001), while $\%VO_{2max}$ described an additional ~4% of total variance. In conclusion, biophysical parameters related to H_{prod}, E_{req}, and body size explain 54-71% of the individual variability in ΔT_{re}, WBSL, and LSR_{ss}, but once accounting for these biophysical factors, parameters related to fitness or fatness explain only 1-4% of the total variance.

INTRODUCTION

Individual human thermoregulatory responses to exercise are highly variable. For example, changes in core temperature from rest can vary between individuals by as much as 1.1°C at a fixed absolute rate of metabolic heat production (H_{prod}) of ~350 W (28), and by up to 1.9°C at a fixed relative exercise intensity corresponding to 75% of the maximum rate of oxygen uptake (VO_{2max}) (35). As such, predicting individual heat stress risk in both occupational and sport-related settings remains a challenge. This high inter-individual variability may be explained by a host of physiological and biophysical characteristics. Among young healthy individuals of the same sex, previous studies have identified aerobic fitness (i.e., VO_{2max}) and body fatness (body fat percentage, BF%) as important predictors of individual core temperature and sweating responses to exercise (14–18, 31).

More recently, studies from our laboratory suggest that fixing biophysical factors related to H_{prod} per unit total body mass (in W/kg TBM) and evaporative heat balance requirements (E_{req}) per unit body surface area (in W/m^2) can eliminate systematic differences in core temperature and local sweating between groups of different body size (7) and VO_{2max} (22). However, the proportion of the inter-individual variability of thermoregulatory responses independently described by these biophysical factors, and whether fitness- and/or fatness-related variables describe any of the residual variability, is currently unknown.

In many previous studies (5, 14–16, 18), exercise has been performed at a fixed %VO_{2max} or absolute workload by a subject cohort heterogeneous for VO_{2max} and body morphology. Significant correlates of a specific thermoregulatory variable have then been identified using multiple regression analysis. However, this approach may be limited if the prescription of a single absolute or relative intensity resulted in high collinearity between independent biophysical

and physiological variables. For example, at a fixed %VO_{2max}, individuals with a higher VO_{2max} in $ml \cdot kg^{-1} \cdot min^{-1}$ (who tend to be smaller in body size and lower in body fatness) will generate more heat per unit body mass and have greater evaporative heat balance requirements per unit BSA. As a result, greater changes in core temperature, whole-body sweat rates, and local sweat rates would be expected in individuals with a higher VO_{2max} and lower body fatness, but not necessarily due to those characteristics *per se*. Similarly, exercise at a fixed absolute workload (i.e., similar absolute heat production and evaporative heat balance requirements) will typically result in greater H_{prod} (in W/kg TBM) and E_{req} (in W/m^2) in high-VO_{2max}, low-fatness individuals, since they often have a smaller body size. It thus stands to reason that associations between thermoregulatory responses, aerobic fitness, and body fatness reported previously may not necessarily reflect an independent effect of these factors on core temperature and sweating, but perhaps arise from circumstantial collinearity between these independent variables and factors such as H_{prod} (in W/kg TBM) and E_{req} (in W and/or W/m^2).

To resolve this issue, an experimental approach is required that includes exercise intensities spanning a wide range of absolute and relative workloads values in a subject group of heterogeneous morphological and fitness-related characteristics. By using such an approach, the amount of individual variability in the change in core temperature, whole-body sweat rate, and local sweat rate independently explained by H_{prod} (W/kg TBM), E_{req} (W), and E_{req} (W/m^2), respectively, can be identified, and whether factors independently related to aerobic fitness and body fatness explain any residual variance in these thermoregulatory responses may be determined. Fitness-related parameters such as VO_{2max} expressed in terms of lean body mass (LBM) or lean mass of the exercising legs (leg LM) may also influence core temperature (27), while higher levels of adiposity may lead to greater changes in core temperature due to its greater

insulative properties, and/or lower average specific heat capacity (2, 25). Additionally, tissue composition within body regions involved in thermogenesis, such as the legs during cycling or running, could alter heat exchange between neighboring tissues.

The purpose of this study was to test the hypotheses that during exercise in compensable conditions, (i) the best descriptors of the individual variation in the change in rectal temperature (ΔT_{re}), whole-body sweat loss (WBSL), and steady-state local sweat rate (LSR_{ss}) are H_{prod} (W/kg TBM), E_{req} (W), and E_{req} (W/m^2), respectively, and (ii) factors related to aerobic fitness and body fatness contribute minimally, if at all, to the residual variance in these responses.

METHODS

The experimental protocol was approved by the University of Ottawa Health Sciences and Science Research Ethics Board, and conformed to the ethical principles outlined in the Declaration of Helsinki. The procedures and potential risks were explained to all subjects prior to experimentation, after which informed consent was obtained in writing. Subjects also completed a Physical Activity Readiness Questionnaire (PAR-Q) and an American Heart Association/American College of Sports Medicine Health/Fitness Facility Pre-participation Screening Questionnaire. Subject characteristics are summarized in Table 1. A total of 28 healthy male volunteers were tested, and each subject performed multiple trials (69 total trials). All subjects were non-smokers, reported no history of cardiovascular, metabolic, neurological, and respiratory diseases, and were not taking any medications at the time of participation. Some of the data presented herein have been previously reported in separate studies (7, 22).

Preliminary trial

Subjects arrived at the laboratory at least 2 h postprandial, having avoided alcohol, caffeine, and exercise in the 12 h prior to testing. Upon arrival, subjects voided their bladders before standing height and body mass were measured with a wall-mounted stadiometer and digital scale (HR-200 and BWB-800, Tanita, Arlington Heights, IL). The formula of DuBois and DuBois (9) was later applied to calculate BSA. While wearing only a hospital gown and underwear, body composition was measured using dual-energy X-ray absorptiometry (GE Medical Systems, Madison, WI). Scans were analyzed for BF%, fat mass, and non-osseous lean body mass (LBM) on the left and right sides of the arm, leg, and trunk. Lean mass of the legs (leg LM) was taken as the total lean mass of left and right legs.

Following anthropometry, an incremental test to exhaustion was performed during semi-recumbent cycling at a self-selected cadence to determine VO_{2max}. The test began at an external workload of 80 W and increased by 20 W/min until volitional exhaustion according to Canadian Society for Exercise Physiology guidelines (8). In all trials, the rate of oxygen uptake (VO_2) was measured breath-by-breath, and the highest 1-min average value was taken as VO_{2max}. At least 48 h separated the preliminary trial from the first experimental trial.

Experimental trials

Experimental trials were performed at the same time of day to avoid potential effects of circadian rhythm, and were separated by at least 48 h. A light meal with ~500 ml of water was consumed 2 h before arrival. Upon arrival, urine specific gravity (USG) was measured first to determine hydration status. Euhydration was accepted as a USG below 1.025 (24). Subjects then changed into standard athletic clothing (running shorts, socks, and shoes) and inserted a rectal thermocouple. A body mass measurement was then taken, followed by instrumentation and 30

min of baseline data collection. The exercise protocol consisted of semi-recumbent cycling at 80 revolutions per minute for 60 min. External workload (119 ± 29 W) was set to elicit either 60% of VO_{2max} (502-898 W) or a H_{prod} of ~500 W (32.2-67.6% of VO_{2max}), 6.5 W/kg (40.3-59.6% of VO_{2max}), or 9.0 W/kg (52.7-77.1% of VO_{2max}). Ambient conditions were 24.8 ± 0.7°C and 33.4 ± 12.2% RH, and an air velocity of 1.2 ± 0.1 m/s was provided by a mechanical fan placed 1.25 m in front of the ergometer (2 m in front of the subject). Core temperature, skin temperatures, and LSR measurements were taken continuously. Body mass was measured immediately prior to exercise (i.e., at baseline) and upon completion of exercise while fully instrumented, with all instrument cables secured to the same spot on an adjacent equipment cart. Neither food nor fluid was ingested between instrumentation and the end of exercise.

Instrumentation

A general-purpose pediatric thermocouple probe (Mallinckrodt Medical, St. Louis, MO) was inserted ~12 cm beyond the anal sphincter to determine T_{re}; ΔT_{re} is expressed as the difference between end-exercise and baseline values, which were taken as 5-min averages during the final minutes of exercise and rest, respectively. Skin temperatures were measured using thermistors (Concept Engineering, Old Saybrook, CT) at eight skin sites. A weighted average of forehead (0.07), shoulder (0.07), triceps (0.07), chest (0.175), scapula (0.175), hand (0.05), thigh (0.19), and calf (0.20) skin temperatures was used to calculate T_{sk} (21), which was then employed to estimate E_{req} (see below). Temperatures were measured every 5 s with a data acquisition unit (NI cDAQ-9172, National Instruments, Austin, TX, USA) and LabView software (Version 7.0, National Instruments, Austin, TX).

Body mass was measured in triplicate during experimental trials using a precision scale with an accuracy of ± 2 g (Combics 2, Sartorius, Mississauga, ON, Canada). Values for WBSL

were determined as the 60-min change in body mass minus respiratory vapor exchange and metabolic mass losses (29).

Measurements of LSR were taken on the forearm using a ventilated capsule ~5 cm distal to the antecubital space or an absorbent patch (#2164 laminated Airlaid; Technical Absorbents, Grimsby, UK). Dry air flowed through the capsule at 1.80 L min^{-1} (FMA-A2307, Omega Engineering, Stamford, CT), and the humidity of effluent air was measured every 5 s by a capacitance hygrometer (HMT333, Vaisala, Vantaa, Finland). Pre-cut absorbent patches were sealed in a plastic bag, and then weighed on a digital scale (Denver Instrument, Bohemia, NY). Every 15 min, a patch was placed on the ventral side of the forearm and secured with a compression garment (Under Armor Inc., Baltimore, MD). After the sampling period, the patches were removed, sealed in the original plastic bag, and reweighed. Steady-state forearm local sweat rate (LSR_{ss}) values are expressed in milligrams of sweat per square centimeter of surface area covered by a capsule or absorbent patch per minute ($mg \cdot cm^{-2} \cdot min^{-1}$) over the final 20 min of exercise. Since steady-state local sweating measurements with absorbent patches strongly agree with those from ventilated capsules (32), forearm LSR measurements using both methods were included in the LSR_{ss} analyses.

Heat balance calculations

Using 1-min average values for VO_2 and the respiratory exchange ratio (RER) collected with a metabolic cart (Vmax Encore, CareFusion, Yorba Linda, CA), metabolic rate (M) was estimated as:

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

Where: e_c and e_f are the energetic equivalents for carbohydrate (21.13 kJ/L O_2) and fat (19.62 kJ/L O_2), respectively. H_{prod} was calculated as the difference between metabolic rate and the external work rate, which was regulated by a semi-recumbent cycle ergometer (Lode Corival, Groningen, the Netherlands). The rate of dry heat exchange (H_{dry}) was calculated as:

$$H_{dry} = C + R \ [W/m^2]$$

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

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

Where: C and R represent convective and radiant heat exchange, respectively; T_a and T_{sk} denote ambient and mean skin temperatures (°C), respectively; h_c is the convective heat transfer coefficient; and h_r is the radiant heat transfer coefficient:

$$h_c = 8.3v^{0.6} \ [W \cdot m^{-2} \cdot K^{-1}]$$

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

Where: v is air velocity (m/s); ε is skin emissivity (0.95); σ is the Stefan-Boltzmann constant ($5.67 \cdot 10^{-8}$ $W \cdot m^{-2} \cdot K^{-4}$); BSA_r/BSA is the non-dimensional effective radiant surface area for a seated individual, valued at 0.70 (26); and T_r is the mean radiant temperature (°C), which was assumed to be equivalent to ambient temperature in the laboratory setting.

Respiratory heat exchange (H_{resp}) was calculated as:

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

Where: E_{res} and C_{res} are evaporative and convective heat loss from the respiratory tract, respectively; P_a is the ambient vapor pressure (kPa). The rate of evaporation required for heat balance (E_{req}) was expressed as:

$$E_{req} = H_{prod} - H_{dry} - H_{resp} \ [W/m^2]$$

The calculation of E_{req} was based on the 60-min average values of each heat balance parameter included in the equation. The maximum rate of evaporation to the environment (E_{max}) was determined by:

$E_{max} = h_e(P_{s,sk} - P_a)$ [W/m^2]

Where: h_e is the evaporative heat transfer coefficient, calculated as the product of h_c and the Lewis relation coefficient (16.5 K/kPa), and $P_{s,sk} - P_a$ is the skin–air vapor pressure gradient. Absolute humidity was measured using a dew point mirror (RH systems, Albuquerque, NM), and P_a was determined as:

P_a = (absolute humidity)(T_a)/2.17 [kPa]

The value of $P_{s,sk}$ was calculated based on T_{sk} using Antoine's equation:

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

As per convention, heat balance parameters were calculated in W/m^2; however, these values are expressed in W or W/kg where appropriate.

Statistics

Individual data are presented as means ± standard deviations. Statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY). Data were initially screened for normality by calculating skewness and kurtosis; values within ± 2.00 were deemed acceptable (38). Correlation coefficients (r) were established between thermoregulatory (ΔT_{re}, WBSL, LSR_{ss}) and relevant morphological (BSA/mass), fitness-related (relative VO_{2max} in ml·kg^{-1}·min^{-1}, ml·(kg LBM)$^{-1}$·min^{-1}, and ml·(kg leg LM^{-1})·min^{-1}; %VO_{2max}), body fatness-related (BF%), and other biophysical variables related to H_{prod} and E_{req} (H_{prod} in W, W/m^2, W/kg TBM, W/kg LBM, W/kg leg LM; E_{req} in W and W/m^2; E_{req}/E_{max}). Correlations were considered significant at the $P < 0.05$ level.

Stepwise multiple regression analyses were conducted using a forward selection entry method. A total of 69 cases were included. Parameters were included in each model based on significant ($P < 0.05$) correlation with the residual variance. To avoid unacceptable collinearity between predictors within the final model, independent variables were only included if the resultant tolerance value was greater than 0.5 (1). Data were screened for influential cases using Cook's distances and standardized residuals, and the normality of the residuals was confirmed by calculating their skewness and kurtosis. Since some subjects performed multiple trials, residuals from each final regression model were tested for autocorrelation using the Durbin-Watson test (*d*). Based on the number of independent variables and cases included in each model, positive autocorrelation would have been indicated by $d < 1.525$ (ΔT_{re}) and $d < 1.554$ (WBSL, LSR_{ss}), while negative autocorrelation would have been indicated by $d > 2.465$ (ΔT_{re}) and $d > 2.446$ (WBSL, LSR_{ss}), at the 0.05 level (36).

RESULTS

Individual characteristics and mean trial values

Subjects were similar in age, but demonstrated high variability in their absolute VO_{2max} and morphological traits (Table 1). This variability, coupled with different target work rates, resulted in a wide range of H_{prod}, E_{req}, and $\%VO_{2max}$ values (Table 2). Calculated skewness and kurtosis were < 2.00 for all parameters, indicative of normally distributed values (Table 2).

Correlation analysis

Bivariate correlation analyses for the thermoregulatory responses are presented in Fig. 1. The BF% correlated negatively ($P = 0.045$) with ΔT_{re}, while BSA/mass, relative VO_{2max} ($ml \cdot kg^{-1} \cdot min^{-1}$ and $ml \cdot (kg\ leg\ LM^{-1}) \cdot min^{-1}$), $\%VO_{2max}$, and H_{prod} (W, W/m^2, W/kg TBM, and W/kg

LBM) correlated positively with ΔT_{re} ($P < 0.05$). Neither relative VO_{2max} ($ml \cdot (kg\ LBM^{-1}) \cdot min^{-1}$) nor H_{prod} (W/kg leg LM) demonstrated any significant association with ΔT_{re}. Both WBSL and LSR_{ss} were positively correlated with $\%VO_{2max}$, E_{req} (W and W/m^2), and E_{req}/E_{max} ($P < 0.001$), but WBSL also showed a negative correlation with BSA/mass ($P = 0.011$). Both BF% and relative VO_{2max} (in $ml \cdot kg^{-1} \cdot min^{-1}$, $ml \cdot (kg\ LBM^{-1}) \cdot min^{-1}$, and $ml \cdot (kg\ leg\ LM^{-1}) \cdot min^{-1}$) were not associated with WBSL or LSR_{ss}. The relationships between each dependent thermoregulatory variable and the most strongly associated independent variable are illustrated in Fig. 2.

Multiple regression models

Tests for autocorrelation revealed *d* statistic values of 2.363 for ΔT_{re}, 1.877 for WBSL and 1.950 for LSR_{ss}, indicating no evidence of positive or negative autocorrelation in the models.

The output of the stepwise multiple regression models with all relevant statistics is shown in Table 3 and Fig. 3. The final models included H_{prod} (W/kg), BSA/mass, and BF% for ΔT_{re}; E_{req} (W) and BF% for WBSL; and E_{req} (W/m^2) and $\%VO_{2max}$ for LSR_{ss}. Together, H_{prod} (W/kg TBM), BSA/mass, and BF% correlated significantly with the individual variation in ΔT_{re}, explaining ~56% of the total variance. However, H_{prod} (W/kg TBM) alone described ~50% of the variance in ΔT_{re} (adjusted $R^2 = 0.496$, $P < 0.001$), while BSA/mass and BF% only described an additional 4.3% and 2.3% of the total variability, respectively. While E_{req} (W) and BF% correlated significantly with WBSL, explaining 72.6% of the total variance, the contribution of BF% was only 1.3% above E_{req} (W) alone (adjusted $R^2 = 0.713$, $P < 0.001$). Similarly, E_{req} (W/m^2) and $\%VO_{2max}$ both correlated significantly with LSR_{ss}, explaining ~64% of the total variance, but E_{req} (W/m^2) itself explained ~60% of the variance in LSR_{ss} (adjusted $R^2 = 0.603$, $P < 0.001$), with $\%VO_{2max}$ only explaining an additional ~4% of the total variance.

DISCUSSION

The primary findings of the present study were that biophysical parameters related to H_{prod} (and thus E_{req}), TBM, and BSA alone explain 54-71% of the individual variability in ΔT_{re}, WBSL, and LSR_{ss}. Residual variance in ΔT_{re} and WBSL correlated with BF%, while residual variance in LSR_{ss} correlated significantly with $\%VO_{2max}$; however, these factors only explained ~1-4% of the remaining variability in each thermoregulatory response. As such, biophysical factors predominantly described the individual variability in core temperature and sweating responses to exercise, whereas aerobic fitness and body fatness described minimal variability.

Changes in core temperature

After 60 min of exercise, H_{prod} (W/kg TBM) was found to be the best predictor of the individual ΔT_{re} response (Fig. 2). Previous studies have demonstrated that core temperature rises with absolute metabolic rate (i.e., heat production) (18, 22, 33, 34), and negatively correlates with TBM (5, 15–18, 34). However, we recently reported similar ΔT_{re} at fixed rates of heat production in W/kg between independent participant groups with a ~24-kg difference in TBM and consequently large differences in absolute heat production in W (7). This approach was shown to permit unbiased independent-group comparisons of core temperature between groups unmatched for TBM, and the current data extend these findings, showing that ~50% of the individual variability in ΔT_{re} can be explained by H_{prod} (W/kg TBM) alone.

In addition, BSA/mass and BF% correlated positively with the residual variance in ΔT_{re} (Table 3). BSA/mass independently explained an additional ~4% of variability, with a higher BSA/mass apparently leading to a greater ΔT_{re}. This finding, while minor, was unexpected. While a positive relationship between BSA/mass and core temperature has been previously reported (5, 15, 18), albeit not independently of H_{prod} (W/kg TBM), a greater BSA/mass should

in theory lead to a greater heat loss potential per unit mass and thus a negative association between BSA/mass and ΔT_{re} (37). The reason for this relationship is presently unclear, but could be indicative of an influence of body shape for a given TBM on internal heat distribution.

Theoretically, the lower specific heat capacity of adipose tissue should lead to greater changes in core temperature for a given level of heat storage and TBM (2, 23). Nevertheless, the relationship between core temperature and body fatness appears equivocal, as studies have (16, 18) or have not (5, 15, 17, 34) demonstrated an association between core temperature and BF%. Independent-group comparisons have been equally puzzling. For example, similar ΔT_{re} were reported in lean *versus* obese adult and pre-pubertal females (4, 19), but greater in pre-pubertal *versus* adult males (20), during treadmill walking at a fixed metabolic rate per unit TBM in warm/hot and dry conditions. Similarly, we have previously found that differences in BF% of ~10% did not affect ΔT_{re} at fixed levels of H_{prod} (W/kg TBM) (6, 7, 22). In the present study, once H_{prod} (W/kg TBM) and BSA/mass were included in the regression model, BF% correlated with the residual variance in ΔT_{re}, but only explained ~2% of the total variability. If an independent effect of BF% on core temperature truly exists, it appears to be relatively minor over the range of BF% tested (6.8-32.5%; Table 2). Future studies should assess the influence of BF% on core temperature and WBSL at more extreme levels of adiposity.

Although bivariate analysis showed that H_{prod} (W/kg LBM) was correlated with ΔT_{re}, neither H_{prod} (W/kg LBM) nor H_{prod} (W/kg leg LM) explained any individual variation in ΔT_{re} independently of H_{prod} (W/kg TBM). As noted above, changes in internal temperature should partially reflect total mass for a given change in heat content. Since H_{prod} (W/kg LBM) and H_{prod} (W/kg leg LM) ignore components of TBM that could otherwise store heat during exercise, it is not surprising that these factors were excluded from the final ΔT_{re} model.

Strong associations between absolute (L/min) or relative ($ml \cdot kg^{-1} \cdot min^{-1}$) VO_{2max} and core temperature (15–17), and similar end-exercise core temperatures between fit and unfit individuals at a given $\%VO_{2max}$ (12, 13, 31) appear to support the contention that aerobic fitness influences core temperature regulation (30). However, we found that no fitness-related parameters independently described the individual variation in ΔT_{re} (Table 3; Fig. 3). The discrepancy between findings likely reflects the experimental protocols used and the independent variables included in previous regression models. Since VO_{2max} is often inversely related to TBM (15, 16), greater changes in core temperature would be expected in high-VO_{2max} individuals at a fixed $\%VO_{2max}$ due to higher H_{prod} (W) and a lower TBM, and at a fixed absolute workload due to smaller TBM despite similar H_{prod} (W), both of which result in greater H_{prod} (W/kg TBM) (7). As a result, previously reported associations between VO_{2max} and changes in core temperature may not be due to an influence of fitness *per se*, but perhaps reflect collinearity between VO_{2max} and H_{prod} (W/kg TBM), which has not been dissociated in previous studies.

Whole-body sweat loss

Gagnon *et al*. (10) demonstrated recently that E_{req} (W) alone explains 93% of the variance in steady-state whole-body sweat rate. The present data reaffirm those results, as E_{req} (W) was the principal determinant of WBSL (Fig. 2), explaining ~71% of the individual variability in WBSL. The stronger association between E_{req} (W) and whole-body sweat rate reported by Gagnon *et al*. (10) may reflect some differences in sweating efficiency (i.e., the proportion of secreted sweat that evaporates). The combination of environmental conditions and fan-forced air flow likely resulted in near-complete sweat evaporation in most trials in the present study; however, this may not have been the case at higher exercise intensities. A small

amount of dripping sweat could have thus introduced some variation to our WBSL measurements unexplained by E_{req} (W).

Gagnon *et al*. (10) did not assess the potential role of BF% in describing the variation in individual WBSL responses. The inclusion of BF% in the present study, added 1.3% to the explained variance in WBSL – a very minor contribution compared to E_{req} (W) alone (~71%). It is unclear why BF% would be included in the WBSL model, but given that BF% alone was not associated with WBSL (Fig. 1), it is unlikely that higher body fatness directly causes greater whole-body sweat production for a given E_{req} (W). Additionally, no fitness-related parameters (including $\%VO_{2max}$) correlated with the residual variance in WBSL (Table 3), a finding in contrast to previous studies (14, 18). As in the case of ΔT_{re}, the absence of any effect of fitness on WBSL was likely the result of circumstantial collinearity in previous studies between VO_{2max} and E_{req} (W) at the same $\%VO_{2max}$.

Steady-state local sweat rate

In a recent study, we showed that average local sweat rate is similar between groups unmatched for BSA at fixed E_{req} (W/m^2), but different for a given E_{req} (W) (7). In the present study, ~60% of the individual variability in LSR_{ss} was explained by E_{req} (W/m^2) alone, with no additional contribution of E_{req} (W). For a given E_{req} (W) in conditions permitting full evaporation, whole-body sweat production will be similar regardless of body size (7, 10); however, in individuals with lower BSA, an equivalent amount of sweat will be secreted over smaller skin surface area. Since local sweat rate is expressed relative to the measurement area, LSR_{ss} should be higher in smaller people for a given E_{req} (W). Alternatively, a fixed E_{req} (W/m^2) should lead to similar LSR_{ss} irrespective of body size, but very different WBSL responses, as a higher E_{req} (W) would be attained in individuals with a larger BSA. This latter point emphasizes

the need for investigators to examine sweating responses using different variants of E_{req}/E_{max} ratio for whole-body sweating responses and E_{req} (W/m^2) for local sweating responses.

In addition to E_{req} (W/m^2), $\%VO_{2max}$ correlated positively with the residual variance in forearm LSR_{ss}, suggesting that exercise at a given E_{req} (W/m^2) will lead to a higher LSR_{ss} if the exercise intensity corresponds to a greater $\%VO_{2max}$. During exercise at a set E_{req} (W/m^2), and despite similar core and skin temperature responses, an independent effect $\%VO_{2max}$ on local sweat rate has been shown previously (6, 23), but this effect was observed only on the forehead, not the forearm, and without any influence on whole-body sweat rate (6). This finding suggested possible differential control of regional sweating in glabrous (forehead) *versus* non-glabrous (forearm) in response to greater relative strain; however, this would not explain the present findings as individual variance in forearm LSR_{ss} was partially explained by $\%VO_{2max}$ (Fig. 3). Nevertheless, it is important to highlight that the additional contribution of $\%VO_{2max}$ (~4%) to the explanation of residual variability in LSR_{ss}, while statistically significant, was very minor.

Perspectives

The present findings have important implications for modeling thermoregulatory strain, and contribute to a better understanding of the factors that may predispose particular individuals to a greater risk of heat injury during exercise. For example, individuals who are small will demonstrate similar changes in core temperature irrespective of aerobic fitness if they are working at a similar metabolic rate—which would be the case if work rate were externally governed. Likewise, our findings indicate that high sweat rates commonly seen in individuals with high body fat during weight-bearing activities are not necessarily due to fatness *per se*, but are likely due to the greater evaporative heat balance requirements associated with the greater heat production required to carry that mass. Indeed, a lean person of the same mass will

demonstrate similar rates of sweating, and will therefore need to ingest the same volume of fluid to maintain hydration status. Limitations of the present study include the fact that only male subjects were tested. Females demonstrate a lower whole-body sweating sensitivity, resulting in greater ΔT_{re} despite a similar heat production (7.5 W/kg) during exercise in hot, dry conditions (11). Therefore, in addition to biophysical factors, sex must also be considered when examining individual factors contributing to the core temperature response. Additionally, the present findings may only be applied to physiologically compensable conditions. In conditions of reduced sweating efficiency, E_{req}/E_{max} is likely a better predictor of individual whole-body and local sweating responses (3); and during uncompensable heat stress, the degree of uncompensability expressed relative to total body mass (i.e., $E_{req} - E_{max}$ in W/kg) may be a better predictor of core temperature changes during exercise. Future studies should assess this notion.

Finally, Havenith and colleagues previously used standardized regression coefficients to compare the contribution of different predictors to the explained variance in absolute core temperature during exercise in the heat (16, 18). Adopting such an analysis method in the present study yields similar results to those reported in Table 2, with a total of ~9 to 18% of the contribution of the main predictor transferred to the other predictor(s) in each model. It is important to recognize however that each analytical approach answers a different question about a model. Presenting the relative contribution of each parameter to the explained variance without standardization (Table 2) demonstrates the predictive capability of a model. Since our study was primarily designed to determine the best predictors of each thermoregulatory variable in question, and whether additional parameters contribute to the description of any of the residual variance, we argue that this was the most suitable approach. Nonetheless, both analysis methods

underline that biophysical factors are of primary importance when explaining individual variability of core temperature and sweating responses.

Conclusion

Biophysical factors related to heat production and body size explained ~54-71% of the individual variability in the core temperature and thermoregulatory sweating responses to exercise in a compensable environment. Specifically, our results show that individual changes in core temperature, whole-body sweat loss, and steady-state local sweat rate are described primarily by the individual variation in the rate of heat production relative to total body mass, the absolute rate of evaporation required for heat balance, and the rate of evaporation required for heat balance relative to body surface area, respectively. In contrast, the role of aerobic fitness and body fatness on these individual responses was minimal, explaining only ~1-4% of residual variability.

Acknowledgements

This research was supported by a Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant (no. 386143-2010, O.J.). M.N.C. was supported by an NSERC Postgraduate Doctoral Scholarship (PGS-D) and a University of Ottawa Excellence Scholarship. We greatly appreciate the participation of all subjects, and acknowledge the contributions of Anthony Bain, Christopher Bell, Tomasz Deren, Nicole Lespérance, Nathan Morris, Zuzana Novak, and Matthew Sacheli for assistance with data collection, as well as Dr. Éric Doucet, Ms. Ann Beninato, and Ms. Isabelle LaForest for the DXA scans.

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Table 1. *Mean subject characteristics*

	Units	Mean	SD	Min	Max
Age	years	23.6	3.5	20.0	32.6
TBM	kg	78.2	11.3	59.8	100.4
BSA	m^2	1.96	0.15	1.68	2.26
Absolute VO_{2max}	L/min	3.86	0.68	2.73	5.27
Fat mass	kg	12.9	6.6	4.9	26.4
LBM	kg	63.3	8.3	48.1	85.8
Leg LM	kg	23.5	3.4	17.3	31.5

Data are presented for 28 subjects. TBM, total body mass; BSA, body surface area; VO_{2max}, maximum rate of oxygen uptake; LBM, lean body mass; Leg LM, lean mass of the legs.

Table 2. *Descriptive statistics for all dependent and independent variables*

	Units	Mean	SD	Min	Max	Median	Skewness	Kurtosis
Dependent variables								
ΔT_{re}	°C	0.92	0.28	0.35	1.89	0.92	0.424	1.080
WBSL	g	474	165	250	978	435	1.178	1.182
LSR_{ss}	$mg \cdot cm^{-2} \cdot min^{-1}$	0.44	0.21	0.13	1.01	0.40	0.859	0.024
Independent variables								
BSA/mass	cm^2/kg	251	19	216	288	252	0.144	–0.846
BF%	%	17.2	6.9	6.8	32.5	16.0	0.544	–0.579
Relative VO_{2max}	$ml \cdot kg^{-1} \cdot min^{-1}$	49.3	8.0	36.0	65.0	50.9	0.007	–0.943
	$ml \cdot (kg\ LBM^{-1}) \cdot min^{-1}$	60.9	8.9	45.8	84.2	60.4	0.714	0.169
	$ml \cdot (kg\ leg\ LM^{-1}) \cdot min^{-1}$	163.0	19.6	132.0	200.1	160.9	0.290	–0.919
$\%VO_{2max}$	%	54.0	10.7	32.2	82.0	54.8	0.327	–0.376
H_{prod}	W	590	127	410	898	550	1.120	0.295
	W/m^2	301	56	232	468	281	1.088	0.389
	W/kg TBM	7.54	1.43	5.22	12.12	7.10	0.904	0.815
	W/kg LBM	9.22	1.65	6.44	13.42	8.74	0.629	–0.442
	W/kg leg LM	41.42	12.32	20.14	65.34	42.78	–0.019	–0.951
E_{req}	W	392	107	256	672	357	1.199	0.556
	W/m^2	200	49	137	350	190	1.170	0.782
E_{req}/E_{max}	ND	0.41	0.11	0.26	0.74	0.39	1.173	1.498

Data are presented for 69 total trials. ΔT_{re}, change in rectal temperature; WBSL, whole-body sweat loss; LSR_{ss}, mean steady-state forearm local sweat rate; BSA/mass, body surface area-to-mass ratio; BF%, body fat percentage; VO_{2max}, maximum rate oxygen uptake; LBM, lean body mass; leg LM, lean mass of the legs; H_{prod}, rate of metabolic heat production; E_{req}, rate of evaporation required for heat balance; E_{max}, maximum potential for evaporative heat loss; ND, no denomination. Skewness and kurtosis values in the range of ± 2.00 were considered acceptable (38).

Table 3. *Final multiple regression models for changes in rectal temperature, whole-body sweat loss, and steady-state local sweat rate*

	b	SE	*P*	Tolerance	r^2
		ΔT_{re} (°C)			
Constant	–1.502	0.423	0.001		
H_{prod} (W/kg TBM)	0.135	0.015	< 0.001	0.856	49.6%
BSA/mass (cm^2/kg)	0.005	0.001	0.001	0.660	4.3%
BF%	0.009	0.003	0.038	0.612	2.3%
Adjusted R^2	***0.562***				
SE_E	***0.197***				
		WBSL (g)			
Constant	–107.683	48.374	0.030		
E_{req} (W)	1.362	0.105	< 0.001	1.000	71.3%
BF%	2.987	1.632	0.048	1.000	1.3%
Adjusted R^2	***0.726***				
SE_E	***0.187***				
		LSR_{ss} ($mg \cdot cm^{-2} \cdot min^{-1}$)			
Constant	–0.387	0.080	< 0.001		
E_{req} (W/m^2)	0.003	<0.001	< 0.001	0.583	60.3%
$\%VO_{2max}$	0.005	0.001	0.006	0.583	3.8%
Adjusted R^2	***0.641***				
SE_E	***0.184***				

Tolerance values indicate acceptable collinearity and thus model stability. *b*, unstandardized regression coefficients; SE, standard error of the slope coefficient or intercept; SE_E, standard error of the estimate for the regression equation; r^2, partial contribution to total variance; ΔT_{re}, change in rectal temperature; WBSL, whole-body sweat loss; LSR_{ss}, steady-state forearm local sweat rate. H_{prod}, rate of heat production; TBM, total body mass; BSA/mass, body surface area-to-mass ratio; BF%, body fat percentage; E_{req}, rate of evaporation required for heat balance; $\%VO_{2max}$, relative exercise intensity.

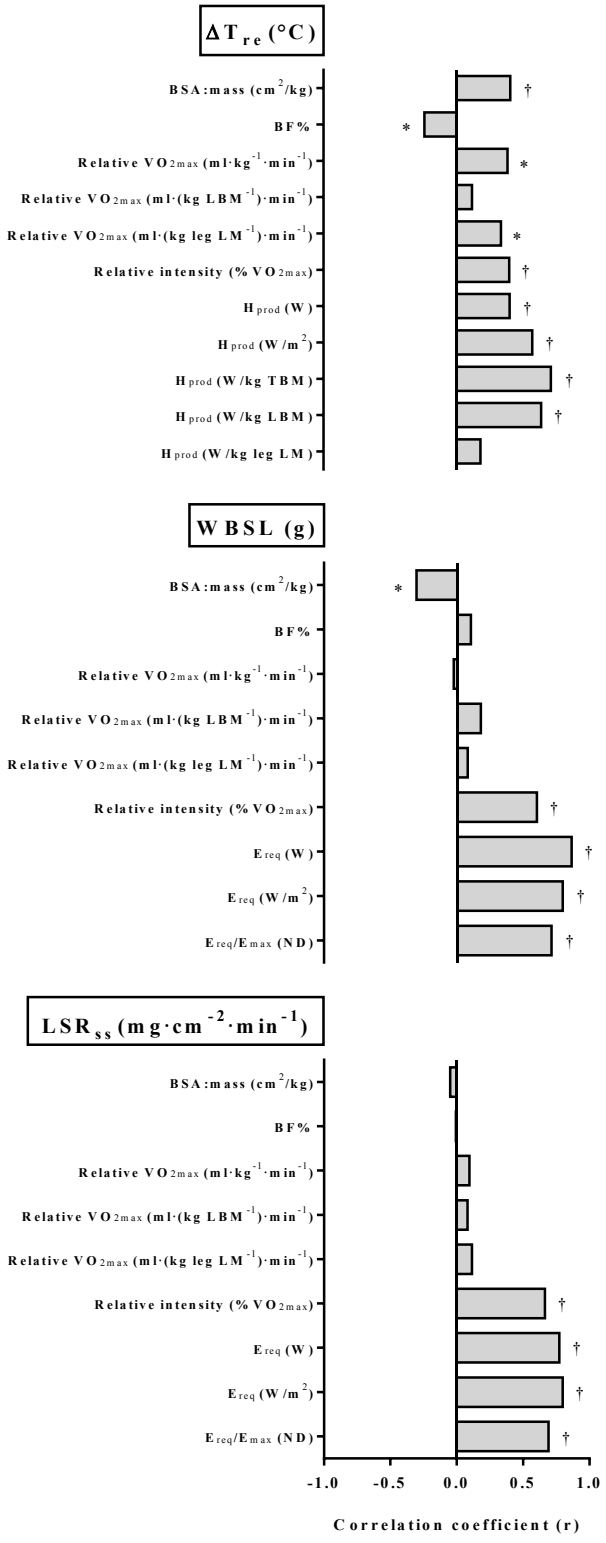

Figure 1. Correlation coefficients (r) for associations between thermoregulatory responses and the relevant independent variables. * indicates $P < 0.05$; † indicates $P \leq 0.001$.

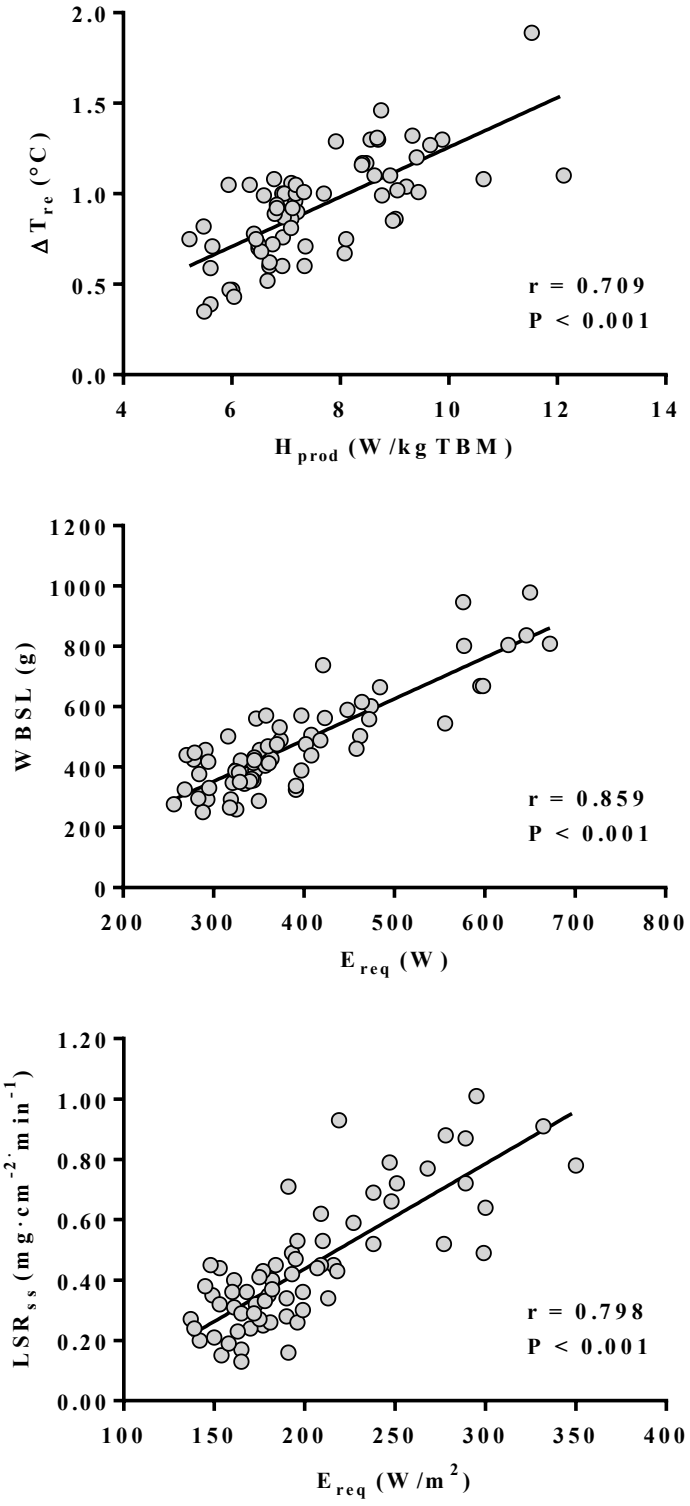

Figure 2. Scatter plots illustrating the relationship between each thermoregulatory response and the independent variable demonstrating the strongest association.

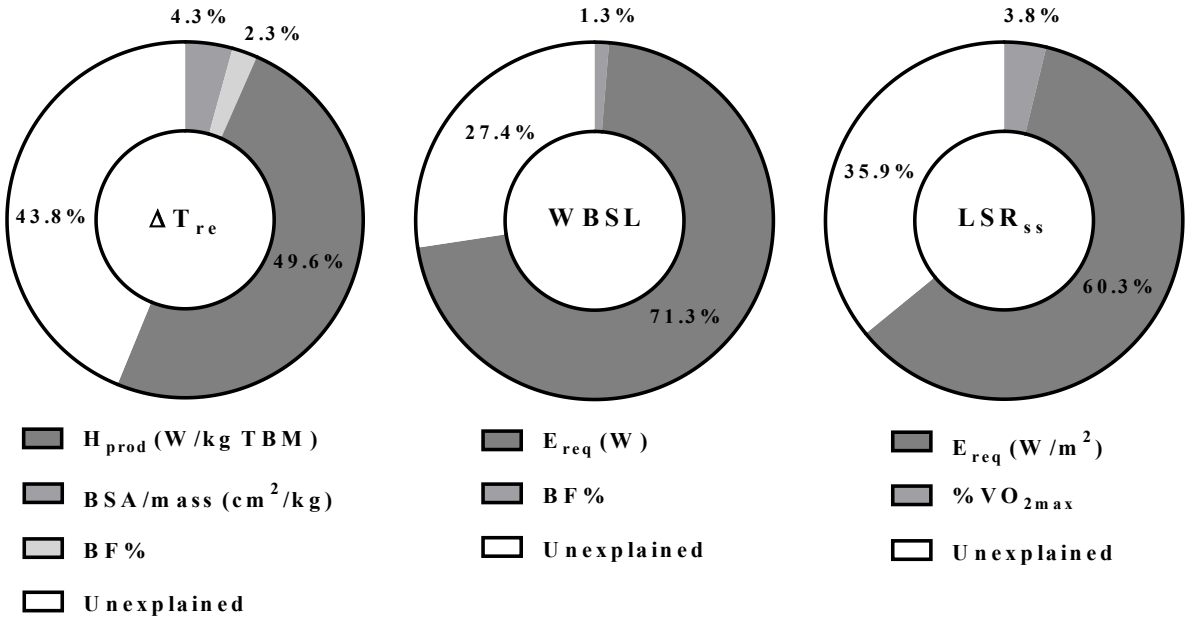

Figure 3. Output from multiple regression analyses. Each segment represents the contribution of an independent variable to the total variability in the change in rectal temperature (ΔT_{re}), whole-body sweat loss (WBSL), and steady-state local sweat rate of the forearm (LSR_{ss}).

3.3 Thesis article #3

An attenuated skin blood flow response does not lower the threshold of physiological compensability during non-encapsulated passive heat stress

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Running head: Skin blood flow and heat loss potential

Author contributions: M.N.C., D.G., C.G.C, and O.J. conceived and designed experiments; M.N.C. and D.G. performed experiments; M.N.C analyzed data; M.N.C., D.G., C.G.C, and O.J. interpreted data; M.N.C. drafted manuscript; M.N.C., D.G., C.G.C, and O.J. edited, revised, and approved final draft of the manuscript.

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ABSTRACT

Attenuated skin blood flow (SkBF) in response to passive heating is thought to critically impair heat dissipation from the skin to the external environment; however, this has not been previously tested. The purpose of the present study was to investigate changes in heat loss potential, indicated by a shift in the critical ambient vapor pressure (P_{crit}) for core temperature (T_c), following alterations in SkBF. Seven healthy males (28±4 y) sat in an environmental chamber set to 41°C, while ambient vapor pressure was increased from 2.57 kPa by 0.17 kPa (2% RH) every 6 min until an upward inflection in T_c was observed. Three separate treatments were administered to elicit different changes in plasma volume (ΔPV) with the goal of eliciting different levels of SkBF: control (CON), diuretic-induced isoosmotic dehydration to lower SkBF (DEH), and continuous saline infusion to maintain high SkBF (SAL). T_c, mean skin temperature (T_{sk}), heart rate (HR), ΔPV, mean laser-Doppler flux (forearm, thigh; LDF_{mean}), mean local sweat rate (same sites; LSR_{mean}), and metabolic rate (M) were measured. In DEH, a –14.2±5.7% ΔPV resulted in a lower LDF_{mean} (treatment effect: P=0.034) by ~20% compared to CON and SAL. However, P_{crit} for T_c was not different between treatments (P=0.166), while no differences in LSR_{mean} (P=0.279), T_{sk} (P=0.197), M (P=0.674), and changes in T_c (P=0.536) were observed. HR was significantly elevated throughout DEH (treatment effect: P=0.001). In conclusion, during severe passive heat stress, skin surface heat loss is not impaired by attenuated increases in SkBF sufficiently to alter the critical ambient humidity at which core temperature can no longer be physiologically compensated.

Key words: thermoregulation; heat stress; heat balance; critical vapor pressure; core temperature; heart rate

INTRODUCTION

The ability to effectively dissipate heat is critical for the maintenance of body temperature within a safe range. In response to rising core and/or skin temperatures, reflex and locally-mediated mechanisms initiate cutaneous vasodilation (23), which leads to greater perfusion of the cutaneous vasculature. Since internal heat flux is governed primarily by the core-skin thermal gradient and skin blood flow (SkBF), it is generally accepted that physiological conditions that impair cutaneous vasodilatory and thus SkBF responses directly diminish heat loss from the skin surface to the surrounding environment (4, 19).

Heat exchange between the skin and the environment is determined by the physical properties of the skin-air interface. Specifically, dry heat exchange is driven predominantly by the skin-air temperature gradient, while evaporative heat loss is dependent on the skin-air vapor pressure gradient and the degree of skin sweat coverage (16). Theoretically, under fixed ambient conditions, the effect of an attenuated SkBF on skin surface heat loss should therefore arise from consequent changes in mean skin temperature (T_{sk}), sweat production, and/or evaporative efficiency. Wingo et al. (45) recently showed that profound supraphysiological reductions in SkBF via norepinephrine infusion can attenuate the rate of local sweat production for a given thermal drive (i.e. change in core temperature, ΔT_c) during passive heating with a water-perfused garment. However, whether reductions in SkBF of a more commonly observed magnitude diminish whole-body heat loss, to the extent that the range of physiologically compensable environmental conditions experienced during severe non-encapsulated thermal stress (e.g. a heat wave) is altered, has not been investigated.

While SkBF may indeed alter skin surface heat loss, many previous studies have examined cutaneous vasodilatory and SkBF responses during passive heating in an encapsulated

environment with T_{sk} controlled at a very high level (e.g., using a water-perfused suit) or during exercise with submaximal thermolytic requirements (i.e., compensable conditions). An alternative approach is an incremental humidity ramp protocol consisting of short-duration steps of increasing ambient vapor pressure (P_a) at a constant ambient temperature (T_a) and metabolic rate. Above the critical ambient vapor pressure (P_{crit}), an upward inflection in core temperature is observed, indicating that the thermolytic requirements of the heat exposure (a combination of metabolic heat production and dry heat gain from the environment) have exceeded the maximum rate of heat loss that can be physiologically attained. Values for P_{crit} can then be compared between different conditions in which SkBF levels are manipulated to assess whether skin surface heat loss is significantly altered. Historically, this approach has been used to define critical environmental limits among populations (11, 22, 28), at various air velocities and ambient temperatures (2, 21, 38), and with different clothing ensembles (2, 22, 26), and may be especially useful to assess the relationship between SkBF and heat loss potential due to the nonencapsulated nature of the protocol.

Attenuated increases in SkBF with body heating occur in a variety of populations, including the elderly (31), those with hypertension (3), type-2 diabetes mellitus (41, 44), heart failure (6, 17), skin grafts (8, 9), and following dehydration (35). Therefore, information regarding the effect of altered SkBF on heat loss potential would be useful to determine the risk of heat-related injury in these populations during periods of severe heat exposure (e.g., heat waves). Using the aforementioned incremental humidity protocol, the current investigation tested whether lower SkBF following an isoosmotic dehydration (DEH) resulted in a lower P_{crit} for core temperature, and whether fluid replacement via saline infusion (SAL) raised SkBF and P_{crit} for core temperature, compared to a control condition (CON) in which no treatment was

administered. It was hypothesized that (i) diminished SkBF would result in a lower P_{crit} for core temperature, and (ii) fluid replacement would lead to higher SkBF and therefore a greater P_{crit} for core temperature.

METHODS

Subjects

Seven males (age: 28 ± 4 years; body mass: 82.3 ± 17.2 kg; height: 1.76 ± 0.07 m; body surface area: 1.98 ± 0.23 m^2) were recruited to participate in this study. Based on previously reported data (38), and using conventional β (0.2) and α (0.05) values, seven subjects was estimated to be a sufficient sample size to detect a significant difference in the P_{crit} for core temperature (G*power version 3.1.9.2). Subjects were non-smokers; reported no history of cardiovascular, metabolic, respiratory, or neurological disease; were not taking any medications; and were not acclimated to the heat. The protocol was first explained to each subject before obtaining written informed consent, and a complete medical history was obtained prior to testing. The experimental protocol was approved by the University of Ottawa Health Sciences and Science Research Ethics Board and the Institutional Review Boards of the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital of Dallas. All procedures conformed to the standards set forth by the Declaration of Helsinki.

Instrumentation and measurements

Red blood cell flux, an index of skin blood flow, was measured using laser-Doppler flowmetry (Moor Instruments Ltd., Devon, UK). Probes were placed on the dorsal forearm and the mid-point of the anterior thigh. Mean laser Doppler flux (LDF_{mean}) is reported in arbitrary

perfusion units (PU) as the average of the two sites. Arterial blood pressures were measured with an electrosphygmomanometer (Tango, SunTech Medical Instruments, Inc., Raleigh, NC), and mean arterial pressure was calculated as: (1/3 · pulse pressure) + diastolic blood pressure. Heart rate was taken from an electrocardiogram (Solar 8000M, GE Medical Systems, Madison, WI). Venous blood samples (4 ml) were collected from a forearm vein in lithium-heparin tubes (BD Vacutainer, Franklin Lakes, NJ, USA) and analyzed in triplicate for hemoglobin concentration (Hemoximeter, OSM3, Radiometer, Copenhagen, Denmark), hematocrit, and plasma osmolality (Micro-Osmometer, Model 3MO plus, Advanced Instruments Inc., Norwood, MA). Changes in plasma volume (ΔPV) were estimated with the equations of Dill and Costill (10).

Esophageal temperature (T_{es}) was measured with a general-purpose thermocouple probe (Mon-a-therm, Mallinckrodt Medical, St. Louis, MO) inserted to a maximum depth of 40 cm, which is a level estimated to be adjacent to the left ventricle (30). Skin temperatures were measured on the chest, shoulder, abdomen, lower back, thigh, and calf using thermocouples secured to the skin with soft cloth medical tape (Medipore, 3M), and mean skin temperature (T_{sk}) was calculated as a weighted average of these six sites (42). Both esophageal and skin temperatures were measured with thermocouple readers (Sable Systems International, Las Vegas, NV). Gastrointestinal temperature (T_{gi}) was also measured in six subjects using a telemetric core temperature pill (HQ Inc, Palmetto, FL) ingested ~4 h prior to baseline data collection.

Local sweat rates were measured using two 4.1-cm^2 ventilated capsules placed adjacent to each laser Doppler probe. Nitrogen gas was supplied to each capsule at a flow rate of 0.3 L/min, and the effluent air was analyzed for vapor concentration using capacitance hygrometry (Vaisala, Vantaa, Finland). Local sweat rate for each site was calculated as the product of the

vapor concentration and flow rate relative to the skin surface area covered by a sweat capsule ($mg \cdot cm^{-2} \cdot min^{-1}$). Mean local sweat rate (LSR_{mean}) values are reported, representing an average of the two sites measured.

Expired gases were analyzed with a metabolic cart (TrueOne 2400, Parvo Medics, Sandy, UT). The rate of oxygen uptake (VO_2) and the respiratory exchange ratio (RER) were used to determine metabolic rate (M) via indirect calorimetry (37):

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

Where: e_c and e_f are the energetic equivalents for carbohydrate (21.13 kJ/L O_2) and fat (19.62 kJ/L O_2), respectively.

Experimental protocol

In a randomized, counterbalanced order separated by at least 3 days, subjects performed three experimental trials: a control condition (CON) in which no treatment was administered, a diuretic-induced isoosmotic dehydration trial (DEH) with a goal of lowering SkBF relative to CON, and a continuous saline infusion trial (SAL) with a goal of elevating SkBF relative to CON. Prior to experimentation, subjects were instructed to avoid cold, allergy, and anti-inflammatory medicines for 36 h, alcohol consumption and exercise for 24 h, and caffeine intake for 12 h. They were also asked to consume plenty of water the night before and the morning of each visit to ensure adequate hydration, and to eat breakfast before leaving for the laboratory.

Subjects arrived at the lab between 0800 and 0900. Nude body mass, standing height, and urine specific gravity (USG) were first recorded, with euhydration accepted at a USG $\leq$ 1.025 (24). A forearm venous catheter was then inserted, and after 30 min of supine rest, an initial

blood sample was drawn. In DEH, 40-80 mg of furosemide was then administered orally, after which the subjects rested for ~3.5 h to allow the drug to take effect (18). Furosemide was selected to induce hypovolemia without any change in plasma osmolality (P_{osm}), which can independently affect sweating responses (13). In CON and SAL, subjects rested for an equivalent duration to ensure that heating commenced at a similar time of day during each visit. Drinking water was provided *ad libitum* in CON and SAL only, but only a small volume of fluid was ingested in DEH to facilitate insertion of a T_{es} probe. Urine output was also recorded during this period. Nude body mass was measured again at the end of the rest period.

Following instrumentation, subjects entered the chamber. The protocol included a 30-min baseline equilibration period at 41°C and 2.57 kPa followed by an incremental humidity protocol consisting of 0.17 kPa steps of increasing P_a every 6 min up to 5.95 kPa (maximum: 20 stages or 120 min). Throughout the protocol, T_a was tightly controlled at 41.0 ± 0.1°C, and air velocity was measured to be <0.2 m/s. Similarly, the pattern of change in P_a over time was nearly identical between trials, resulting in steps of 0.17 ± 0.01 kPa per 6-min stage. Termination criteria were (i) completion of the 20th stage, (ii) reaching a 1.0°C ΔT_c from baseline, (iii) hypotension (MAP < 75 mmHg), or (iv) voluntary withdrawal due to excessive discomfort. Trials were conducted in an upright position (n=4) while seated in a steel-framed mesh chair (height: 83 cm) or in a supine position (n=3) on a hospital bed. Experimentation was initially in the upright posture, but because of episodes of hypotension in some DEH trials, testing was completed in a supine posture by the remaining subjects to minimize the possibility of hypotension. During SAL, 0.9% saline was infused continuously at a rate of 0.05 $ml \cdot kg^{-1} \cdot min^{-1}$ (total: 479 ± 105 ml). No fluids were administered during the experimental protocol in CON and DEH. Core and skin temperatures, local sweat rates, skin blood flow, and heart rate were

measured continually. Blood pressure was measured at the end of each stage; expired gases were sampled at baseline and every four stages. Upon completion of the heating protocol, a final blood sample was drawn.

Data analysis

Continually measured variables were sampled at 25 Hz (MP150, Biopac Systems, Inc., Santa Barbara, CA). For each 6-min stage of the protocol, data were averaged over the final 2 min. In accordance with a recent work by Ravanelli *et al*. (38), these values were subsequently used to define P_{crit} for core temperature and heart rate using segmental regression. This latter statistical approach is based on the biphasic core temperature response during an incremental humidity protocol: the first phase is a baseline phase during which the relationship between core temperature and P_a is approximately zero, and an "inflected" phase during which core temperature rises abruptly and linearly from its baseline level as the heat loss requirement has exceeded heat loss potential due to the increasing P_a. The segmental regression analysis identifies the P_a value at the intersection between these two slopes, which is then taken as P_{crit}. The core temperature P_{crit} was determined from T_{es} in six subjects, but T_{gi} in one subject due to poor tolerance of the esophageal temperature probe.

Statistical analysis

All data are presented as means ± standard deviations. A one-way repeated measured analysis of variance (ANOVA), using the independent factor of treatment (3 levels: CON, DEH, SAL), was employed to compare USG, fluid intake and urine output during rest, whole-body sweat loss, P_{crit} values, and metabolic rate. A two-way ANOVA, with the independent factors of

treatment (3 levels: CON, DEH, SAL) and time, was also employed to compare ΔBV, ΔPV, and P_{osm} (4 levels: initial, baseline, at 60 min, and at the end of the protocol); and LDF_{mean}, LSR_{mean}, T_{sk}, and ΔT_c (15 levels: every 6-min stage up to ~5.0 kPa or 84 min of the protocol). A Greenhouse-Geisser correction was applied if the assumption of sphericity had been violated. In the event of a significant time-by-treatment interaction, post-hoc analysis was performed using Tukey's range test for multiple comparisons. Statistical analyses were performed with Prism 6 for Windows (GraphPad, Software, La Jolla, CA). Alpha was set at the 0.05 level.

RESULTS

Initial rest period

Initial USG values upon arrival were not different between trials (CON: 1.014 ± 0.007, DEH: 1.012 ± 0.007, SAL: 1.013 ± 0.006; P = 0.633). Ad libitum fluid intake in CON (613 ± 239 ml) and SAL (614 ± 184 ml) was greater than in DEH (253 ± 109 ml, i.e. the volume required to facilitate insertion of the T_{es} probe) (P = 0.002). Moreover, urine output in DEH (1997 ± 633 ml) was greater than CON (566 ± 361 ml) and SAL (878 ± 507 ml), throughout the initial rest period (P < 0.001). Consequently, a greater relative change in body mass occurred in DEH (–2.4 ± 0.7%) compared to CON (–0.4 ± 0.6%) and SAL (–0.5 ± 0.5%) during this time (P < 0.001). Similarly, ΔPV was relatively greater in DEH compared to CON and SAL (P < 0.001, Fig. 1). No differences in fluid intake, urine output, body mass changes, or ΔPV were observed between CON and SAL during this time (P > 0.168).

Incremental humidity protocol

As shown in Fig. 1, the greater reduction in PV, during DEH persisted throughout the incremental humidity protocol ($P < 0.001$), but no differences in P_{osm} were observed between treatments ($P = 0.546$). This greater hypovolemia resulted in a significantly lower LDF_{mean} in DEH ($P = 0.007$, Fig. 2) that averaged 139 ± 23, 176 ± 22, and 186 ± 22 PU in DEH, CON, and SAL, respectively and represented a relative difference of 21.6 ± 19.6% between CON and DEH, and 24.5 ± 23.7% between SAL and DEH. Fluid replacement in SAL did not change PV (Fig. 1). No concurrent differences in MAP were observed between treatments (Fig. 2; $P = 0.189$).

For clarity, an example of the incremental humidity protocol used presently has been provided in Fig. 3, with a sample T_{es} trace and the identification of P_{crit}. Despite the lower SkBF during DEH, P_{crit} for core temperature was not different across treatments ($P = 0.166$, Fig. 4). The overall ΔT_c response with an increasing P_a was similar among treatments ($P > 0.999$, Fig. 5), with a ~0.3°C drift in ΔT_c observed prior to inflection, and a similar rate of increase in ΔT_c post-inflection (CON: 0.020 ± 0.003°C/min, DEH: 0.019 ± 0.004°C/min, SAL: 0.018 ± 0.002°C/min; $P = 0.353$). No effect of treatment on T_{sk} and LSR_{mean} were observed ($P > 0.934$, Fig. 5), and similar whole-body sweat losses were found in all trials (CON: 1.1 ± 0.3 kg, DEH: 0.9 ± 0.4 kg, 1.1 ± 0.3 kg; $P = 0.482$). Additionally, a consistent metabolic rate was observed across trials, averaging 119 ± 11, 115 ± 12, and 106 ± 17 W in CON, DEH, and SAL, respectively ($P = 0.674$).

Volume depletion caused a significantly higher HR throughout DEH compared to CON and SAL ($P = 0.009$, Fig. 6), resulting in a consistent difference of 8 ± 2 beats/min in CON vs. DEH, and 11 ± 2 beats/min in SAL vs. DEH, throughout the protocol. However, the change in HR from baseline was similar between trials, representing a rise of 35 ± 10, 30 ± 8, and 36 ± 9

beats/min in CON, DEH, and SAL, respectively (P = 0.273). The P_{crit} for HR, indicating the threshold for rapidly increasing circulatory strain, was slightly but significantly elevated in SAL compared to CON and DEH (Fig. 6).

DISCUSSION

In the present study, the influence of large differences in SkBF on skin surface heat loss were assessed by employing an incremental humidity protocol that identified the critical ambient vapor pressure (P_{crit}) above which T_c could no longer be physiologically compensated. That is, above P_{crit}, the rate of metabolic heat production plus the dry heat gained from a 41°C environment could no longer be balanced by the rate of sweat evaporation from the skin. Using an isosmotic volume-depletion model, an ~20% reduction in SkBF had no effect on the P_{crit} for core temperature compared to control and volume-infusion treatments (Fig. 2), suggesting that the upper limit of heat dissipation from the skin is not compromised by an attenuated SkBF in a very hot/humid environment at rest.

In many previous studies, cutaneous vasodilation and SkBF have been examined during passive heating to a fixed ΔT_c using a water-perfused suit [e.g., (7, 8, 14, 31, 44)], which controls T_{sk} at a set level (~38°C) and simultaneously impedes evaporative heat loss over most of the skin surface. Given the encapsulated nature of this experimental approach, the influence of SkBF on skin surface heat loss could not possibly be established. Similarly, studies conducted during exercise (33, 34) or non-encapsulated passive heat stress (17) with submaximal heat loss requirements would not necessarily observe any effect on core temperature as any reductions in skin surface heat loss due to lower SkBF are likely to be physiologically compensated. In contrast, the incremental humidity protocol used presently, modified from those of Belding and Kamon (2) and Kenney et al. (26), permits the evaluation of whole-body heat loss potential in

nonencapsulated conditions of high environmental heat stress. The basis for this approach lies in examining how various factors/interventions affect the heat loss side of the conceptual heat balance equation (16). Since the rate of heat storage is equal to the difference between rates of heat production and loss, P_{crit} represents the threshold P_a above which thermal balance (rate of heat storage = zero) cannot be maintained. Therefore, a shift in P_{crit} at a fixed metabolic heat production and ambient temperature (attributed to the factor/intervention in question) directly indicates a change in whole-body skin surface heat loss potential. The current experiment represents a novel use of this protocol, which was originally designed to establish environmental critical limits for workers in occupational settings (2).

Changes in body mass (–2.4%) and plasma volume (–14.0%) following oral furosemide administration, but prior to heat exposure, were consistent with those reported previously (18, 39), and the subsequent reduction in SkBF (approximately –13% in DEH vs. CON) was similar to that observed with exercise- (33) or diuretic-induced (18) hypohydration compared to euhydration. Despite the lower SkBF in DEH (Fig. 2), P_{crit} was similar irrespective of treatment (Fig. 4), suggesting that maximum heat dissipation was not affected by the lower SkBF. At a constant metabolic rate and ambient temperature, a difference in heat loss potential (i.e., P_{crit}) secondary to altered SkBF would theoretically arise from changes in the physical properties affecting heat exchange at the skin surface, specifically T_{sk}, maximum skin wettedness, and/or evaporative efficiency. No differences in local and whole-body sweating responses, as well as T_{sk}, were evident between treatments (Fig. 5). Although a functional relationship between SkBF and sweating has been reported previously (45), the profound supraphysiological local reduction in SkBF induced pharmacologically (norepinephrine infusion) in the study of Wingo et al. cannot be compared to the whole-body observations reported in the present study (Fig. 2).

Although this is the first study to investigate the direct link between altered SkBF and skin surface heat loss, previous data suggest that high levels of SkBF may not be a prerequisite to prevent disproportionately greater changes in core temperature. For example, a 15% reduction in forearm vascular conductance (FVC) did not alter local sweat rates, T_{sk}, and ΔT_c in hypoxic vs. normoxic conditions (32), or following a –2.6% reduction in body mass with diuretic-induced hypohydration (18) during exercise. Additionally, chronic heart failure patients with a 20% lower cutaneous vascular conductance (CVC) demonstrated similar ΔT_c and T_{sk} (sweat rate was not measured) compared to healthy controls during passive heat stress (38°C, 50% RH) (17). Similarly, a diminished forearm blood flow (FBF) by 40% in older versus younger individuals resulted in similar ΔT_c, T_{sk}, and sweat rates during exercise in the heat despite similarities in the rate of metabolic heat production, body size, and aerobic fitness between groups (25). Although this has not been a consistent finding in older vs. younger groups (27), it is important to note that older individuals also demonstrate physiologically impaired sudomotor responses and therefore evaporative heat loss, which perhaps contribute to greater ΔT_c independently of any parallel reductions in SkBF (1, 29). Collectively, current and previous data suggest that core temperature is regulated similarly despite a ≥15% reduction in SkBF, provided that sweating responses and evaporative heat loss are not limited. It follows that populations demonstrating concurrent vasodilatory and sudomotor impairments, such as the elderly (31), type-2 diabetics (41, 44), skin graft recipients (8, 9), and spinal cord injury victims (14), may be at greater risk of thermal injury during severe heat stress due to problems associated with sweat gland function and/or evaporation, and not due to impairments of skin blood flow *per se*.

In previous studies, saline infusion has been an effective approach to elevate SkBF above non-infusion levels (5, 36); however, this was not the case in the present study, perhaps due to a

relatively modest infusion rate. Nevertheless, it is unlikely that a relative hypervolemia attending a greater infusion rate would have resulted in a higher P_{crit} for core temperature. Previously during exercise, saline infusion at 0.15 $ml \cdot kg^{-1} \cdot min^{-1}$ effectively raised FBF, but did not influence T_{sk} or sweat rate, and had only a minor effect on changes in core temperature (36). Similarly, reinfusion of withdrawn blood resulted in similar core temperature changes and T_{sk} during exercise despite a higher thermosensitivity of the FBF response (12). Although saline infusion did not augment the P_{crit} for core temperature in the current study, replacement of nearly 50% of sweat losses did result in a greater P_{crit} for heart rate in SAL compared to CON and DEH (Fig. 6). This delayed P_{crit} with volume infusion is likely due to the ability to maintain higher levels of venous return, cardiac filling pressure, and stroke volume in the face of rising thermal strain. Since underlying cardiovascular conditions are risk factors for thermal injury during heat exposure (40), strategies ensuring high levels of venous return (e.g., fluid replacement) can mitigate circulatory strain during severe environmental heat stress, despite having no effect on skin surface heat loss.

Limitations

Although the current iteration of the incremental humidity protocol used similar stepwise increases in P_a (~0.17 kPa per stage) and stage durations (6 min) as in previous studies (2, 26, 38), it could be argued that the present approach may lack the sensitivity required to detect differences in P_{crit} secondary to a reduction in SkBF. One way to demonstrate the sensitivity of the current protocol is through the effect of stepwise increases in P_a on skin wettedness (15). Theoretically, skin wettedness reflects the fraction of the skin surface that must be covered with sweat to achieve a certain rate of evaporative heat loss, while maximum skin wettedness refers to

the value of skin wettedness at the threshold for compensability (i.e., P_{crit}). Presently, stepwise increases in P_a by 0.17 kPa corresponded to average elevations in skin wettedness of 0.05 ± 0.02 (range: 0.02-0.10). Given that interventions (e.g. heat acclimation) alter maximum skin wettedness by ~0.15, a possible shift in the maximum skin wettedness by < 0.05 (and thus P_{crit}) by an attenuated SkBF response would have been practically negligible.

In addition to T_{es}, T_{gi} was also measured in six subjects in the event that the esophageal probe could not be tolerated. While including both T_{es} and T_{gi} may be perceived as a limitation, all analyses were performed within-subject and P_{crit} values calculated using T_{gi} only similarly showed no effect of treatment compared to those calculated using T_{es} (CON: 4.8 ±0.4, DEH: 4.9 ± 0.1, SAL: 5.0 ± 0.3 kPa; P = 0.641).

Due to instances of hypotension, body posture was adjusted from an upright seated position to a supine posture (note: seven total subjects were tested, with four in the upright and three in the supine postures). Although it could be argued that body position may have influenced our results, it should be noted that (i) all analyses were performed within-subject; (ii) comparisons within posture still revealed no effect of treatment on P_{crit} for core temperature, metabolic rate, whole-body sweat rate, LSR_{mean}, and T_{sk}; (iii) the slightly higher P_{crit} for core temperature in the upright position (CON: 5.2 ±0.1, DEH: 5.0 ± 0.2, SAL: 5.2 ± 0.1 kPa; n=4) compared to the supine posture (CON: 4.9 ±0.4, DEH: 4.9 ± 0.1, SAL: 5.1 ± 0.1 kPa; n=3) can be explained by the greater effective body surface area from which heat loss could occur while seated.

In many studies, SkBF responses are expressed as CVC or FVC normalized to a baseline or maximum value. While CVC reflects vasomotor control, heat exchange at the skin will be dependent on the absolute level of blood flow through cutaneous vessels; therefore, the arbitrary

LDF perfusion units were chosen to represent SkBF. Absolute SkBF was also measured as FBF using venous occlusion plethysmography (43), but we did not detect any effect of treatment on the FBF responses (data not shown). Previously, Johnson et al. (20) demonstrated good agreement between LDF and FBF values measured during passive heating. In that study, the experimental conditions were very different to those in the present study, specifically, LDF and FBF measurements would have been performed on an arm exposed to the ambient air, with skin much cooler than skin under the heating garment (20). As such, LDF and FBF values would have represented reflex drive for vasodilation only. While the severity of the heat stress imposed in the present study would have likely induced both reflex- and locally-mediated cutaneous vasodilation, there is no conspicuous reason for the present discrepancy between laser-Doppler and plethysmographic measurements. Nevertheless, the consistent reduction in LDF_{mean} among all subjects during DEH suggests that SkBF was effectively altered, and a reduction in SkBF following diuretic-induced dehydration has been previously observed (18).

The applicability of the present findings is limited to healthy young male subjects at one high ambient temperature (41°C), under resting conditions, and with minimal clothing. Future studies should examine the implications of lower SkBF on environmental compensability in special populations with well-known impairments of cutaneous vasodilation, between sexes, at different ambient temperatures, with various clothing ensembles, and during exercise at different intensities.

Conclusions

The present study examined whether diminished levels of SkBF lower the critical threshold for physiological compensability, indicating a reduced maximum heat loss potential,

during non-encapsulated passive whole-body heat stress. Despite an attenuated SkBF response achieved using a volume-depletion model, the critical environmental limit above which core temperature could no longer be maintained was not altered compared to control and volume infusion treatments due to the maintenance of similar skin temperatures and sweating rates.

ACKNOWLEDGEMENTS

This study was performed by M.N. Cramer in partial fulfillment of the degree Doctor of Philosophy from the University of Ottawa. The authors are grateful for the participation of all volunteers; to Amy Adams, Naomi Kennedy, Paula Poh, Steven Romero, and Zachary Schlader for assistance with data collection; and to Dr. Robert Kenefick for his valuable input in the development of the current protocol.

GRANTS

This research was supported by National Institutes of Health R01GM068865 (C.G.C) and by a Discovery Grant (#386143-2010) from the Natural Sciences and Engineering Research Council (O.J). M.N.C. was supported by an Excellence Scholarship and a Student Mobility Bursary from the Faculty of Graduate and Postdoctoral Studies at University of Ottawa, as well as an Ontario Graduate Scholarship (OGS). D.G. was supported by a Natural Sciences and Engineering Research Council of Canada Postdoctoral Fellowship.

DISCLOSURES

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

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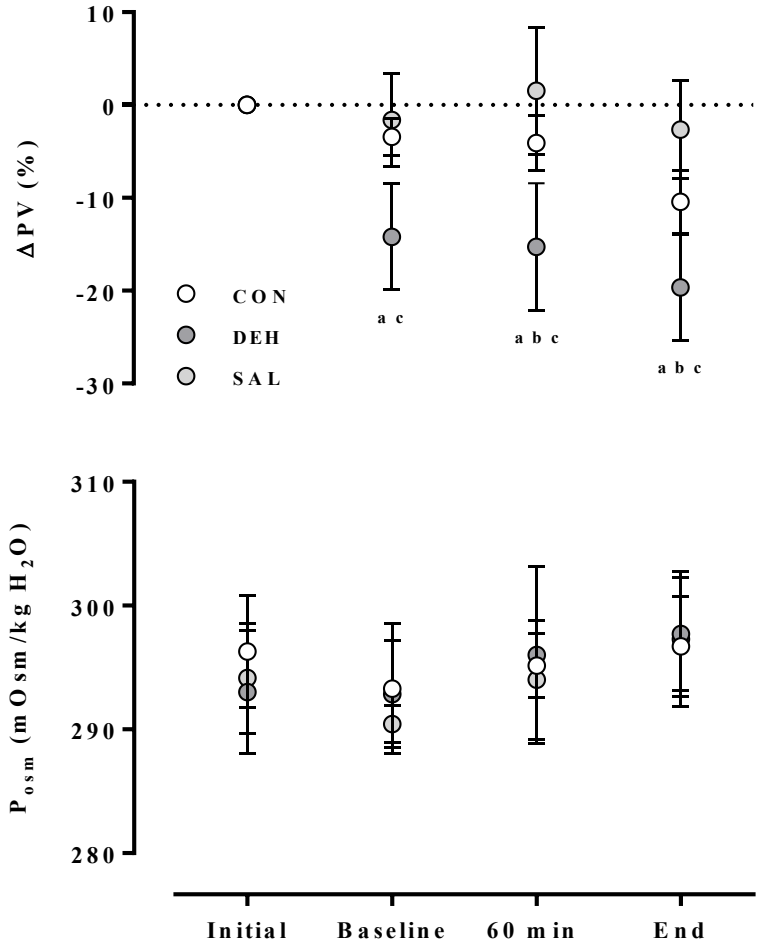

Figure 1. Changes in plasma volume (ΔPV) and plasma osmolality (P_{osm}) throughout experimentation during the control condition (CON), following diuretic-induced dehydration (DEH), and with continuous saline infusion (SAL). Data are for seven subjects. a, b, c indicate differences between CON and DEH, CON and SAL, and DEH and SAL, respectively ($P < 0.001$).

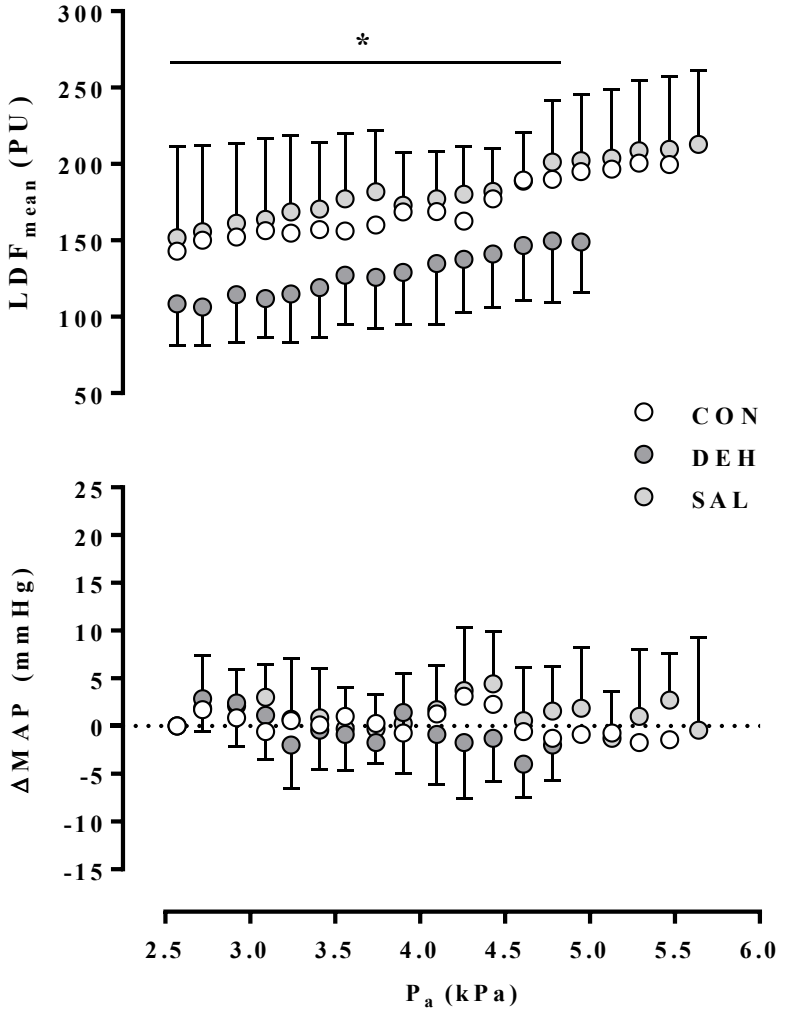

Figure 2. Hemodynamic responses throughout the incremental humidity protocol in a control condition (CON), following diuretic following diuretic-induced dehydration (DEH), and with continuous saline infusion (SAL). LDF_{mean}, mean laser Doppler flux (forearm, thigh); ΔMAP, change in mean arterial pressure from baseline; P_a, ambient vapor pressure. Analyses were performed for seven subjects up to 5 kPa (84 min), after which early termination criteria were met at different times. * indicates a main effect of treatment.

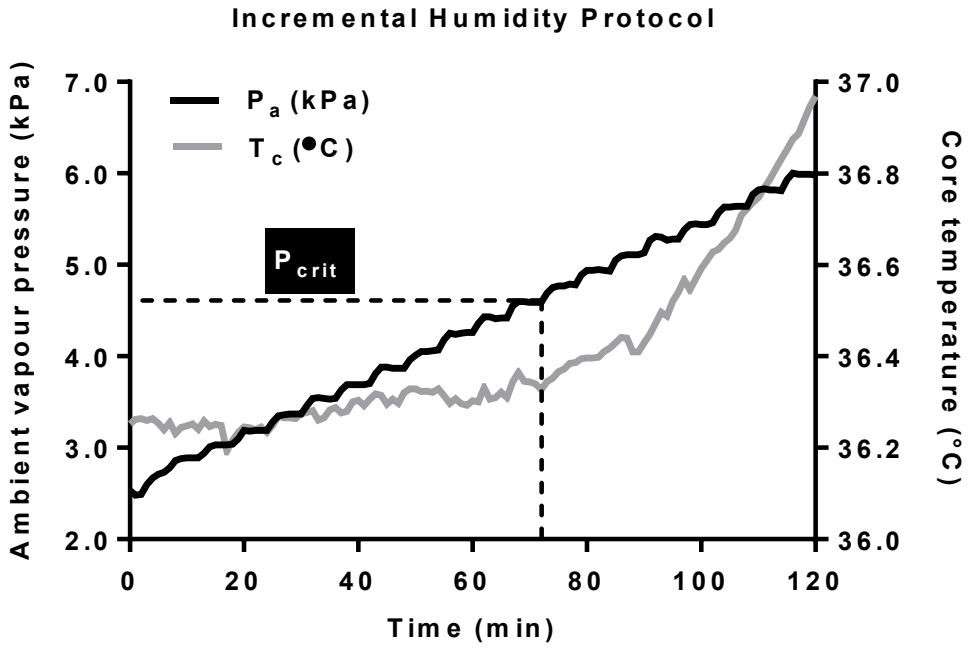

Figure 3. Example of the incremental humidity protocol used in the present study with a sample core temperature (T_c) trace and the identification of the critical ambient vapor pressure (P_{crit}). P_a, ambient vapor pressure.

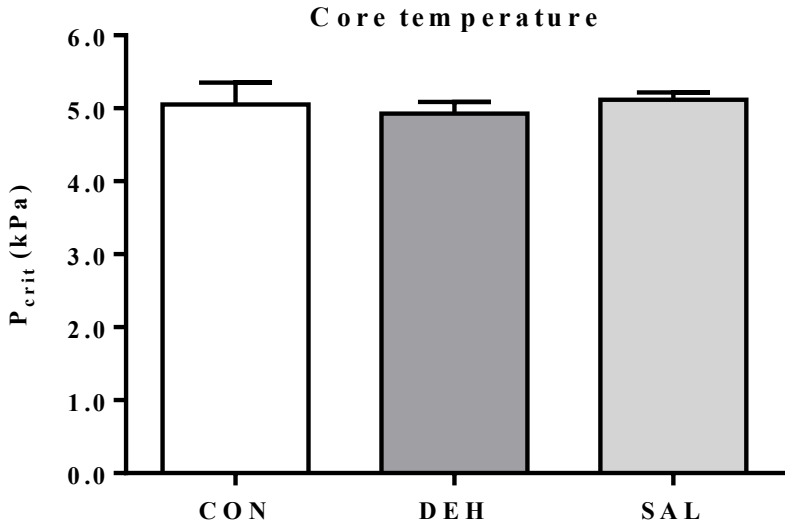

Figure 4. Critical ambient vapor pressures (P_{crit}) for core temperature in a control condition (CON), following diuretic-induced dehydration (DEH), and with continuous saline infusion (SAL) for seven subjects.

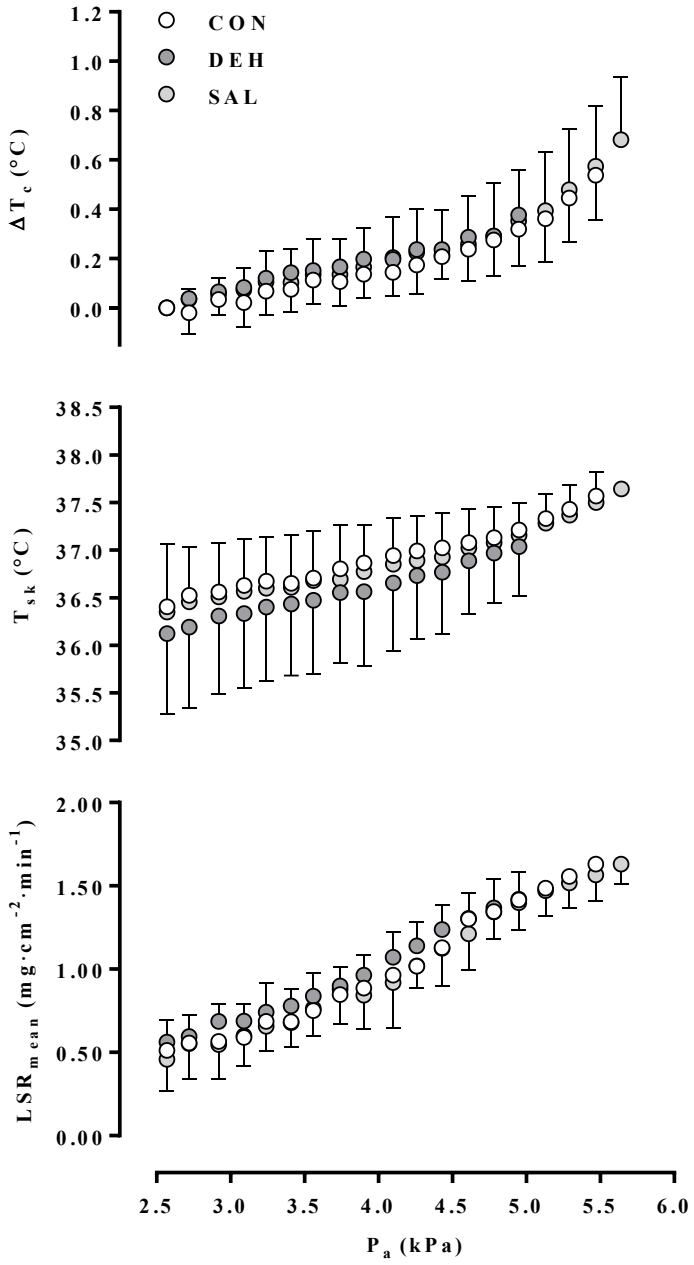

Figure 5. Thermal and local sweating responses throughout the incremental humidity protocol in a control condition (CON), following diuretic-induced dehydration (DEH), and with continuous saline infusion (SAL). ΔT_c, change in core temperature; T_{sk}, mean skin temperature; LSR_{mean}, mean local sweat rate (2 sites: forearm, thigh); P_a, ambient vapor pressure. Analyses were performed up to 5 kPa (84 min) in seven subjects. Beyond this point, early termination criteria were met at different times.

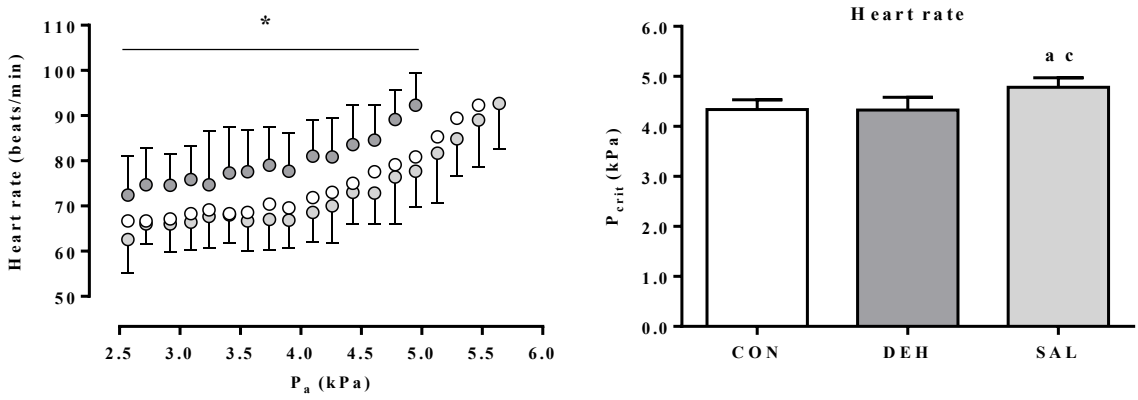

Figure 6. Heart rate responses throughout the incremental humidity protocol in a control condition (CON), following diuretic-induced dehydration (DEH), and with continuous saline infusion (SAL). P_a, ambient vapor pressure; P_{crit}, critical ambient vapor pressure. Heart rate analysis was performed up to 5 kPa (84 min) in seven subjects. Beyond this point, early termination criteria were met at different times. As in Figure 1, a and c indicate significant differences between CON and DEH and between DEH and SAL, respectively ($P < 0.001$).

CHAPTER 4: THESIS DISCUSSION

4.1 Summary

Although core temperature and sweating responses to exercise have been traditionally compared at a fixed $\%VO_{2max}$ to normalize the putative influence of aerobic fitness (i.e., VO_{2max}) on core temperature, recent evidence suggests that prescribing an exercise intensity that accounts for heat production (and thus E_{req}) and body size (body mass and BSA) may eliminate systematic bias that can be attributed to between-group differences in heat production or body size. Additionally, previous studies have associated factors related to VO_{2max} and body fatness to core temperature and thermoregualtory sweating responses; however, the administration of fixed $\%VO_{2max}$ or absolute workloads may result in high circumstantial collinearity between biophysical (e.g. heat production, body size) and physiological (e.g. VO_{2max}, body fat percentage) factors. While diminished levels of skin blood flow are thought to limit the ability to dissipate heat from the skin to the external environment, studies supporting a link between skin blood flow and heat loss potential have been largely performed in encapsulated conditions or in non-encapsulated conditions without any corresponding reductions in sweat rate and skin temperature. Therefore, the present thesis sought to answer four specific questions related to the individual variability of thermoregulatory responses to exercise, and the influence of skin blood flow on heat loss potential:

1. In compensable conditions, should changes in core temperature be compared between independent groups at the same absolute rate of heat production or at a rate of heat production per unit body mass (W/kg) irrespective of body mass and $\%VO_{2max}$?
2. In compensable conditions, should local sweat rate be compared between independent groups at the same absolute rate of heat production (and thus E_{req}) or at the same rate of

heat production (and thus E_{req}) per unit body surface area (W/m^2), regardless of body surface area?

3. Are heat production (W/kg), E_{req} (W), and E_{req} (W/m^2) the primary determinants of changes in core temperature, whole-body sweat losses, and steady-state local sweat rates, respectively, during exercise in compensable conditions, and do factors related to aerobic fitness and body fatness explain any of the residual variance in these thermoregulatory responses?
4. Do manipulations of skin blood flow alter heat loss potential?

Table 1. Summary of main thesis findings.

Study 1	1. Exercise at a fixed absolute heat production (W) resulted in greater changes in rectal temperature among individuals of lower body mass. 2. Exercise at a fixed absolute E_{req} (W) resulted in greater mean local sweat rates among individuals of smaller BSA. 3. Changes in rectal temperature were not different between groups of large and small body mass during exercise at a fixed heat production per unit of body mass (W/kg) despite differences in absolute heat production and $\%VO_{2max}$. 4. Mean local sweat rate was not different between groups of large and small BSA during exercise at a fixed E_{req} per unit of BSA (W/m^2) despite differences in absolute E_{req} (W).
Study 2	1. Individual variability in the change in core temperature, whole-body sweat loss, and steady-state local sweat rate was explained predominantly by biophysical factors related to heat production and body size. 2. Factors related to aerobic fitness (i.e., VO_{2max}) and body fatness contributed marginally to the residual variance.
Study 3	1. The critical environmental limit for core temperature (and thus heat loss potential) was unaltered by a reduction in skin blood flow. 2. Volume infusion raised the critical environmental limit for heart rate.

To address these questions, three studies were performed, and the main findings are summarized in Table 1. The results and limitations of these studies have been discussed in Chapter 3. Therefore, the following sections will consider the broader implications of the present findings, and explore future research directions in this area.

4.2 Implications of the present findings and future directions

The results of study 1 suggest that the most appropriate protocols for comparing core temperature changes and local sweat rate responses to exercise involves the prescription of exercise intensity to elicit target rates of heat production per unit body mass (W/kg) and E_{req} per unit BSA (W/m^2), respectively. The principal application of these findings is in the design of experiments seeking to identify potential thermoregulatory dysfunction in special populations *versus* a healthy control group without the confounding influence of different rates of heat production and morphological traits. Thermoregulatory dysfunction has been apparently determined in a number of special populations; however, previous findings may be confounded by biophysical features of the experimental protocol or groups selected [e.g., heart failure patients (7, 132)]. The protocols currently advocated offer a new experimental approach that eliminates systematic bias that could be attributed to differences in heat production and body size, permitting the true isolation of a single physiological variable.

Identifying potential thermoregulatory dysfunction in special populations is important for a variety of reasons. Physical activity is widely recognized as an important component of disease management in conditions that may result in impaired heat loss, such as multiple sclerosis (34, 86) and diabetic peripheral neuropathy (42). However, with sub-optimal heat loss capabilities, individuals within these populations may be discouraged, or even prevented, from participating in regular exercise, resulting in an exacerbated disease state and/or a poorer quality of life. This

is similarly true for workers (e.g., mining) who perform physically-demanding occupational tasks in hot/humid environments. Diseases/conditions that impair heat loss in these settings could severely limit productivity and challenge worker safety. It is therefore important to identify the extent to which such diseases affect heat loss, and subsequently develop therapeutic treatments to counteract potentially harmful elevations in heat strain.

It is important to emphasize that in using the protocols advocated in study 1, the selected exercise intensity must be tailored to the research question under investigation (Figure 1). For example, if the question relates the independent effect of some physiological variable on the change in core temperature, and groups are not matched for body mass, only the rate of heat production in W/kg must be considered. However, if investigators want to compare changes in core temperature, whole-body sweat rates, and local sweating rates using an independent-group experimental design, two options are available: (i) match groups for body size and prescribe a fixed heat production (and E_{req}) to compare allow comparison of all responses with only one experimental trial, or (ii) leave groups unmatched for body size, but perform multiple experimental trials at different intensities to elicit target heat production (W/kg) and E_{req} (W, W/m^2) values. Researchers would have to weigh the costs (financial, scheduling, personnel) of running multiple experimental trials against their ability to recruit many individuals of the same morphological characteristics.

It is also important to recognize that the findings of studies 1 and 2 are limited to physiologically compensable conditions, and future work should aim to similarly identify how to perform unbiased comparisons of core temperature and sweating responses in uncompensable environments. Indeed, under such conditions, the effect of large between-group differences in body size may not be eliminated by simply prescribing a fixed heat production in W/kg.

Theoretically, heat storage in uncompensable environments is determined by the cumulative difference between H_{prod} and the maximum rate of heat loss (i.e. E_{max}), and expressed in W/kg to account for the influence of body mass. For a given set of ambient conditions and mean skin temperature, individuals with a low BSA-to-mass ratio (i.e. large body size) will also have a lower E_{max} in W/kg. Therefore, when exercise is performed at a fixed H_{prod} in W/kg in an uncompenasble environment by groups of very different body size, the cumulative heat storage should be higher in the group of large body size because of a greater H_{prod}–E_{max} difference in W/kg, and thus a greater change in core temperature in larger individuals (29). It follows that core temperature changes in uncompensable conditions should be compared between groups of different body size at a fixed H_{prod}–E_{max} difference in W/kg. Whether large differences in BSA-to-mass ratio in fact lead to sufficiently different H_{prod}–E_{max} (W/kg) values that result in systematic differences in the change in core temperature during exercise at a fixed heat production (W/kg) is unknown.

In addition to being physiologically compensable, the experimental conditions in studies 1 and 2 were such that sweating efficiency – the ratio of evaporated *versus* secreted sweat – was ~100%. In such conditions, and in accordance with the recent work of Gagnon et al. (56), BSA does not appear to independently alter whole-body sweat rate for a given absolute E_{req}. However, this may not be true in all environmental conditions. At low ω_{req} of <0.5 (e.g., high air velocity, low ambient temperature and/or humidity, minimal clothing), all secreted sweat is evaporated (i.e., sweating efficiency is 100%). At ω_{req} of >0.5 (e.g., minimal air flow, high ambient temperature and/or humidity, clothing a high degree of insulation and/or resistance to evaporation), sweating efficiency declines exponentially as the rate of sweat secretion must exceed the sweat rate required for heat balance to achieve ω_{req} (2, 18). Since ω_{req} is defined by

E_{req}/E_{max} (Eq. 20), and differences in BSA will influence absolute E_{max} (Eq. 19) such that a greater BSA will lead to a higher absolute E_{max}, exercise at intensities that elicit a fixed absolute E_{req} should theoretically result in disproportionately greater whole-body sweat rates in individuals with a smaller BSA due to a lower absolute E_{max}, higher ω_{req}, and thus a lower sweating efficiency. Our laboratory has explored this possibility by comparing actual whole-body sweat losses from changes in body mass to the calculated whole-body sweat rate requirement during steady-state exercise in hot/humid conditions; however, inconsistent preliminary findings suggest that a more reliable protocol is needed in the future to properly test this hypothesis.

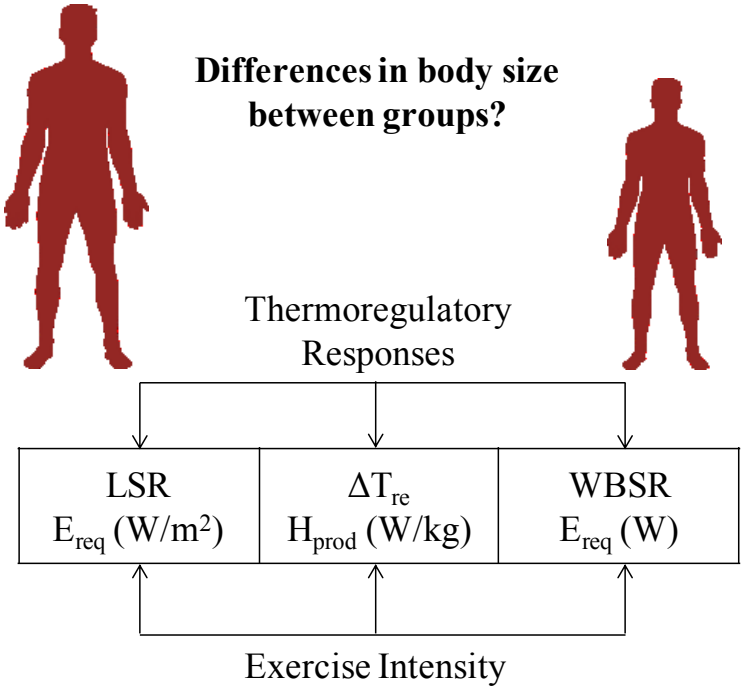

Figure 1. Suggested methods to compare changes in core temperature (ΔT_{re}), whole-body sweat rate (WBSR), and local sweat rate (LSR) between independent groups based on the findings of Cramer and Jay (28).

Based on the findings of study 1, we suggested that exercise intensity should be administered at a fixed E_{req} (in W/m^2) to account for differences in the evaporative requirements

and BSA, both of which can independently alter local sweat rate. In the design of future experiments, investigators are cautioned that this approach may only apply if local sweat rates are measured in non-glabrous skin regions. We have recently demonstrated that exercise at a higher $\%VO_{2max}$ leads to a greater local sweat rate on the forehead (glabrous skin), but not the forearm (non-glabrous skin), despite the same E_{req} (W/m^2) (27). The reason for this effect is unclear, but suggests an additive effect on forehead sudomotor function by thermoregulatory and non-thermoregulatory reflexes, the latter of which being perhaps the result of greater exercise-related stress *per se*. The use of a single forehead local sweat rate measurement to examine acute or adaptive thermoregulatory responses may have been confounded by interventions that also influence $\%VO_{2max}$ (97, 98, 112). It follows that inclusion of a forehead measurement site in a mean local sweat rate measurement should be avoided for independent-groups comparisons unless groups are matched also for VO_{2max}. Future studies should examine whether similar effects occur in other glabrous skin areas as on the forehead.

With the exception of local sweat rate responses on the forehead (27), the present (studies 1 and 2) and previous work (92) do not support an influence of VO_{2max} on thermoregulatory responses, once accounting for biophysical factors. Recent research suggests this may not be the case in all populations, and under all environmental conditions. Although an age-related effect on heat loss mechanisms has been shown (107, 114), Stapleton *et al*. (176) recently reported that young and middle-aged aerobically fit individuals demonstrate similar changes in esophageal temperature, but these changes were significantly attenuated compared to middle-aged unfit and older individuals. All four groups were matched for sex and body size, and exercise was conducted at the same absolute heat production in fixed ambient conditions, yet the heat load appeared to be uncompensable in the middle-aged unfit and older subjects only. These data

suggest that VO_{2max} may have an independent effect on heat loss in these populations. It is possible that at ω_{req} of near-unity, regular physical activity (and thus higher VO_{2max}) permits a higher ω_{max} and thus a greater rate of whole-body heat loss sufficient to ensure compensability in the trained and young individuals, but uncompensability in the untrained and old individuals in the study of Stapleton *et al*. (176). A ω_{max} value of ~0.85 has been found in non-heat acclimated individuals (18), but aerobic training may confer a degree of partial heat acclimation at the peripheral level (15, 16) such that ω_{max} is higher than 0.85 but less than 1.0 in aerobically trained individuals. It remains to be determined whether ω_{max} and critical environmental limits are augmented by a high VO_{2max}.

Study 3 was conducted with subjects at rest in an effort to best replicate previous studies performed with a water-perfused suit, and to simulate conditions experienced during extreme heat events. The results show that altered skin blood flow does not affect heat loss potential, indicated by no change in P_{crit}. A high ambient temperature of 41°C resulted in a negligible core-skin thermal gradient throughout most of the protocol. Consequently, any level of skin blood flow would have been ineffective in driving more or less heat transfer to the skin. In fact, if skin temperature exceeds core temperature, high levels of skin blood flow should theoretically facilitate greater body heat gain, if no concomitant increases in evaporation occur in parallel. Although it is possible alterations in skin blood flow could influence heat loss potential at lower ambient temperatures that permit the maintenance of a positive core/skin thermal gradient and thereby favour heat transfer to the periphery, this possibility remains to be tested. Additionally, skin blood flow may be important in conditions that result in a physiological limitation to increasing skin wettedness. For instance, in very hot conditions with high air velocity, high levels of skin blood flow may be needed to augment sweat rate to achieve ω_{max}. Future studies

should also explore whether an effect of skin blood flow on heat dissipation exists in conditions that result in a competition for blood flow (e.g. high-intensity exercise).

Future studies examining a link between skin blood flow and heat loss potential should also consider using a similar incremental humidity protocol during exercise. This approach would provide information on working individuals, and could therefore have better inform heat exposure guidelines in occupational setting for individuals with established skin blood flow impairments. Additionally, independent-group comparisons should be conducted between healthy and those with well-known skin blood flow impairments, including the elderly (104, 107), diabetics (174, 192), heart failure patients (7, 68, 132), and hypertensive individuals (105, 106), during rest and exercise to see if disease-related attenuations in skin blood flow affect critical environmental limits. Follow-up studies examining potential cooling interventions (e.g., fans) or strategies that could enhance skin blood flow (e.g., pharmacological agents, fluid replacement) should also be performed. This information would be invaluable given the projection for increasingly frequent and severe extreme heat events (45), the rising costs of electrical energy that could make affordable electronic cooling devices inaccessible to low-income individuals (142, 185), and a growing number of elderly individuals with multiple co-morbidities (126) who are the most vulnerable during heat waves (162).

4.3 Thesis conclusions

The findings presented in this thesis demonstrate the following: Firstly, body mass and BSA independently affect the change in core temperature and the mean local sweat rate during exercise in compensable conditions. However, by performing comparisons of core temperature and local sweat rate responses at exercise intensities that elicit the same rate of metabolic heat

production per unit of total body mass (W/kg) and the same heat production (and thus evaporative requirement) per unit body surface area (W/m^2), respectively, the effects of heat production and body morphology can be effectively normalized, and true independent physiological effects can thus be isolated between groups. Additionally, individual variability in the change in core temperature, whole-body sweat loss, and steady-state local sweat rate are primarily determined by biophysical factors related to heat production and body size, with only a marginal contribution from factors related to aerobic fitness and adiposity. Finally, a diminished skin blood flow response did not alter the critical environmental limits, and thus heat loss potential, during severe hot/humid heat stress. This is likely explained by the lack of any effect of low skin blood flow on skin temperature and sweating for a given resting metabolic rate. The inability of certain individuals (e.g. diabetics, the elderly) to maintain high levels of skin blood flow may not be as important for mitigating heat strain during non-encapsualted passive heat stress as previously thought, provided sweat production is not physiologically limited.

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APPENDIX

APPENDIX A: Notices of ethical approval for thesis studies

File Number: H12-11-05 **Date (mm/dd/yyyy):** 01/13/2012

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
Ollie	Jay	Health Sciences / Human Kinetics	Principal Investigator
Matthew	Cramer	Health Sciences / Human Kinetics	Co-investigator

File Number: H12-11-05

Type of Project: Professor

Title: The Influence of Body Morphology on the Core Temperature Response to Exercise

Approval Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
01/13/2012	01/12/2013	Ia

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

Special Conditions / Comments:
N/A

550, rue Cumberland, pièce 154 550 Cumberland Street, room 154
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http://www.recherche.uottawa.ca/deontologie/index.html

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
Ollie	Jay	Health Sciences / Human Kinetics	Principal Investigator
Matthew	Cramer	Health Sciences / Human Kinetics	Co-investigator

File Number: H12-12-04

Type of Project: Professor

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

Approval Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
01/17/2013	01/16/2014	Ia

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

Special Conditions / Comments:
N/A

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http://www.research.uottawa.ca/ethics/index.html
http://www.recherche.uottawa.ca/deontologie/index.html

File Number: H 01-14-08 Date (mm/dd/yyyy): 02/25/2014

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
Matthew	Cramer	Health Sciences / Human Kinetics	Student Researcher

File Number: H 01-14-08

Type of Project: PhD Thesis

Title: Do modifications to skin blood flow alter heat dissipation?

Approval Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
02/25/2014	02/24/2015	Ia

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

Special Conditions / Comments:
This certificate is valid for the portion of the research conducted in Canada. Ethics certificate from the US should be submitted before full approval can be granted.

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UT SOUTHWESTERN MEDICAL CENTER eIRB System

From: **John Sadler**
Institutional Review Board Chairperson
IRB - 8843

To: Craig Crandall , Jena Langlois , Elaine Salinas

Date: May 6, 2014

Re: Study Approval
IRB Number:
STU 032014-022
Title: Do modifications to skin blood flow alter the potential for heat dissipation?

Documents: Protocol, Consent Form, HIPAA Authorization, and all smartform attachments

The UT Southwestern Institutional Review Board (IRB) reviewed the above-referenced research study at a convened meeting of the full board on April 16, 2014. Having met all applicable requirements, the research study is approved. The approval period for this research study begins on May 6, 2014 and lasts until April
15, 2015.

Having met all regulatory criteria outlined in 45 CFR 164.512, the IRB also approved a waiver of authorization for the release of protected health information for this study.

The research study cannot continue beyond the approval period without continuing review and approval by the IRB. In order to avoid a lapse in IRB approval, the Principal Investigator must apply for continuing review of the protocol and related documents before the expiration date. A reminder will be sent to you approximately 90 days prior to expiration of study approval.

The approved number of subjects to be enrolled is 15**.** The IRB considers a subject to be enrolled once s/he signs a Consent Form. If, additional subjects are needed, you first must obtain permission from the IRB to increase the sample size.

If you have any questions related to this approval letter or about IRB policies and procedures, please telephone the IRB office at 214-648-3060.

General Instructions

To maintain IRB approval in good standing, please observe the following requirements:

1. All subjects must sign the consent form before undergoing any research study procedures, including screening procedures. A photocopy of the signed consent form(s) should be given to each participant. The copy of the consent form(s) bearing original signature(s) should be kept with other records of this research for at least six years past the completion of the research study.
   - A photocopy of the signed HIPAA Authorization should be given to each participant. A copy of the HIPAA Authorization bearing original signatures should be kept with other records of this research for at least six years past the completion of the research study.
     - Obtain prior IRB approval for any modifications including addition of new recruiting materials, changes in research personnel or site location, sponsor amendments or other changes to the protocol or associated documents. Only those changes that are necessary to avoid an immediate apparent hazard to a subject may be implemented without prior IRB approval.
     - Report all adverse events, protocol violations, and study closures promptly to the IRB.
     - Make study records available for inspection. All research-related records and documentation may be inspected by the IRB for the purpose of ensuring compliance with UT Southwestern policies and procedures and federal regulations governing the protection of human subjects. The IRB has authority to suspend or terminate its approval if applicable requirements are not strictly adhered to by all research study personnel.
     - If the IRB has approved the use of an oral presentation of informed
     - consent information in conjunction with a short form written consent document (stating that the elements of consent have been presented orally), when enrolling subjects who do not speak or read English, a witness to the oral presentation is required, and the subject must be given copies of the short form document and the summary. When this procedure is used (1) the oral presentation and the short form written document should be in a language understandable to the subject; (2) the IRB-approved English language informed consent document may serve as the summary; and (3) the witness should be fluent in both English and the language of the subject. At the time of consent, (1) the short form document should be signed by the subject (or the subject's legally authorized representative); (2) the summary (i.e., the English language informed consent document) should be signed by the person obtaining consent as authorized under the protocol; and (3) the short form document and the summary should be signed by the witness. When the person obtaining consent is assisted by a translator, the translator may serve as the witness.
     - When enrolling subjects who do not speak or read English, a bilingual translator must be available to facilitate communications between research personnel and a subject.

University of Texas Southwestern Medical Center
Institutional Review Board

5323 Harry Hines Boulevard
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APPENDIX B: Final published version of thesis article #1

J Appl Physiol 116: 1123–1132, 2014.
First published February 6, 2014; doi:10.1152/japplphysiol.01312.2013.

Selecting the correct exercise intensity for unbiased comparisons of thermoregulatory responses between groups of different mass and surface area

Matthew N. Cramer[1] and Ollie Jay[1,2]

[1]*Thermal Ergonomics Laboratory, School of Human Kinetics, University of Ottawa, Ottawa, Canada; and* [2]*Exercise and Sport Science, Faculty of Health Sciences, University of Sydney, New South Wales, Australia*

Submitted 4 December 2013; accepted in final form 4 February 2014

Cramer MN, Jay O. Selecting the correct exercise intensity for unbiased comparisons of thermoregulatory responses between groups of different mass and surface area. *J Appl Physiol* 116: 1123–1132, 2014. First published February 6, 2014; doi:10.1152/japplphysiol.01312.2013.—We assessed whether comparisons of thermoregulatory responses between groups unmatched for body mass and surface area (BSA) should be performed using a metabolic heat production ($\dot{H}_{prod}$) in Watts or Watts per kilogram for changes in rectal temperature (ΔT_{re}), and an evaporative heat balance requirement (E_{req}) in Watts or Watts per square meter for local sweat rates (LSR). Two groups with vastly different mass and BSA [large (LG): 91.5 ± 6.8 kg, 2.12 ± 0.09 m^2, n = 8; small (SM): 67.6 ± 5.6 kg, 1.80 ± 0.09 m^2, n = 8; $P < 0.001$], but matched for heat acclimation status, sex, age, and with the same onset threshold esophageal temperatures (LG: +0.37 ± 0.12°C; SM: +0.41 ± 0.17°C; P = 0.364) and thermosensitivities (LG: 1.02 ± 0.54, SM: 1.00 ± 0.38 mg·cm^{-2}·min^{-1}·°C^{-1}; P = 0.918) for sweating, cycled for 60 min in 25°C at different levels of $\dot{H}_{prod}$ (500 W, 600 W, 6.5 W/kg, 9.0 W/kg) and E_{req} (340 W, 400 W, 165 W/m^2, 190 W/m^2). ΔT_{re} was different between groups at a $\dot{H}_{prod}$ of 500 W (LG: 0.52 ± 0.15°C, SM: 0.92 ± 0.24°C; $P < 0.001$) and 600 W (LG: 0.78 ± 0.19°C, SM: 1.14 ± 0.24°C; P = 0.007), but similar at 6.5 W/kg (LG: 0.79 ± 0.21°C, SM: 0.85 ± 0.14°C; P = 0.433) and 9.0 W/kg (LG: 1.02 ± 0.22°C, SM: 1.14 ± 0.24°C; P = 0.303). Furthermore, ΔT_{re} was the same at 9.0 W/kg in a 35°C environment (LG: 1.12 ± 0.30°C, SM: 1.14 ± 0.25°C) as at 25°C ($P > 0.230$). End-exercise LSR was different at E_{req} of 400 W (LG: 0.41 ± 0.18, SM: 0.57 ± 0.13 mg·cm^{-2}·min^{-1}; P = 0.043) with a trend toward higher LSR in SM at 340 W (LG: 0.28 ± 0.06, SM: 0.37 ± 0.15 mg·cm^{-2}·min^{-1}; P = 0.057), but similar at 165 W/m^2 (LG: 0.28 ± 0.06, SM: 0.28 ± 0.12 mg·cm^{-2}·min^{-1}; P = 0.988) and 190 W/m^2 (LG: 0.41 ± 0.18, SM: 0.37 ± 0.15 mg·cm^{-2}·min^{-1}; P = 0.902). In conclusion, when comparing groups unmatched for mass and BSA, future experiments can avoid systematic differences in ΔT_{re} and LSR by using a fixed $\dot{H}_{prod}$ in Watts per kilogram and E_{req} in Watts per square meter, respectively.

core temperature; local sweat rate; body mass; body surface area; thermoregulation

STUDIES OF HUMAN THERMOREGULATION often employ a between-groups experimental design to isolate the independent effect of a particular physiological factor, e.g., age (5, 24, 50), sex (18, 25), aerobic fitness (19, 39), disease (29, 30), injury (21), on the core temperature and sudomotor responses to exercise.[1] The exercise intensity prescribed to facilitate these comparisons is fundamentally important, since the introduction of any inherent bias to an experimental design may lead researchers to incorrectly attribute different changes in core temperature and/or sweating between groups to the physiological factor under examination.

Since the seminal work of Saltin and Hermansen in 1966 (44), many exercise and thermal physiologists have interpreted their findings to mean that a fixed relative exercise intensity [a percentage of the maximum rate of oxygen uptake (%$\dot{V}O_{2max}$)] should be administered to compare thermoregulatory responses between independent groups due to the prevailing notion that $\dot{V}O_{2max}$ profoundly influences the change in core temperature and sweating during exercise (13, 19, 20, 39). However, we recently reported that two groups matched for body mass and body surface area (BSA), but differing greatly in $\dot{V}O_{2max}$, exhibit almost identical changes in core temperature and whole body sweat loss (WBSL) during exercise at the same absolute rate of metabolic heat production ($\dot{H}_{prod}$) (540 W) in a physiologically compensable environment, despite large differences in relative intensity (58 vs. 40% of $\dot{V}O_{2max}$) (27). It is now also clear that protocols utilizing %$\dot{V}O_{2max}$ can lead to systematically different changes in core temperature and sweating between groups that may otherwise respond similarly from a physiological perspective, due to differences in $\dot{H}_{prod}$ and the evaporation required for heat balance (E_{req}) (16, 27). However, since the participants in our previous study were matched for body mass (27), it is still unknown whether an absolute $\dot{H}_{prod}$ [in Watts (W)] should be used to prescribe exercise intensity for between-group experimental designs, or if $\dot{H}_{prod}$ should be normalized for body mass (W/kg), if groups are unmatched for this physical trait. The practical importance of this question is emphasized by the fact that matching groups for body mass may, in some cases, be impossible for researchers investigating the consequences of potential thermoregulatory dysfunction in special populations, such as multiple sclerosis patients (10), the obese (23, 33), spinal cord injury victims (21, 49), sympathectomy patients (8), and skin-graft recipients (36, 47).

From a biophysical perspective, changes in core temperature are determined by the cumulative imbalance between $\dot{H}_{prod}$ and net heat loss to the environment (i.e., body heat storage), body mass (i.e., internal heat sink), and body composition (i.e., specific heat capacity of body tissue). Previous studies have shown that large variations in body mass lead to diverse core temperature responses during exercise at the same absolute work rate or $\dot{H}_{prod}$ (15, 22, 35, 43). It therefore stands to reason that normalizing $\dot{H}_{prod}$ for body mass should lead to similar changes in core temperature between groups of dissimilar body

[1] This article is the topic of an Invited Editorial by Samuel N. Cheuvront (5a).

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mass, unless heat loss is altered as a function of the physiological parameter under investigation (e.g., age, sex, etc.).

Using direct calorimetry and, therefore, under conditions permitting full evaporation, Gagnon et al. (16) recently demonstrated that whole body sweat rate (WBSR) in grams per minute is determined by the absolute rate of E_{req} in W, irrespective of $\%\dot{V}O_{2max}$, core temperature, BSA, and body mass. However, local sweat rate (LSR) is typically measured in milligrams per square centimeter per minute over a fixed surface area with either a ventilated capsule (18, 25, 50) or absorbent patch (3, 7, 11, 48); therefore, a higher mean LSR would be expected at a fixed absolute E_{req} (and therefore WBSR) in individuals with a lower BSA, because the same absolute amount of sweat would have to be secreted over a smaller area. The prescription of an exercise intensity that elicits the same absolute E_{req} may, therefore, lead to a systematically different LSR between independent groups unmatched for BSA, yet an intensity eliciting the same E_{req} per unit BSA (in W/m^2) may remove this inherent bias (11, 18).

The purpose of this study was to derive the optimal methods for comparing changes in rectal temperature (ΔT_{re}) and LSR between groups unmatched for body mass and BSA so that any inherent bias due to biophysical factors is removed. To this end, we compared responses between groups vastly different in body mass (~90 vs. ~65 kg) and BSA (~2.10 vs. 1.80 m^2), but matched for age, sex, and heat acclimation status, and with identical operational parameters for sudomotor control (i.e., onset threshold and thermosensitivity). Values for ΔT_{re} were compared using fixed levels of *1*) absolute $\dot{H}_{prod}$ (in W), and *2*) $\dot{H}_{prod}$ per unit total body mass (in W/kg). Values for mean LSR were compared using fixed levels of *1*) absolute E_{req} (in W), and *2*) E_{req} per unit BSA (in W/m^2). It was hypothesized that *1*) $\dot{H}_{prod}$ in W would yield a greater ΔT_{re} in the small body mass group due to a greater Watts per kilogram (W/kg), but $\dot{H}_{prod}$ in W/kg would lead to a similar ΔT_{re} between groups, despite differences in body mass, and *2*) E_{req} in W would yield similar WBSR between large and small BSA groups, but mean LSR would be greater in the small BSA group due to a greater E_{req} in Watts per square meter (W/m^2); however, E_{req} in W/m^2 would lead to similar mean LSR between groups, despite differences in BSA.

METHODS

Ethical approval. Approval of the experimental protocol was obtained from the University of Ottawa Health Sciences and Science Research Ethics Board (file no. H12-11-05). All procedures conformed to the principles set forth in the Declaration of Helsinki. Volunteers were fully informed of the experimental protocol and potential risks before providing written, informed consent. Also, a Physical Activity Readiness Questionnaire and an American Heart Association/American College of Sports Medicine Health/Fitness Facility Pre-participation Screening Questionnaire were completed before participation.

Participants. Using a power calculation (G*power version 3.1.5) with conventional β- (0.1) and α-values (0.05), a minimum sample size of 12 participants (6 per group) was required based on a mean ΔT_{re} of 0.35°C and a standard deviation of 0.15°C following 60 min of exercise at a fixed $\dot{H}_{prod}$ of 500 W between independent groups with a 17.7-kg difference in body mass (15). Sixteen men of large (LG; $n = 8$) or small (SM; $n = 8$) body mass and BSA volunteered for this study. Groups were matched for age, but not aerobic fitness, to ensure differences in $\%\dot{V}O_{2max}$ at each Watt per kilogram, and thereby isolate whether systematic differences in ΔT_{re} are avoided by prescribing a fixed W/kg between groups unmatched for body mass. All participants were nonsmokers, reported no history of cardiovascular, respiratory, neurological, or metabolic disease, and were not taking any medications at the time of participation.

Preliminary session. Each participant visited the laboratory for a preliminary session that included an explanation of the experimental protocol, anthropometric measurements, and an exercise test. Height was measured using a wall-mounted stadiometer (HR-200, Tanita, Arlington Heights, IL), and body mass was measured using a digital scale (BWB-800, Tanita, Arlington Heights, IL). These values were used subsequently to estimate BSA (12). Body composition was measured via dual-energy X-ray absorptiometry (GE-LUNAR Prodigy module, GE Medical Systems, Madison, WI).

The exercise test was performed in a climate-controlled room set to 22°C on a semirecumbent cycle ergometer (Lode Corival, Groningen, the Netherlands) in two phases. The first phase was performed to determine the relationship between external work rate and steady-state rate of oxygen consumption ($\dot{V}O_2$) (and thus $\dot{H}_{prod}$) for each participant over the full range of $\dot{H}_{prod}$ targeted in the experimental trials. This procedure permitted greater accuracy in achieving each target $\dot{H}_{prod}$ from the onset of exercise (see APPENDIX for step-by-step instructions for prescribing exercise intensity to achieve target $\dot{H}_{prod}$). Participants completed four 5-min submaximal stages, which began at 80 W (SM) or 100 W (LG) and increased by 20 W/stage. Expired gases were analyzed throughout exercise via indirect calorimetry using a metabolic cart (Vmax Encore, CareFusion, Yorba Linda, CA). Following a 10-min rest period, the second phase of exercise included an incremental exercise test to exhaustion to determine $\dot{V}O_{2max}$. This protocol commenced at an external work rate of 80 W and increased by 20 W/min until volitional exhaustion, in accordance with guidelines from the Canadian Society for Exercise Physiology (9).

Heat acclimation. Before experimentation, each participant performed 7 consecutive days of low-intensity cycling at 35°C and 35% relative humidity (RH) for 90 min/day to improve exercise tolerance and to minimize potential variance in the operational parameters of sudomotor activity (i.e., onset threshold and thermosensitivity) that could possibly explain differences in LSR between groups (45).

Experimental design. Experimental trials were separated by 2–3 days and were performed in a randomized, counterbalanced order at the same time of day to eliminate any systematic differences between groups due to circadian variation. Participants were asked to abstain from alcohol and caffeine, avoid strenuous exercise in the 12 h before each experimental session, and consume a light meal and 500 ml of water ~2 h before arriving at the laboratory. On arrival, each participant provided a urine sample, which was immediately analyzed for urine specific gravity (USG) to ensure preexercise hydration status was similar between groups. A USG cutoff value of 1.025 was enforced, as values below this threshold have been suggested to indicate normal hydration (28). Participants then inserted the rectal thermocouple, and, while wearing only a standardized pair of cotton running shorts, an initial body mass measurement was taken to determine the rate of $\dot{H}_{prod}$ for each Watt per kilogram trial. Next, the participants put on a pair of cotton socks and running shoes and sat on the ergometer while they were instrumented. Following 30 min of baseline data collection while seated on the ergometer, participants then performed 60 min of semirecumbent cycling in one of four experimental conditions: three trials in neutral ambient conditions (25.1 ± 0.5°C, 36.8 ± 12.7% RH, and 1.2 ± 0.1 m/s air velocity) at exercise intensities eliciting 500 W, 6.5 W/kg, or 9.0 W/kg of $\dot{H}_{prod}$, and one trial in the heat (34.7 ± 1.7°C, 34.1 ± 8.7% RH, and 1.1 ± 0.3 m/s air velocity) at 9.0 W/kg. This latter trial was performed to determine whether similar ΔT_{re} would be observed within each group in different, but compensable, ambient conditions that remained within the "prescriptive zone" (34). Two LG subjects could not complete the protocol in the heat and were, therefore, not included. Air flow was provided by three 46-cm mechanical fans stacked

vertically and positioned 1.25 m in front of the ergometer. By virtue of the targeted differences in body mass between LG and SM groups, comparisons of ΔT_{re} at $\dot{H}_{prod}$ of 600 W were also possible from data collected in the 6.5 W/kg and 9.0 W/kg trials in the LG and SM groups, respectively. Due to differences in BSA between LG and SM, LSR comparisons were possible at E_{req} of 165 and 190 W/m^2. Specifically, exercise at 500 W in LG and 6.5 W/kg in SM corresponded to an E_{req} of 165 W/m^2, while exercise at 6.5 W/kg for LG and 500 W for SM corresponded to an E_{req} of 190 W/m^2, in both groups. Cycling cadence was maintained at 80 revolutions/min in all trials. Core temperature, skin temperature (T_{sk}), and LSR on the upper back and forearm were measured continuously. Body mass measurements were taken in triplicate while clothed and fully instrumented immediately before exercise (i.e., as a baseline for WBSL estimations) and every 15 min throughout exercise, which required a 2-min break from cycling.

Instrumentation. Core temperatures were measured using general-purpose pediatric thermocouple probes (Mon-a-therm, Mallinckrodt Medical, St. Louis, MO). T_{re} was measured at a depth of 12 cm beyond the anal sphincter. Esophageal temperature (T_{es}) was measured at a maximum depth of ~40 cm (37) for the first 15 min of exercise to determine the sudomotor onset threshold and thermosensitivity (see below). Both T_{re} and T_{es} are expressed as changes from baseline (i.e., ΔT_{re} and ΔT_{es}). Skin temperature was measured at eight sites with thermistors integrated into 2.5-cm^2 heat flux sensors (Concept Engineering, Old Saybrook, CT). These sensors were affixed to the skin using double-sided adhesive disks (3M Health Care, Neuss, Germany) and surgical tape (Transpore, 3M, London, ON, Canada). Mean T_{sk} was calculated using weighting coefficients according to ISO 9886 (26): forehead, 0.07; shoulder, 0.07; triceps, 0.07; chest, 0.175; scapula, 0.175, hand, 0.05; thigh, 0.19; and calf, 0.20. Values for T_{sk} are reported as an average over the 60 min of exercise. Core temperature and T_{sk} were recorded with a data acquisition system (NI cDAQ-9172, National Instruments, Austin, TX) and LabView software (version 7.0, National Instruments, Austin, TX), sampled at 0.2 Hz.

Estimations of WBSR were made from changes in body mass every 15 min. Body mass was measured in triplicate using a platform scale accurate to the nearest ±2 g (Combics 2, Sartorius, Mississauga, ON, Canada) and corrected for metabolic mass loss and vapor losses from the respiratory tract (38). Values for WBSR are reported for each 15-min time period in grams per minute (g/min). Cumulative WBSL for the 60-min exercise period is also reported in grams.

LSR was measured using ventilated capsules (4.1 cm^2) placed on the forearm ~5 cm distal to the antecubital fossa and the upper back ~5 cm above the scapular spine over the trapezium, and secured with adhesive (Collodion HV, Mavidon Medical, Lake Worth, FL) and surgical tape. The flow of anhydrous air through each capsule was regulated at 1.80 l/min (FMA-A2307, Omega Engineering, Stamford, CT). The vapor concentration of effluent air was measured at 0.2 Hz using factory-calibrated capacitance hygrometers (HMT333, Vaisala, Vantaa, Finland). LSR is reported as the product of the vapor concentration and the flow rate, normalized to the skin surface area covered by the capsule, and expressed in milligrams per square centimeter per minute (mg·cm^{-2}·min^{-1}). The sudomotor onset threshold and thermosensitivity were determined via segmented regression using 1-min averages for the mean LSR response and ΔT_{es} (6).

Heat balance parameters. Heat balance parameters were estimated via partitional calorimetry and are presented as the mean value within each experimental condition. All heat exchange parameters were calculated in W/m^2, but are presented in W, W/m^2, or W/kg, where appropriate. Due to a minimal clothing ensemble, dry insulation and evaporative resistance of clothing were considered negligible.

The rate of metabolic energy expenditure (M) was estimated as:

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

where RER is the respiratory exchange ratio, and e_c and e_f represent the energy equivalent of carbohydrate (21.13 kJ) and fat (19.69 kJ), respectively, per liter of O_2 consumed (l/min). $\dot{H}_{prod}$ was determined as the difference between M and the external work rate (W):

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

Heat loss via radiation (R) was calculated as:

$$R = h_r \cdot (T_{sk} - T_a)(W/m^2) \quad (3)$$

where T_a denotes ambient temperature (°C), and h_r is the radiant heat transfer coefficient:

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

where ϵ is the emissivity of the skin (0.95), σ is the Stefan-Boltzmann constant ($5.67 \cdot 10^{-8}$ W·m^2·K^{-4}); BSA_r/BSA is the effective radiant surface area (ND), equal to 0.70 (31); and T_r is the mean radiant temperature, assumed to be equivalent to T_a (°C). Convective heat exchange from the skin, C, was calculated as:

$$C = h_c \cdot (T_{sk} - T_a)(W/m^2) \quad (5)$$

where h_c is the convective heat transfer coefficient for a seated individual facing an air velocity (v) between 0.2 and 4.0 m/s (41):

$$h_c = 8.3 \cdot v^{0.6}(W \cdot m^{-2} \cdot K^{-1}) \quad (6)$$

Respiratory heat losses through evaporation (E_{res}) and convection (C_{res}) were determined by:

$$E_{res} + C_{res} = 0.0173 \cdot (\dot{H}_{prod}) \cdot (5.87 - P_a) + 0.0014 \cdot (\dot{H}_{prod}) \cdot (34 - T_a)(W/m^2) \quad (7)$$

where P_a is the ambient vapor pressure (kPa). The E_{req} was calculated as:

$$E_{req} = \dot{H}_{prod} - (C + R + C_{res} + E_{res})(W/m^2) \quad (8)$$

Statistical analysis. Mean participant characteristics were compared using independent-samples t-tests. Data for ΔT_{re} and LSR were analyzed as 5-min averages ending at 0, 15, 30, 45, and 60 min of exercise. For each $\dot{H}_{prod}$, a two-way mixed-model ANOVA with the repeated factor of time (five levels: baseline, 15, 30, 45, 60 min) and the nonrepeated factor of body size (two levels: LG and SM) were performed to compare ΔT_{re}, WBSR, and LSR with a Bonferroni correction for multiple comparisons (i.e., at each time point). Independent-samples t-tests were used for single comparisons of heat balance parameters, $\%\dot{V}O_{2max}$, 60-min ΔT_{re}, T_{sk}, and cumulative WBSL, as well as sudomotor onset threshold and thermosensitivity. All statistical analyses were performed with GraphPad Prism (version 6.0, GraphPad Software, La Jolla, CA). All data are expressed as means ± SD. P values ≤ 0.05 were considered statistically significant.

RESULTS

Participant characteristics. Mean participant characteristics are presented in Table 1. No differences in age ($P = 1.000$) existed between groups. Body mass ($P < 0.001$), height ($P = 0.017$), BSA ($P < 0.001$), and body fat percentage ($P < 0.001$) were greater in LG, while relative $\dot{V}O_{2max}$ (expressed in ml·kg^{-1}·min^{-1}) was higher in SM ($P = 0.019$). Preexperimental USG was similar between groups in each trial, with mean

Table 1. *Mean participant characteristics*

	Age, yr	Mass, kg	Height, m	BSA, m^2	Body Fat, %	$\dot{V}O_{2max}$, $ml \cdot kg^{-1} \cdot min^{-1}$
LG	24.4 ± 4.2	91.5 ± 6.8*	1.81 ± 0.05*	2.12 ± 0.09*	22.0 ± 5.2*	44.8 ± 6.2*
SM	24.2 ± 4.8	67.6 ± 5.6	1.73 ± 0.06	1.80 ± 0.09	12.5 ± 2.6	52.9 ± 4.2

Values are means ± SD. LG, large body size group; SM, small body size group; BSA, body surface area; $\dot{V}O_{2max}$, maximum rate of oxygen uptake. *Significantly different from SM group ($P < 0.05$).

values of 1.019 ± 0.006 and 1.015 ± 0.008 in LG and SM, respectively.

T_{re}. In the fixed absolute $\dot{H}_{prod}$ trials of 500 and 600 W (Fig. 1), end-exercise ΔT_{re} after 60 min was significantly greater in SM at both 500 W (LG: 0.52 ± 0.15°C, SM: 0.92 ± 0.24°C; $P < 0.001$) and 600 W (LG: 0.78 ± 0.19°C, SM: 1.14 ± 0.24°C; $P = 0.007$). Differences in ΔT_{re} were observed between groups from 30 min of exercise onwards in both trials. Due to differences in body mass, the corresponding W/kg was greater in SM at both 500 W ($P < 0.001$) and 600 W ($P < 0.001$). Furthermore, the relative exercise intensity ($\%\dot{V}O_{2max}$) was higher in SM at 500 W ($P = 0.038$) and tended to be higher at 600 W ($P = 0.053$).

In contrast, when comparing SM and LG groups at the same fixed $\dot{H}_{prod}$ per unit mass trials of 6.5 and 9.0 W/kg (Fig. 1), end-exercise ΔT_{re} after 60 min was similar between groups at both 6.5 W/kg (SM: 0.85 ± 0.14°C, LG: 0.79 ± 0.21°C; $P = 0.433$) and 9.0 W/kg (SM: 1.14 ± 0.24°C, LG: 1.02 ± 0.22°C; $P = 0.303$). Furthermore, no differences in ΔT_{re} were observed between SM and LG at any time at 6.5 W/kg ($P = 0.129$) or 9.0 W/kg ($P = 0.635$). While there were no differences in ΔT_{re}, the corresponding absolute $\dot{H}_{prod}$ in W were higher in LG due to their greater mass at both 6.5 W/kg ($P < 0.001$) and 9.0 W/kg ($P < 0.001$). The $\%\dot{V}O_{2max}$ was also greater in LG at 6.5 W/kg ($P = 0.019$) and 9.0 W/kg ($P = 0.002$).

When exercise at 9.0 W/kg was repeated in a hotter environment (35°C), a similar ΔT_{re} was observed over time relative to a neutral environment (25°C) within both the LG ($P = 0.398$) and SM ($P = 0.646$) groups (Fig. 2).

WBSR and LSR. Absolute E_{req} was ~340 W for both LG and SM at a fixed $\dot{H}_{prod}$ of 500 W ($P = 0.330$), and absolute E_{req} was ~400 W for both LG and SM at a fixed $\dot{H}_{prod}$ of 600 W ($P = 0.453$). In parallel, similar WBSR values were observed between groups in both trials (Fig. 3), resulting in almost

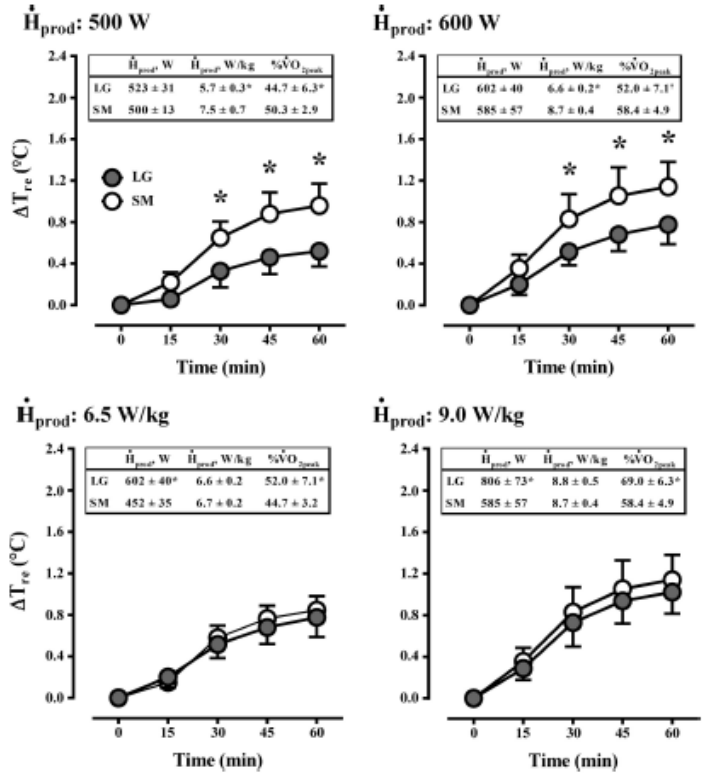

Fig. 1. Changes in rectal temperature (ΔT_{re}) in large (LG) and small (SM) groups during exercise at fixed rates of heat production (H_{prod}) in Watts (W; 500 and 600 W) and Watts per unit of total body mass (W/kg; 6.5 and 9.0 W/kg). Values are means ± SD. Tables at *top* indicate mean ± SD for H_{prod} and relative exercise intensity ($\%\dot{V}O_{2peak}$). *Significant difference between LG and SM ($P \leq 0.05$). †$P = 0.053$.

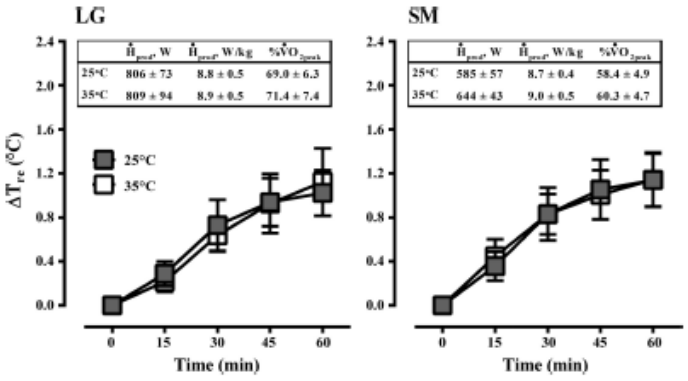

Fig. 2. ΔT_{re} during exercise at 9.0 W/kg in 25 and 35°C between LG (n = 6; *A*) and SM (n = 8; *B*) groups. Values are means ± SD. Tables at *top* indicate mean ± SD for $\dot{H}_{prod}$ and $\%\dot{V}O_{2peak}$.

identical cumulative WBSL values at an E_{req} of 340 W (LG: 383 ± 108 g, SM: 380 ± 52 g; P = 0.956) and 400 W (LG: 473 ± 156 g, SM: 493 ± 65 g; P = 0.734). At 6.5 and 9.0 W/kg, WBSR was greater in the LG group in parallel to a higher absolute E_{req} in the LG group in both conditions (Fig. 3), leading to greater cumulative WBSL in the LG compared with the SM group at 6.5 W/kg (LG: 473 ± 156 g, SM: 298 ± 35 g; P = 0.008) and 9.0 W/kg (LG: 774 ± 210 g, SM: 493 ± 65 g; P = 0.003). Although $\dot{H}_{prod}$ and ΔT_{re} were similar between groups, absolute E_{req} was higher in the heat for both LG (35°C: 792 ± 83 W, 25°C: 575 ± 73 W; $P < 0.001$) and SM groups (35°C: 585 ± 60 W, 25°C: 391 ± 44 W; $P < 0.001$). Accordingly, cumulative WBSL was greater in the heat for LG (35°C: 1,067 ± 218 g, 25°C: 774 ± 210 g; $P < 0.001$) and SM (35°C: 817 ± 159 g, 25°C: 493 ± 65 g; $P < 0.001$) groups.

Despite similar WBSR and WBSL values, LSR was greater in the SM group when absolute E_{req} was 340 W (P = 0.007) and 400 W (P = 0.032) (Fig. 4). These greater LSR values in the SM group at the same absolute E_{req} corresponded with a greater E_{req} in W/m^2 in the SM group in both cases (Fig. 4). In contrast, when comparing LG and SM groups at the same E_{req} values in W/m^2, no differences in LSR were evident throughout exercise at an E_{req} of 165 or 190 W/m^2, despite very different absolute E_{req} values in W in both conditions (Fig. 4). After 60 min of exercise, LSR was similar between groups at an E_{req} of 165 W/m^2 (LG: 0.28 ± 0.06 mg·cm^{-2}·min^{-1}, SM:

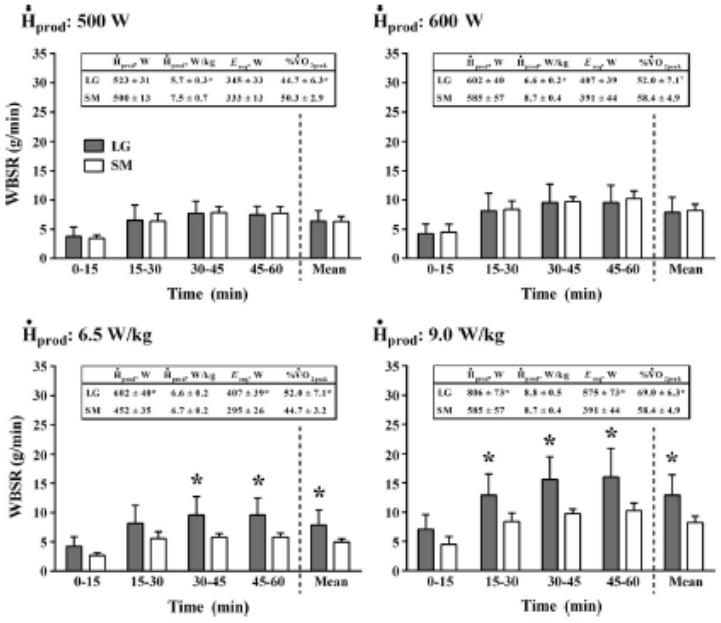

Fig. 3. Whole body sweat rate (WBSR) at fixed rates of $\dot{H}_{prod}$ in W (500 and 600 W) and W/kg (6.5 and 9.0 W/kg) in LG and SM groups. Values are means ± SD. Tables at *top* indicate mean ± SD for $\dot{H}_{prod}$ in W and W/kg, absolute evaporation required for heat balance (E_{req}; in W), and $\%\dot{V}O_{2peak}$ for each condition. *Significant difference between LG and SM ($P \leq 0.05$). †P = 0.053.

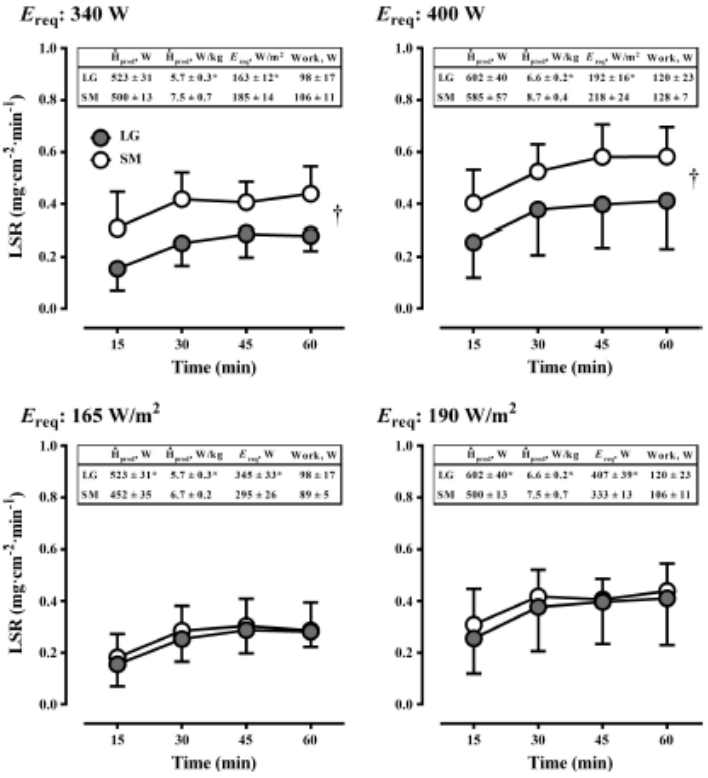

Fig. 4. Mean local sweat rate (LSR) at rates of E_{req} of 340 W, 400 W, 165 W/m^2, and 190 W/m^2 in LG and SM groups. Values are means ± SD. Tables at *top* indicate mean ± SD for $\dot{H}_{prod}$ in W and W/kg, the corresponding E_{req} in W or W/m^2, and work rate for each E_{req}. *Significant difference between LG and SM. †Significant main effect of body size ($P \leq 0.05$).

0.28 ± 0.12 mg·cm^{-2}·min^{-1}; $P = 0.988$) and 190 W/m^2 (LG: 0.41 ± 0.18 mg·cm^{-2}·min^{-1}, SM: 0.37 ± 0.15 mg·cm^{-2}·min^{-1}; $P = 0.902$).

Onset threshold and thermosensitivity. The mean LSR response relative to ΔT_{es} is shown in Fig. 5, and the onset threshold ΔT_{es} and thermosensitivity of the mean LSR response are presented in Table 2. In support of our aim to ensure that no differences in the physiological control parameters for sudomotor activity existed between the SM and LG group, neither the onset threshold ΔT_{es} ($P \geq 0.360$) nor thermosensitivity ($P \geq 0.351$) of the mean LSR response was different between groups during any of the experimental trials.

Mean T_{sk}. Values for T_{sk} were similar between groups at $\dot{H}_{prod}$ of 500 W (LG: 31.31 ± 0.52°C, SM: 31.30 ± 0.48°C; $P = 0.965$), 600 W (LG: 31.39 ± 0.45°C, SM: 31.54 ± 0.40°C; $P = 0.493$), and 6.5 W/kg (LG: 31.39 ± 0.45°C, SM: 31.02 ± 0.50°C; $P = 0.139$). A higher T_{sk} was observed in LG at 9.0 W/kg in 25°C (LG: 32.10 ± 0.40°C, SM: 31.54 ± 0.40°C; $P = 0.016$). Similar T_{sk} were also observed at each E_{req} of 165 W/m^2 (LG: 31.31 ± 0.52°C, SM: 31.02 ± 0.50°C; $P = 0.275$) and 190 W/m^2 (LG: 31.39 ± 0.45°C, SM: 31.30 ± 0.48°C; $P = 0.692$).

DISCUSSION

The present study clearly demonstrates that a large difference in body mass systematically alters ΔT_{re} during exercise at a fixed $\dot{H}_{prod}$ (in W; Fig. 1) between independent groups that are otherwise matched for age, sex, heat acclimation status, and physiologically identical in terms of their control parameters for sudomotor activity (i.e., onset threshold and thermosensitivity; Fig. 5, Table 2). However, when an exercise intensity eliciting a fixed $\dot{H}_{prod}$ per unit mass is prescribed (W/kg; Figs. 1 and 2), the systematic difference in ΔT_{re} is eliminated, despite differences in body mass, absolute $\dot{H}_{prod}$ (in W), and relative exercise intensity (%$\dot{V}o_{2max}$). The present study also demonstrates that, despite an almost identical WBSR (in g/min) between groups differing greatly in BSA during exercise at a fixed absolute E_{req} (in W; Fig. 3), as would be expected given the recent findings of Gagnon et al. (16), LSR measured with a ventilated sweat capsule (in mg·cm^{-2}·min^{-1}) is systematically greater in the group with a smaller BSA (Fig. 4). However, when an exercise intensity eliciting a fixed E_{req} per unit surface area (in W/m^2) is prescribed, changes in LSR throughout 60 min of exercise are the same (Fig. 4), despite different BSA and absolute E_{req} in W. These findings demonstrate that future studies aiming to isolate the independent influence of a particular physiological factor (e.g., age, sex, injury, autonomic diseases) on thermoregulatory responses by comparing ΔT_{re} and LSR between experimental and control groups unmatched for body mass and BSA should use a fixed $\dot{H}_{prod}$ in W/kg for ΔT_{re} comparisons and a fixed E_{req} in W/m^2 for LSR comparisons. It follows that, if different ΔT_{re} or LSR responses are subsequently

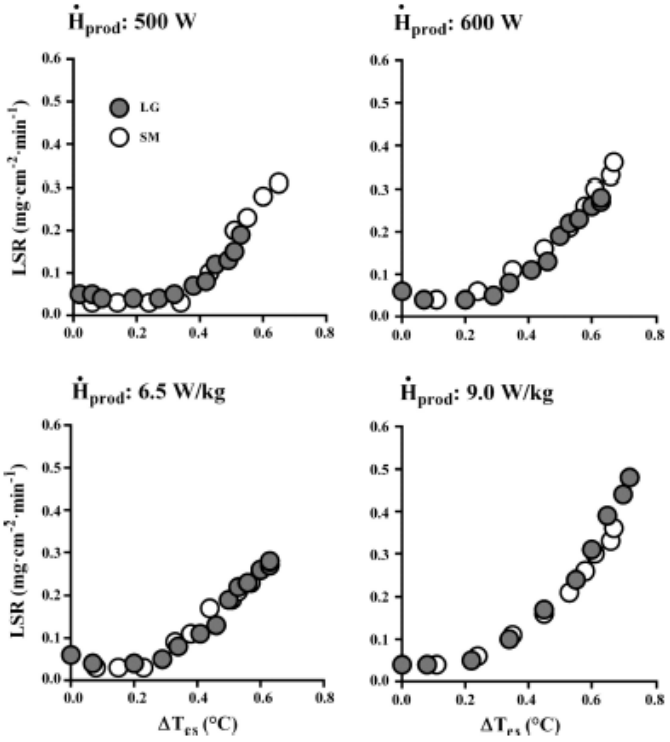

Fig. 5. Mean LSR in LG and SM groups, expressed relative to the change in esophageal temperature (ΔT_{es}), during the first 15 min of exercise at intensities eliciting 500 W, 600 W, 6.5 W/kg, and 9.0 W/kg of $\dot{H}_{prod}$. Error bars have been excluded for clarity.

observed, they can be confidently attributed to the physiological factor under examination and are not a consequence of an inherent bias arising from the prescription of exercise intensity, such as with the $\%\dot{V}O_{2max}$ approach (27).

Core temperature. From a biophysical perspective, different changes in core temperature will arise from differences in heat storage (cumulative differences between $\dot{H}_{prod}$ and heat dissipation throughout exercise), body composition, or body mass. In the present study, the greater ΔT_{re} observed in the SM group at the same absolute rates of $\dot{H}_{prod}$ (Fig. 1) is directly explained by the influence of body mass per se and not by any differences in heat dissipation or body composition. First, while factors such as age (32), sex (17), and heat acclimation status (42) are known to alter thermoeffector responses, sudomotor control, and heat dissipation, all of these factors were controlled in the present study. Second, at a $\dot{H}_{prod}$ of both 500 and 600 W, no differences in T_{sk} and, therefore, dry heat loss were evident between groups, resulting in a similar absolute E_{req} and, therefore, the same WBSR (Fig. 3) and presumably evaporation. Although a high body fat percentage may alter core temperature changes due to a lower average specific heat capacity of adipose tissue (1), a nearly twofold difference (11.9 vs. 22.2%) in body fat percentage does not alter ΔT_{re} in mass-matched participants exercising at the same absolute $\dot{H}_{prod}$ (27). As such, it is unlikely that the difference in body fat percentage between LG and SM (Table 1) contributed to the observed difference in ΔT_{re}. While it may be possible that much larger differences in body fat percentage alter changes in core temperature, the independent influence of high vs. low adiposity (i.e., while controlling for $\dot{H}_{prod}$ and body mass) has not yet been evaluated and merits further investigation.

By prescribing the same $\dot{H}_{prod}$ in W/kg, the influence of body mass is effectively normalized, resulting in similar ΔT_{re} between two groups, despite a 23.9-kg difference in body mass (Fig. 1). A retrospective assessment of data from previous studies examining core temperature responses over a range of

Table 2. *Onset threshold and thermosensitivity of the mean local sweat rate response*

	500 W		600 W		6.5 W/kg		9.0 W/kg	
	LG	SM	LG	SM	LG	SM	LG	SM
Onset threshold, °C	0.35 ± 0.16	0.41 ± 0.17	0.40 ± 0.10	0.44 ± 0.21	0.40 ± 0.10	0.38 ± 0.16	0.35 ± 0.11	0.44 ± 0.21
Thermosensitivity, mg·cm^{-2}·min^{-1}·°C^{-1}	0.79 ± 0.32	1.07 ± 0.43	0.99 ± 0.33	1.02 ± 0.29	0.99 ± 0.33	0.91 ± 0.46	1.21 ± 0.76	1.02 ± 0.29

Values are means ± SD.

relative intensities (i.e., $\%\dot{V}o_{2max}$) in groups unmatched for aerobic fitness and body mass also supports the use of the W/kg method for eliminating systematic differences in ΔT_{re}. For example, aerobically trained individuals exercising at 50% $\dot{V}o_{2max}$ demonstrated a similar rate of $\dot{H}_{prod}$ (~9.0 W/kg) and ΔT_{es} (~0.8°C) as aerobically untrained individuals exercising at 70% $\dot{V}o_{2max}$, despite an 8.2-kg difference in body mass between groups (13). Similarly, a closer look at the data of Mora-Rodriguez et al. (39) reveals a ΔT_{re} of ~0.6°C in trained and untrained groups of dissimilar mass (10-kg difference) cycling at 40% and 60% $\dot{V}o_{2max}$, respectively, which actually corresponded to a $\dot{H}_{prod}$ of ~8.2 W/kg in both groups. As noted by Jay et al. (27), it follows that different changes in core temperature attributed to some physiological effect [e.g., age (24, 50), aerobic fitness (19, 39, 44), burn injury (36)] may be explained simply by differences in W/kg of as little as 1.8 W/kg (Fig. 1). Therefore, a reevaluation of some of these potential physiological alterations to heat balance may be warranted. To further demonstrate the validity of the W/kg approach, an additional trial was performed at 9.0 W/kg in a hotter environment (35°C) but within the classical prescriptive zone (34). For both the LG and SM groups, ΔT_{re} was the same compared with 25°C (Fig. 2), with a compensatory rise in sweating and evaporative heat loss in association with the higher E_{req} (34, 40).

The present data provide further evidence that a $\%\dot{V}o_{2max}$ approach is not appropriate for comparing changes in core temperature between individuals and groups of different $\dot{V}o_{2max}$ (27). The LG group had a lower $\dot{V}o_{2max}$ than the SM group (Table 1), and while exercise at 500 and 600 W resulted in a higher $\%\dot{V}o_{2max}$ and a greater ΔT_{re} in SM in both cases (Fig. 1), exercise at 6.5 and 9.0 W/kg resulted in a significantly greater $\%\dot{V}o_{2max}$ in LG, but no differences in ΔT_{re} (Fig. 1). Furthermore, although it may be argued that there was a slightly greater end-exercise ΔT_{re} in the SM group at 6.5 and 9.0 W/kg, $\%\dot{V}o_{2max}$ was in fact lower in the SM group, which, according to conventional wisdom, should have led to a lower, not a higher, change in core temperature. Nevertheless, two points regarding the prescription of $\%\dot{V}o_{2max}$ should be noted. First, the prescription of $\%\dot{V}o_{2max}$ may be used without concern in a within-subjects (repeated measures) experimental design to compare changes in core temperature, provided that the rate of $\dot{H}_{prod}$ is not altered between conditions. Second, it is possible that, despite differences in $\dot{V}o_{2max}$ and body mass between groups, combinations of these factors may yield a similar $\dot{H}_{prod}$ in W/kg, and, therefore, core temperature changes during exercise at a fixed $\%\dot{V}o_{2max}$. However, by maintaining a fixed $\dot{H}_{prod}$ in W/kg, irrespective of relative exercise intensity, the present approach ensures an unbiased comparison at all combinations of $\dot{V}o_{2max}$ and body mass. This approach may be especially useful in studies comparing core temperature responses during weight-bearing exercise (e.g., walking and running), during which $\dot{H}_{prod}$ varies with body mass, and a high interindividual variability in movement economy at a given speed is often observed. Future studies should evaluate the present approach for between-groups comparisons during treadmill exercise.

Sweating. Gagnon et al. (16) recently demonstrated that absolute E_{req} (in W) is the principal determinant of WBSR (in g/min), irrespective of $\%\dot{V}o_{2max}$. Accordingly, WBSR was similar between the SM and LG groups at an E_{req} of 340 W ($\dot{H}_{prod}$: 500 W) and 400 W ($\dot{H}_{prod}$: 600 W), despite greater $\%\dot{V}o_{2max}$ in the SM group, while differences in body mass led to greater absolute E_{req} and WBSR in the LG group at 6.5 and 9.0 W/kg (Fig. 3). However, at an absolute E_{req} of 340 and 400 W, greater mean LSR values (in $mg \cdot cm^{-2} \cdot min^{-1}$) were observed in the SM group (Fig. 4), demonstrating that the conclusions of Gagnon et al. (16) do not necessarily hold for measurements of local sudomotor activity in individuals of different morphological characteristics. Although it has been suggested that LSR is determined by the absolute external work rate (46), there were no differences in work rate between groups at either fixed absolute E_{req} value (Fig. 4). Therefore, the differences in LSR between groups at the same absolute E_{req} are attributed to the influence of body size alone. Considering that LSR is measured across a fixed surface area, it is most logical that this influence is related to BSA; that is, at a given absolute E_{req}, the same absolute rate of sweat production (in g/min) must be secreted over a smaller surface area in the SM group; therefore, the mean rate of sweating per unit area (in $mg \cdot cm^{-2} \cdot min^{-1}$) should be greater with a smaller BSA. For the purpose of comparing LSR responses between groups unmatched for BSA, this systematic difference in LSR due to differences in BSA at a fixed absolute E_{req} can theoretically be removed by prescribing the same E_{req} per unit of BSA (in W/m^2). In the present study, this notion is strongly supported by the similar mean LSR values during exercise at E_{req} values of 165 and 190 W/m^2 (Fig. 4), despite differences in absolute E_{req} and BSA. By removing this systematic difference in LSR due to differences in BSA between groups, researchers can isolate the independent influence of physiological factors on local sudomotor activity, since any difference will be due to the factor under investigation, as opposed to inherent bias associated with the exercise intensity prescribed.

Perspectives. Although previous research has clearly highlighted the importance of changes in core temperature and T_{sk} for sudomotor control (4), the present study emphasizes the large influence of biophysical factors on ΔT_{re}, WBSR, and LSR among individuals of different morphological characteristics (Table 1) but identical functional parameters for the physiological control of sudomotor activity (Fig. 5, Table 2). In participants unmatched for mass and BSA, separate experimental approaches are necessary to isolate the influence of other factors that are different between participants on ΔT_{re}, WBSR, and LSR. For example, WBSR should be compared between groups using a fixed absolute E_{req} in W (16), whereas a fixed $\dot{H}_{prod}$ in W/kg is most appropriate for comparing core temperature changes between groups. The latter, however, would not be valid for simultaneous comparisons of WBSR between groups of dissimilar mass, because absolute E_{req} (in W) would be different. Similarly, LSR can only be compared using a fixed E_{req} in W/m^2, so, if groups are of dissimilar mass, WBSR could not be independently compared, whereas changes in core temperature could only be compared if groups had similar BSA-to-mass ratios, since a fixed W/m^2 would simultaneously yield the same W/kg between groups.

Finally, the present findings may only be applicable in compensable conditions. In an uncompensable environment [i.e., E_{req} exceeds the maximum potential for evaporation (E_{max})] differences in BSA-to-mass ratio will raise E_{req} (in W/m^2) in larger individuals for a given $\dot{H}_{prod}$ in W/kg, while E_{max} is unchanged. The greater difference between E_{req} and

E_{max} in larger individuals should theoretically result in a higher rate of heat storage; however, this remains to be experimentally proven.

Conclusion. In conclusion, to prevent the introduction of systematic bias to an experimental design related to differences in $\dot{H}_{prod}$ and body morphology, the present data suggest that exercise should be prescribed to elicit the same $\dot{H}_{prod}$ in W/kg to compare changes in core temperature and the same E_{req} in W/m^2 to compare LSR responses. These approaches may be particularly useful for researchers investigating thermoregulatory responses between healthy/control and special populations that may potentially demonstrate impaired heat dissipation secondary to alterations in thermoeffector function, such as diseases that lead to autonomic dysfunction (e.g., multiple sclerosis) or injuries that dennervate sweat glands (e.g., spinal cord injury).

APPENDIX

Prescribing Exercise Intensity to Elicit a Fixed $\dot{H}_{prod}$

Step 1. During a preexperimental visit, height and body mass must first be measured if prescribing $\dot{H}_{prod}$ in W/kg. BSA can be estimated using equation of DuBois and DuBois (12).

Step 2. Before testing, identify the target absolute $\dot{H}_{prod}$ (in W) to be used. For example, if a fixed $\dot{H}_{prod}$ of 7.0 W/kg is required and the individual is 75 kg, the target absolute $\dot{H}_{prod}$ is $7.0 \times 75 = 525$ W.

Step 3. The exercise intensity required to elicit each target absolute $\dot{H}_{prod}$ may be estimated from the relationship between the $\dot{V}O_2$ and external work rate. To establish this relationship, have each participant perform a submaximal incremental exercise test that includes a range of work rates that will incorporate the experimental target absolute $\dot{H}_{prod}$. The work rates in this test may be estimated based on pilot testing, previous research, or, in the case of cycling, assumed gross efficiency values. For example, if $\dot{H}_{prod}$ values of 400 and 600 W will be targeted, assuming a gross efficiency of 17% (14), work rates of ~80 and ~125 W, respectively, would be expected. Therefore, during the preliminary test, the initial work rate may be set to 80 W and increased by 20 W/stage for four stages (i.e., up to 140 W) to include all estimated target work rates. The duration of each stage should be sufficient to attain steady-state $\dot{V}O_2$ values (i.e., 3–5 min). Metabolic data (i.e., $\dot{V}O_2$ and RER) should be collected throughout this test.

Step 4. Take the final 1-min (i.e., steady-state) $\dot{V}O_2$ value of each stage and, using conventional equations (i.e., *Eq. 1* in METHODS), calculate M and then subtract W to obtain $\dot{H}_{prod}$ for each stage. As the $\dot{H}_{prod}$-work rate relationship is linear at submaximal intensities (2), the work rate required to elicit each target absolute $\dot{H}_{prod}$ may be estimated using the equation of a straight line ($y = mx + b$). It is also important to note the corresponding $\dot{V}O_2$ value for each required work rate.

Step 5. During experimentation, set the initial work rate as that predicted to elicit the target absolute $\dot{H}_{prod}$. The actual $\dot{H}_{prod}$ should be verified using real-time $\dot{V}O_2$ measurements, with slight work rate adjustments potentially necessary to ensure a constant $\dot{H}_{prod}$ throughout exercise. To this end, it is crucial that $\dot{V}O_2$ is monitored closely.

Prescribing Exercise Intensity to Elicit a Fixed E_{req}

Since E_{req} is primarily determined by $\dot{H}_{prod}$ (see *Eq. 8* in METHODS), prescribing work rates that elicit a fixed $\dot{H}_{prod}$ in W or $\dot{H}_{prod}$ in W/m^2 should result in fixed E_{req} in W or E_{req} in W/m^2, respectively, provided that the experimental environmental conditions (ambient temperature, air velocity) are constant. To calculate the actual E_{req}, dry and respiratory heat exchange must be calculated using mean T_{sk}, air velocity, and ambient temperature measurements (see *Eqs. 3–7* in METHODS).

ACKNOWLEDGMENTS

This study was performed by M. N. Cramer in partial fulfillment of the degree Doctor of Philosophy from the University of Ottawa. The authors thank the volunteers for participation, Zuzana Novak for assistance with data collection, Dr. Éric Doucet for use of the DXA scanner, and Isabelle LaForest for performing DXA scans.

GRANTS

This research was supported by a Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant (no. 386143-2010, O. Jay). M. N. Cramer is supported by a University of Ottawa Excellence Scholarship and a NSERC Postgraduate Scholarship (PGS-D).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: M.N.C. and O.J. conception and design of research; M.N.C. performed experiments; M.N.C. analyzed data; M.N.C. and O.J. interpreted results of experiments; M.N.C. prepared figures; M.N.C. and O.J. drafted manuscript; M.N.C. and O.J. edited and revised manuscript; M.N.C. and O.J. approved final version of manuscript.

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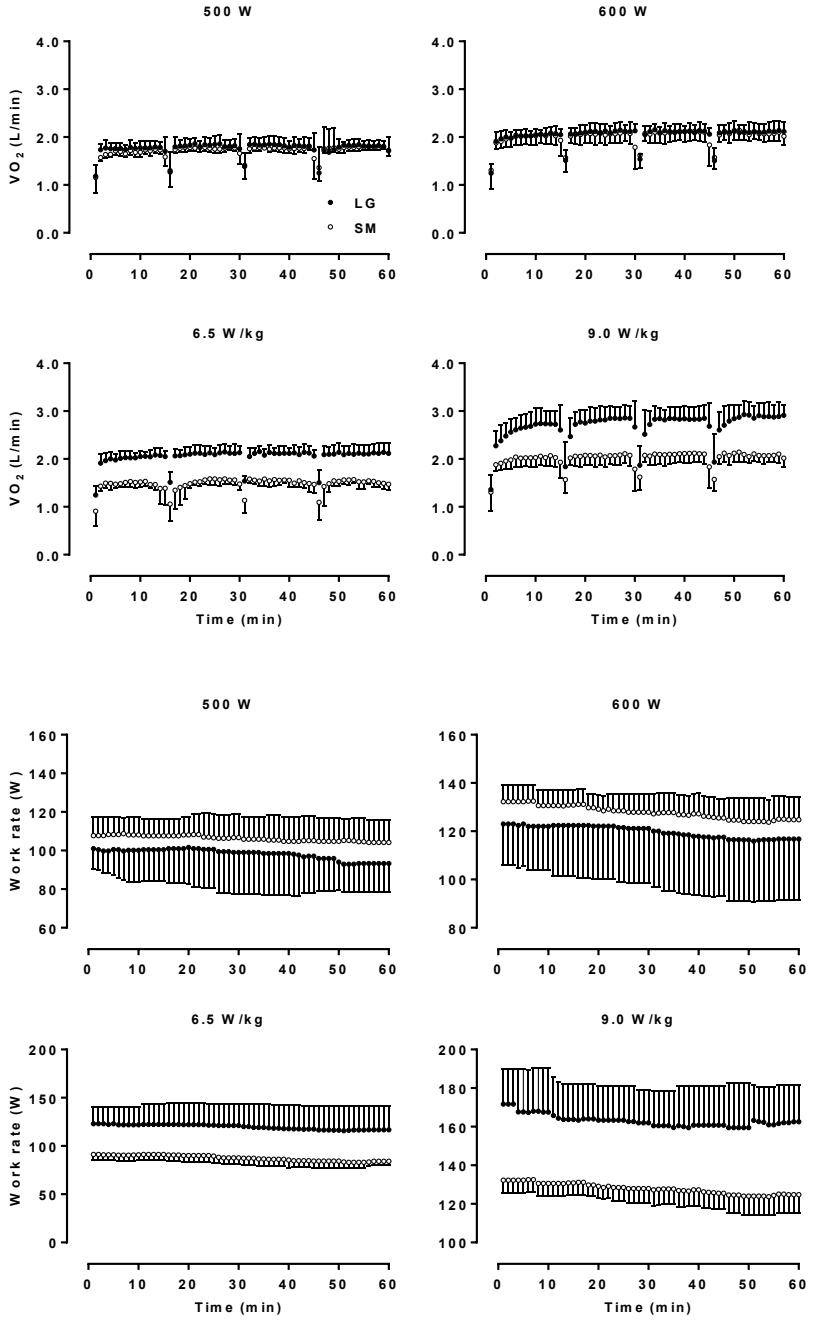
APPENDIX C: Additional figures from thesis article #1.



Trial	Group	VO_2, L/min	RER	M, W
500 W	LG	1.81 ± 0.13	0.89 ± 0.04	620 ± 42
	SM	1.76 ± 0.05	0.91 ± 0.04	605 ± 14
Trial	Group	VO_2, L/min	RER	M, W
600 W	LG	2.11 ± 0.15	0.88 ± 0.05	721 ± 50
	SM	2.06 ± 0.17*	0.89 ± 0.04	709 ± 59
Trial	Group	VO_2, L/min	RER	M, W
6.5 W/kg	LG	2.11 ± 0.15*	0.88 ± 0.05	721 ± 50*
	SM	1.58 ± 0.10	0.88 ± 0.03	539 ± 34
Trial	Group	VO_2, L/min	RER	M, W
9.0 W/kg	LG	2.81 ± 0.26*	0.91 ± 0.04	968 ± 85*
	SM	2.06 ± 0.17	0.89 ± 0.04	709 ± 59

Figure. Changes in VO_2 (*top four panels*) and external work rate (*bottom four panels*) in four experimental trials at 25°C. Table also lists corresponding respiratory exchange ratio (RER) and metabolic rate (M; watts) values. Work rate adjustments were necessary to ensure relatively constant VO_2, and therefore M and heat production values.

APPENDIX D: Editorial accompanying published version of thesis article #1

J Appl Physiol 116: 1121–1122, 2014;
doi:10.1152/japplphysiol.00248.2014.

Invited Editorial

Match maker: how to compare thermoregulatory responses in groups of different body mass and surface area

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THERE IS A LONG AND RICH HISTORY of research comparing thermoregulatory responses between groups of different sex, age, and health. Direct measurements of body temperature, whole body, and local sudomotor activity are the basic tools used by thermal and exercise physiologists to understand and interpret group differences in central and peripheral thermoregulation. A qualitative appreciation for how differences in physical characteristics and fitness between groups can impact thermoregulation drove the historical adoption of imperfect matching solutions meant to isolate factors of interest. A popular example, such as matching relative exercise intensity to control for fitness, does not seem necessary for making unbiased comparisons (6). The >30 yr time span of excellent reviews on the topic of sex differences in thermoregulation (5, 7) represents well the enduring problem; how should thermoregulatory responses be compared between any two groups with inherent or chance differences in physical characteristics that influence thermoregulation?

In this issue of the *Journal of Applied Physiology*, Cramer and Jay (1) provide for the first time a clear quantitative explanation for the important independent influences of body mass and body surface area on thermoregulatory outcome measures of change in body core temperature (ΔT_{re}) and local sweating rate (LSR) during exercise in two compensable environments (25–35°C, 35% relative humidity). They also provide the necessary methodology for selecting an exercise intensity that remedies the historically confounding effects of body morphology. Briefly, the greater heat sink of individuals with larger body mass in their study (~92 kg, LG) resulted in a smaller ΔT_{re} at any absolute rate of metabolic heat production (H_{prod}, W) compared with smaller individuals (~68 kg, SM). Despite this fact, whole body sweating rates (WBSR) were the same because the absolute evaporative sweating requirement (E_{req}, W) was identical for both groups, as previously described (4). As a consequence of having a smaller body surface area in SM (1.8 m^2) compared with LG (2.1 m^2), LSR was significantly higher in SM (LSR expressed as a rate in surface area units by convention). On the surface, outcomes make it appear that LG is less susceptible to heat stress than SM (lower ΔT_{re}), but whether LG sweats at the same rate (WBSR) or less (LSR) than SM depends on which sweating measure is chosen for comparison. It is equally puzzling to decide how best to fairly compare the LSR threshold (T_{re} onset) and sensitivity (LSR slope) between LG and SM in this scenario. The remedy that Cramer and Jay (1) provide for the inconsistent measurement outcomes is to prescribe exercise intensity as either watts per kilogram to control for the effects of body mass on ΔT_{re} (heat sink) or as E_{req} (W/m^2) to control for the effects of surface area on LSR. When LG and SM were compared by matching for watts per kilogram and watts per square meter, differences in ΔT_{re} and LSR disappeared. Figure 1 summarizes how to select exercise intensity to control for ΔT_{re} (H_{prod}; W/kg), WBSR (E_{req}; W), or LSR (E_{req}; W/m^2) when a factor distinct from body mass and surface area is suspected to independently influence central or peripheral thermoregulation.

One obvious application of this research is that it will allow an improved isolation of the factors known or suspected to genuinely influence thermoregulation, thus ultimately enhancing the science and understanding of group differences in human thermoregulation. Good examples include comparisons between groups of different body size, such as men vs. women and especially children vs. adults. A less obvious application is that their methods might also be used to help fairly isolate and understand factors responsible for heat illness susceptibility. For example, absolute workload tests (H_{prod}, W) for assessing heat intolerance (i.e., ΔT_{re} response) (2) might further be improved by use of a more standardized test (H_{prod}, W/kg) that removes the influence of body mass from the observation.

A minor limitation of this study is that not everyone interested in comparing thermoregulation between groups will be well versed or practiced in the use of the biophysics equations necessary for applying some of the methods. For example, although absolute H_{prod} expressed in watts or watts per kilogram is a fairly straightforward set of calculations, the string of necessary biophysical calculations needed to use the required evaporative heat loss, or E_{req}, can be daunting for anyone unaccustomed to their use and meaning. However, an excellent review on this subject (3) will educate readers and provides all the formulas necessary for easy input and automated output using an Excel module or similar software package. In addition, although it is likely that the approach described (Fig. 1) will improve comparisons between groups made during uncompensable heat stress also, it remains possible that smaller vapor pressure gradients between skin and air will suppress sweating and alter the anticipated group differences that otherwise require correction during compensable heat stress (1, 3, 5).

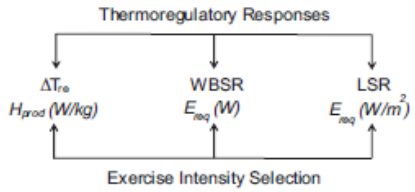

Fig. 1. Correct exercise intensity selection for unbiased comparisons of thermoregulatory responses in groups of different body mass and surface area. ΔT_{re}, change in body core temperature; H_{prod}, metabolic heat production; WBSR, whole body sweating rates; E_{req}, evaporative sweating requirement; LSR, local sweating rate.

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In summary, thermoregulatory responses between any two groups with inherent or chance differences in body mass and surface area can be fairly compared in accordance with the matching methods described by Cramer and Jay (1) (Fig. 1). Widespread application of these techniques is recommended when attempting to isolate and describe the unique role(s) that sex, age, health, and other factors play in affecting thermoregulation.

ACKNOWLEDGMENTS

The opinions or assertions contained herein are the private views of the authors and should not be construed as official or reflecting the views of the Army the Department of Defense.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: S.N.C. drafted manuscript; S.N.C. edited and revised manuscript; S.N.C. approved final version of manuscript.

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APPENDIX E: Contribution to a Journal of Applied Physiology Point:Counterpoint debate on selective brain cooling

surrounding tissues. However, the main regulators of brain temperature are the cerebral blood flow and the temperature of incoming arterial blood (6).

The rate of heat removal from the brain tissue is estimated by the product of regional cerebral blood flow and the temperature difference between brain tissue and inflowing arterial blood (4). The mean brain-body temperature gradient in normothermia varies between 0.3–0.4°C (4) and 2.3°C (1).

Assuming a baseline brain-body temperature gradient of 0.5–1°C at a constant metabolic rate, then just by increasing the cerebral blood flow brain temperature might decrease with ~0.5–1°C. And what if one persists on cooling the incoming blood? In a study by Pretorius et al. (3) isolated dorsal, facial, or whole head cooling induced core cooling rates up to 0.69 ± 0.2°C/h by increased heat loss via the exposed surface while the metabolic rate remained unchanged. The effects were explained by a reflex induced centralization of circulation that increased the blood flow to the head. Brain temperature was not measured but a relatively fast and uniform lowering of brain temperature depending on the baseline gradients and cooling efficiency would be expected.

Are then the results of similar cooling methods an argument for selective brain cooling as presented by White et al. (5) or rather the consequence of ingenious thermal manipulation as showed by Nybo and Secher (2)?

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CAN THERMAL HYPERPNEA REALLY COOL THE BRAIN?

TO THE EDITOR: A disproportionate increase in ventilation clearly occurs with hyperthermia. White et al. (6, 7) appear to favor ventilation-induced brain cooling via heat exchange with the internal carotid artery; however the studies presented only address potential brain cooling during heightened ventilation via enhanced heat exchange across the nasal cavity. The interpretation of this evidence is questionable. The cooling power of a perfluorohexane nasopharyngeal spray (2) and the direct local application of ice strips and circulating 4°C water to the head and neck (3), far exceed the heat dissipation potential of human ventilation and therefore cannot be compared. Indeed, the latter study used "selective brain cooling" in the context of a targeted local hypothermia using external cooling devices. Furthermore, the reductions in intracranial temperature during 3 min of voluntary hyperventilation (18–20 breaths/min), attributed solely to ventilation-induced heat transfer across the cribriform plate (4), appear difficult to explain from a biophysical standpoint. Assuming cerebral heat balance prior to hyperventilation, and using a cerebral heat capacity of 3.64 $J \cdot g^{-1} \cdot °C^{-1}$ and brain mass of 1,500 g, an intracranial temperature decrease of 0.05 to 0.10°C/min requires an increased heat dissipation from the brain of 4.6 to 9.1 W. While the change in total inspiratory heat loss across the nasal cavity during hyperventilation (using a 1 L tidal volume) would be ~26.3 W (1), three-dimensional modeling of the nasal cavity demonstrates that even with unlimited blood perfusion of the nasal walls, a maximum heat loss of only ~1.3 W would occur at anatomical structures juxtaposed to the brain (5).

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NO EVIDENCE THAT MAMMALS WITHOUT A CAROTID RETE CAN SELECTIVELY COOL THEIR BRAINS

TO THE EDITOR: White et al. (7) argue that a carotid rete is not a prerequisite for selective brain cooling (SBC) because several mammals without a rete "clearly demonstrate SBC." They clearly have ignored the published research showing that hypothalamic temperature always exceeds arterial blood temperature in species without a rete, even during hyperthermia (for summary, see Ref. 1). While brain and arterial blood temperature have not been measured directly in healthy humans, they have been measured accurately in other mammals, including baboons, which have a similar cranial vascular anatomy to humans. Not one of more than 3,400 measurements of brain temperature per animal in baboons exposed to heat and deprived of water, with brain temperatures sometimes exceeding 40°C, was lower than the concurrent arterial blood temperature (2).

APPENDIX F: Letter-to-the-Editor of Medicine and Science in Sports and Exercise regarding biophysical versus aerobic fitness-related determinants of core temperature during exercise

LETTER TO THE EDITOR-IN-CHIEF

Dissociating Biophysical and Training-Related Determinants of Core Temperature

Dear Editor-in-Chief:

In a recent review, Dr. Mora-Rodriguez (5) concluded that core temperature is predicted by the percentage of peak oxygen uptake ($\%\dot{V}O_{2peak}$) in physiologically compensable conditions and absolute heat production in uncompensable conditions (see Fig. 4 in (5)). Heat balance calculations (3) and recent evidence from our laboratory (4) suggest otherwise. High (HI) and low (LO) $\dot{V}O_{2peak}$ groups matched for mass and body surface area (BSA), exercising at 540 W heat production in compensable conditions, showed similar changes in rectal temperature (T_{re}) and whole-body sweat losses despite vastly different relative intensities (39.7% vs 57.6% $\dot{V}O_{2peak}$) (4). Furthermore, absolute end-exercise T_{re} was ~0.2°C lower in the HI group simply because of lower preexercise values. In contrast, exercise at 60% $\dot{V}O_{2peak}$ (heat production, 844 vs 600 W) yielded greater changes in T_{re} and absolute end-exercise T_{re} values in the HI group, and whole-body sweat losses were greater in the HI group because of higher evaporative heat balance requirements (E_{req}) (4). In compensable conditions, these findings suggest the following after eliminating differences in mass and BSA: (i) changes in T_{re} are determined by heat production, not $\%\dot{V}O_{2peak}$; (ii) any differences in end-exercise absolute T_{re} between fitness groups only arise because of differences in preexercise T_{re}; and (iii) sweating is not altered by a high $\dot{V}O_{2peak}$. We further suggested that groups heterogeneous for body morphology may be compared for changes in T_{re} using a fixed heat production per unit mass ($W \cdot kg^{-1}$) in compensable environments. This approach explains the greater T_{re} changes in trained subjects at $40\%\dot{V}O_{2peak}$ (8.2 vs 6.1 $W \cdot kg^{-1}$) (6), with these greater changes compensated by different preexercise T_{re} values, leading to similar absolute end-exercise temperatures between training groups.

By definition, uncompensable conditions arise when E_{req} exceeds the maximum possible evaporation rate (E_{max}). Dr. Mora-Rodriguez suggests that $E_{req} > E_{max}$ at a similar $\%\dot{V}O_{2peak}$ in trained and untrained groups (see Fig. 4 in (5)). However, at a given $\%\dot{V}O_{2peak}$, E_{req} is lower in untrained individuals because of their lower heat production, and the primary reason that $E_{req} > E_{max}$ at the same $\dot{V}O_{2peak}$ in the proposed model is the lower maximum skin wettedness (ω_{max}) assigned to untrained individuals (ω_{max} = 0.85). Although maximum sweat rate is probably different (1), such large ω_{max} adjustments as a function of training status do not seem justified by the literature. A ω_{max} of 0.85 and 1.00 were proposed originally for nonheat-acclimated and heat-acclimated individuals, respectively (2), but physical training only imparts partial acclimation (7).

Even if ω_{max} differences between training groups are as large as proposed, heat balance calculations (3) show the $\%\dot{V}O_{2peak}$ at which $E_{req} > E_{max}$ still should be greater in unfit/untrained subjects with the same BSA/mass ratio. The $\%\dot{V}O_{2peak}$ at which $E_{req} > E_{max}$ declines with decreasing BSA/mass ratio. Because the BSA/mass ratio of the author's untrained group (6) was lower, it appears that a combination of different physical characteristics and assigned ω_{max} values led to a conclusion with restricted validity. A more robust descriptor of the reported differences in T_{re} between training groups at high relative exercise intensities (6) may be the difference between E_{req} and E_{max} expressed in $W \cdot kg^{-1}$.

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APPENDIX G: Published article providing a possible biophysical explanation for compensatory hyperhidrosis after endoscopic thoracic sympathectomy

Perspectives

Am J Physiol Regul Integr Comp Physiol 302: R352–R356, 2012.
First published November 23, 2011; doi:10.1152/ajpregu.00419.2011.

Compensatory hyperhidrosis following thoracic sympathectomy: a biophysical rationale

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Submitted 29 July 2011; accepted in final form 22 November 2011

Cramer MN, Jay O. Compensatory hyperhidrosis following thoracic sympathectomy: a biophysical rationale. *Am J Physiol Regul Integr Comp Physiol* 302: R352–R356, 2012. First published November 23, 2011; doi:10.1152/ajpregu.00419.2011.—A side-effect of endoscopic thoracic sympathectomy (ETS) is compensatory hyperhidrosis (CH), characterized by excessive sweating from skin areas with intact sudomotor function. The physiological mechanism of CH is unknown, but may represent an augmented local sweat rate from skin areas with uninterrupted sympathetic innervation based on evaporative heat balance requirements. For a given combination of activity and climate, the same absolute amount of evaporation (if any) is needed to balance the rate of metabolic heat production both pre- and post-ETS. However, the rate of local sweating per unit of skin surface area with intact sudomotor activity must be greater post-ETS as evaporation must be derived from a smaller skin surface area. Under conditions with high evaporative requirements, greater degradations in sweating efficiency associated with an increased dripping of sweat should also occur post-ETS, further pronouncing the sweat rate required for heat balance. In conclusion, in addition to the potential role of psychological stimuli for increased sudomotor activity, the existence of CH post-ETS can be described by the interplay between fundamental thermoregulatory physiology and altered heat balance biophysics and does not require a postoperative alteration in physiological control.

heat balance; evaporation; sudomotor activity; sweating; thermoregulation

PRIMARY HYPERHIDROSIS IS CHARACTERIZED by excessive palmar, plantar, and/or axillary sweating beyond thermoregulatory requirements. Severe cases are often treated surgically by endoscopic thoracic sympathectomy (ETS), which involves electrocautery or clipping of the sympathetic chain to interrupt downstream innervation of sweat glands within the hyperhidrotic skin areas (7). While success rates are high (12), the most common and severe side effect of ETS is compensatory hyperhidrosis (CH), which is excessive sweat production from skin areas with preserved sudomotor function (28), such as the abdominal, lumbar, groin, thigh, and popliteal regions (4). The incidence of CH is 0% to 100% following electrocautery (2, 26) and 0% to 89% following clamping (21, 22). Severe CH, characterized by large amounts of sweat production triggered by ambient temperature, psychological stress, and exercise (7), has been reported to be as high as 28% (1, 31).

The etiology of CH is currently unknown, but potentially involves a combination of physical, physiological, and psychological factors. Chou et al. (11) proposed that CH represents a post-ETS reflex response within the hypothalamic sweat center, altered primarily by psychological (i.e., anxiety or stress) factors, and is therefore not compensatory in nature. Physiological mechanisms contributing to CH may also include a local adaptation of the sweat gland itself and/or an increased thermosensitivity of the thermal controller arising from repeated postoperative sweat gland activity. However, the presence and severity of CH following ETS may be primarily explained from a biophysical perspective by considering the reduced effective body surface area for evaporative heat loss and the greater local sweat rate needed to attain heat balance in skin areas with intact sudomotor function with various combinations of clothing, activity and climate.

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Human Heat Balance

The effective goal of the human thermoregulatory system is to maintain a steady-state core temperature by keeping the rate of heat storage ($\dot{S}$) at zero and therefore maintain a balance between the rates of metabolic heat production and net heat dissipation (in watts [W]) as described by the conceptual heat balance equation (15)

$$\dot{S} = \left(\dot{M} - \dot{W}\right) \pm \dot{K} \pm \dot{C} \pm \dot{R} \pm \dot{C}_{res} - \dot{E}_{res} - \dot{E}_{sk}\ [W] \quad (1)$$

where metabolic heat production ($\dot{M} - \dot{W}$) is the difference between the rates of metabolic energy expenditure ($\dot{M}$) and external work ($\dot{W}$). Dry heat exchange is the sum of conductive ($\dot{K}$), convective ($\dot{C}$), and radiative ($\dot{R}$) rates of heat loss. The rate of total respiratory heat loss is determined by ventilatory heat exchange via convection ($\dot{C}_{res}$) and evaporation ($\dot{E}_{res}$). Evaporative heat loss from the skin ($\dot{E}_{sk}$) occurs via the vaporization of sweat.

A modest thermal gradient between skin and ambient air is typically maintained through increases in skin blood flow and subsequent elevations in skin temperature during exercise and/or heat exposure. However, as ambient air temperature increases, dry heat loss is reduced due to a progressive decline of the skin-to-air temperature gradient, and the body primarily relies on the evaporation of sweat to dissipate heat. Likewise, during exercise, elevated rates of metabolic heat production must also be compensated by increased heat loss via evaporation. The rate of evaporative heat loss required to attain heat balance ($\dot{E}_{req}$) may be defined by rephrasing the conceptual heat balance equation (25)

$$\dot{E}_{req} = \left(\dot{M} - \dot{W}\right) \pm \dot{K} \pm \dot{C} \pm \dot{R} \pm \dot{C}_{res} - \dot{E}_{res}\ [W] \quad (2)$$

At a given skin temperature, this rate of heat loss may not exceed the maximum capacity for evaporative heat loss to the environment ($\dot{E}_{max}$), defined as (25)

$$\dot{E}_{max} = \frac{\omega(P_{sk} - P_a)}{\left[\frac{1}{R_{e,cl}(h_e f_{cl})}\right]} \left[W/m^2\right] \quad (3)$$

where ω is skin wettedness, which is the fraction of the body surface covered in sweat (considered to be 1.00 during maximal sweating) (14); $(P_{sk} - P_a)$ is the vapor pressure difference between saturated skin (P_{sk}) and air (P_a); $R_{e,cl}$ is the evaporative resistance of clothing; h_e is the evaporative heat transfer coefficient; and f_{cl} is the ratio of clothed to nude body surface area. Values for $\dot{E}_{max}$ are expressed in Watts per m^2 of effective B5A with sudomotor function.

While sweating responses are primarily initiated and mediated by changes in core and skin temperatures (33) and to a lesser extent nonthermal factors (18, 29), the rate of whole body sweat production at steady state is ultimately determined by $\dot{E}_{req}$ (23), since once heat balance is attained, further increases in core temperature and therefore hypothalamic load error no longer occur (3, 25, 27). If $\dot{E}_{req}$ exceeds ~50% of $\dot{E}_{max}$, sweating efficiency (S_{eff}), which is the amount of evaporated sweat relative to the amount of sweat produced, declines rapidly (17), meaning that a greater amount of sweat production is required for a given $\dot{E}_{req}$. Values for $\dot{E}_{max}$ are correlated positively with the surface area available for evaporation as determined by the area of skin with innervated sweat glands, which in healthy individuals is equal to total body surface area (BSA). The ratio of $\dot{E}_{req}$ to $\dot{E}_{max}$ represents the effective skin wettedness required for heat balance (ω_{req}), or the proportion of BSA that must be covered in sweat to provide the required rate of evaporation.

Heat Balance and Sympathectomy

By disrupting part of the sympathetic chain, ETS reduces the number of functional sweat glands not only in the targeted area but also in surrounding skin areas within the same dermatome, thus altering the pattern of sweat distribution (30) leading to varying degrees of anhidrosis in dennervated skin areas (28). As depicted in Fig. 1, the head, upper arms, and torso above the nipple line become anhidrotic with a more extensive ETS (16, 28), e.g., T2–T4, leading to a ~30% reduction in the effective BSA (32), which is actually closer to a ~40% reduction when accounting for regional variations in sweat gland density that tend to be greater on the head and upper back (19, 28). When a combination of activity and climate yields an $\dot{E}_{req}$ greater than zero (i.e., some evaporation is needed for heat balance), reducing the effective BSA by ~30% (i.e., from 2.0 m^2 to 1.4 m^2) would demand a greater rate of local sweating per unit surface area from skin areas with preserved sweating function to produce a given absolute amount of evaporation. For example, activity that generates 350 W of metabolic heat production in an environment that presents a near-zero skin-to-air temperature gradient (e.g., 35°C) would, assuming 100% evaporation and a latent heat of vaporization of sweat of 2,426 J/g, require a whole body sweat production of ~8.6 g/min to attain heat balance. With a pre-ETS effective BSA of 2.0 m^2, average local sweat rate per unit surface area would be 0.43 $mg \cdot cm^{-2} \cdot min^{-1}$; however, with a post-ETS effective BSA of 1.4 m^2, average local sweat rate increases to 0.62 $mg \cdot cm^{-2} \cdot min^{-1}$. Because $\dot{E}_{max}$ would also be reduced with a decreased effective BSA post-ETS, reductions in S_{eff} would likely exacerbate the divergence between pre- and post-ETS average local sweat rates.

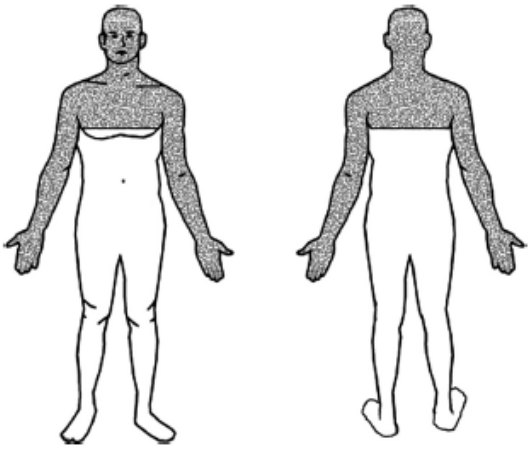

Fig. 1. Regions of body surface area anhidrosis post-endoscopic thoracic sympathectomy (post-ETS). Following extensive ETS (i.e., T2-T4), collateral dennervation of sweat glands across the head, neck, upper chest, and arms can occur (grey), resulting in surface area anhidrosis of ~30% of body surface area (BSA). However, when accounting for regional differences in sweat gland density, surface area anhidrosis is closer to 40%. The area of intact sudomotor function (white) is considerably reduced post-ETS.

While the biophysical mechanisms of heat exchange have been well characterized in healthy individuals (15), alterations to heat balance following ETS have not been quantified. Using a conceptual heat balance approach, we have created a hypothetical model of the average local sweat rate (on skin areas with preserved sudomotor function) required to maintain heat balance pre- and post-ETS over a range of ambient temperatures (at a fixed relative humidity of 30%) with different combinations of activity and clothing insulation. Figure 2, *top*, demonstrates that following a 30% reduction in effective BSA with ETS, an augmented average local sweat rate is required under equivalent conditions with the divergence between pre- and post-ETS average sweat rates exacerbated with increasing ambient temperature due to a lower S_{eff} accompanying the greater local skin wettedness following ETS. Relative to pre-ETS, the same average local sweat rate is only achieved post-ETS at a lower ambient temperature both during rest and exercise while wearing a variety of clothing ensembles. Our model also shows that, even at rest, individuals living in warm/hot climates will inevitably require CH following ETS to attain heat balance. Clinical observations apparently supporting our model include the observation that CH presents more frequently and severely during exercise (6, 13), as well as in hot/humid climates (10, 20). Moreover, resting local sweat rates at an ambient temperature of 41°C were proportionally greater in the thigh and lumbar regions relative to the reductions in forehead and upper chest sweat rate following T2–T3 ETS compared with a control group (30). These findings indicate that CH is a necessary thermoregulatory response post-ETS, since local sweat rates maintained at pre-ETS levels across the reduced effective surface area would result in a lower total evaporative heat loss and would lead to sustained

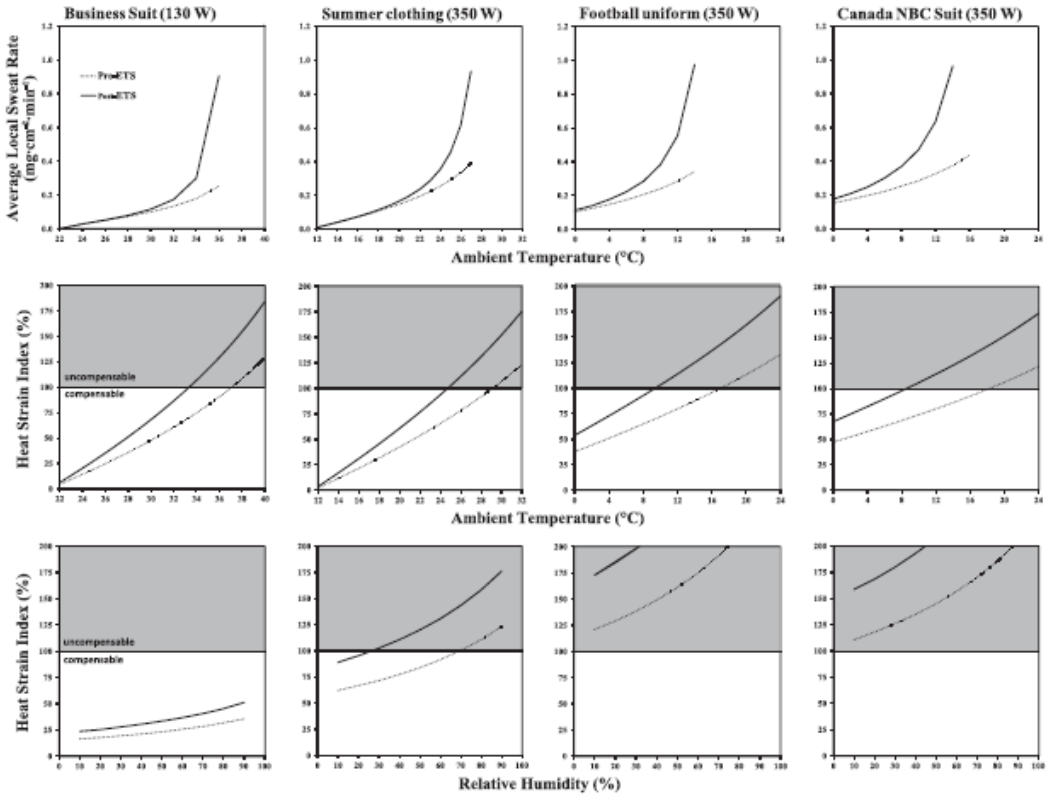

Fig. 2. Average local sweat rate to achieve heat balance and the heat strain index (HSI) pre- and post-ETS. The calculated average local sweat rate to achieve heat balance from skin areas with preserved sudomotor function is shown over a range of ambient temperatures (*top*). The HSI, expressed as % $\dot{E}_{max}$, is shown over a range of ambient temperatures (*middle*) and over a range of relative humidity levels (*bottom*). Shaded areas indicate physiological uncompensability (i.e., $\dot{E}_{req} > \dot{E}_{max}$). Calculations were based on an individual with a BSA of 2.0 m², which is effectively reduced by 30% to 1.4 m² post-ETS; a relative humidity of 30% (*top* and *middle*); an ambient temperature of 25°C (*bottom*); two rates of metabolic heat production indicating either rest (130 W) or moderate exercise (350 W); and while wearing various clothing ensembles: rest wearing a business suit (25); exercise wearing summer athletic clothing (25); exercise wearing an American football uniform (24); and exercise wearing the Canada nuclear, biological, and chemical protective clothing system (9).

increases in body heat storage and core temperature. However, even with maximal CH, our model demonstrates that post-ETS patients remain at a greater risk of hyperthermia. Figure 2 also presents the effect of ETS on the heat strain index (HSI) (5) over a range of ambient temperature (Fig. 2, *middle*) and relative humidity (Fig. 2, *bottom*) values. The HSI expresses $\dot{E}_{req}$ as a percentage of $\dot{E}_{max}$. In physiologically compensable environments (i.e., $\dot{E}_{req} \leq \dot{E}_{max}$) human/environmental heat exchange is sufficient to achieve heat balance and, consequently, a steady-state core temperature. In uncompensable environments (i.e., $\dot{E}_{req} > \dot{E}_{max}$) a persistent heat imbalance and a progressive increase in core temperature will occur. Following ETS, the same HSI is achieved at a lower (~4–6°C) ambient temperature and relative humidity (~50–60%) due to a reduction in $\dot{E}_{max}$ by virtue of a decreased effective surface area available for evaporation. Our model shows that ETS patients with CH would *1*) require additional fluid intake to offset the exacerbated sweat loss associated with a reduced sweating efficiency and mitigate any dehydration-related increases in the risk of heat-related illnesses when operating in warmer environments, and *2*) need to limit exposure time, use supplementary cooling methods, such as fans or air conditioning, and/or select clothing that improves evaporation (i.e., low $R_{e,cl}$) to minimize the risk of heat injury and maintain work performance.

Limitations of our model include the assumption that air movement promoting dry and evaporative heat losses is uniform across the body, whereas convective flow is likely much lower across clothed skin areas. However, since clothing primarily covers skin areas with preserved sweating function post-ETS [other than the nuclear, biological, and chemical protection clothing system that covers the entire body (Fig. 2)], our model would overestimate sweating efficiency in the post-ETS condition and therefore underestimate the divergence between pre- and post-ETS average local sweat rates.

The proposed mechanism by which CH occurs is as follows: post-ETS, a reduction in sympathetically innervated sweat glands impairs evaporative heat loss, resulting in a greater elevation in core and intermediate tissue temperatures for a given $\dot{E}_{req}$ (i.e., exercise intensity and climate). This greater hypothalamic load error initiates an enhanced sweating response, augmenting sweat output from glands with uninterrupted sympathetic innervations, thereby achieving the required amount of evaporation for heat balance. Under conditions with high evaporative requirements, greater degradations in sweating efficiency due to a diminished $\dot{E}_{max}$ from surface area anhidrosis result in an increased dripping of sweat, further core temperature increases, and even greater elevations in local sweat rate with preserved sudomotor function. Finally, CH may be exacerbated by repeated sweat gland activity akin to the effects of heat acclimation (8) and may be further augmented by psychological stimuli (e.g., anxiety).

To our knowledge, only one study has reported any core temperature data in ETS patients relative to a control group (30). While differences in core temperature were not observed between groups despite evidence of CH in ETS patients, there were clear limitations with the thermometric method employed. Core temperature was measured with an in-glass oral thermometer placed under the tongue, and the lack of sensitivity of this measure to changes in thermal state are evidenced by the fact that the core temperature reported after 50 min of passive exposure to a 41°C environment, which is likely beyond the limits of thermoregulatory compensability, was the same as after 50 min in a 22°C environment. The paucity of simultaneous core and skin temperatures with local and whole body sweat rate measurements clearly needs to be addressed in future research.

Perspectives and Significance

In the absence of psychological stimuli for sweat production, we suggest that CH is primarily a biophysically mediated thermoregulatory response that compensates for the collateral dennervation of nontarget skin areas within a dermatome by augmenting sweat production from areas with intact sudomotor function. Under these conditions, a psycho-physiological adjustment is not necessarily required; the increase in sweat production associated with CH would be primarily determined by heat balance requirements.

The debilitating nature of CH demands a re-evaluation of its putative mechanisms. Understanding these mechanisms will facilitate a more accurate prediction of the incidence and severity of CH following ETS based on the degree of surface area anhidrosis and the range of climate and activity levels to which the individual is typically exposed, leading to more informed decisions by those with primary hyperhidrosis considering an ETS procedure. Future research should be directed at *1*) defining the magnitude of surface area anhidrosis following ETS procedures of varying extents, *2*) quantifying the associated changes and distribution in whole body and local sweating, *3*) determining whether ETS results in functional adaptations to sweat glands and alterations to sudomotor thermosensitivity, and *4*) dissociating psychologically-mediated sweat production following ETS from the increased local sweat rate associated with the altered local evaporative requirements for heat balance.

ACKNOWLEDGMENTS

We thank Michael Kohl for providing the illustration in Fig. 1.

GRANTS

This work was supported by a Natural Sciences and Engineering Research Council of Canada Discovery Grant (to O. Jay).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s). Part of this work was originally conducted by Dr. Jay for inclusion in a court case report commissioned by Jonathan Bishop, Quebec City, Canada.

AUTHOR CONTRIBUTIONS

M.N.C. and O.J. analyzed data; M.N.C. and O.J. interpreted results of experiments; M.N.C. and O.J. prepared figures; M.N.C. and O.J. drafted manuscript; M.N.C. and O.J. edited and revised manuscript; M.N.C. and O.J. approved final version of manuscript; O.J. conception and design of research.

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APPENDIX H: Published article investigating local sweat rate responses between aerobically trained and untrained individuals

Experimental Physiology

Research Paper

Local sweating on the forehead, but not forearm, is influenced by aerobic fitness independently of heat balance requirements during exercise

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The present study investigated the influence of maximal oxygen uptake ($\dot{V}_{O_2\,max}$) on local steady-state sudomotor responses to exercise, independently of evaporative requirements for heat balance (E_{req}). Eleven fit (F; $\dot{V}_{O_2\,max}$ 61.9 ± 6.0 ml kg^{-1} min^{-1}) and 10 unfit men (UF; $\dot{V}_{O_2\,max}$ 40.4 ± 3.8 ml kg^{-1} min^{-1}) cycled for 60 min at an air temperature of 24.5 ± 0.8°C and ambient humidity of 0.9 ± 0.3 kPa at a set metabolic heat production per unit surface area, producing the same E_{req} in all participants (BAL trial) and, in a second trial, at 60% of $\dot{V}_{O_2\,max}$. During the BAL trial, absolute power (F 107 ± 2 and UF 102 ± 2 W; $P = 0.126$), E_{req} (F 175 ± 5 and UF 176 ± 9 W m^{-2}; $P = 0.855$), steady-state whole-body sweat rate (F 0.44 ± 0.02 and UF 0.47 ± 0.02 mg cm^{-2} min^{-1}; $P = 0.385$) and local sweat rate on the arm (F 0.29 ± 0.03 and UF 0.35 ± 0.03 mg cm^{-2} min^{-1}; $P = 0.129$) were not different between groups; however, local sweat rate on the forehead in UF (1.67 ± 0.20 mg cm^{-2} min^{-1}) was almost double ($P = 0.002$) that of F (0.87 ± 0.11 mg cm^{-2} min^{-1}). Heart rate, ratings of perceived exertion and relative exercise intensity were also significantly greater in UF ($P < 0.05$). There was a trend towards an elevated minute ventilation in UF ($P = 0.052$), while end-tidal P_{CO_2} was significantly lower in UF ($P = 0.028$). At 60% $\dot{V}_{O_2\,max}$, absolute power (F 174 ± 6 and UF 110 ± 5 W; $P < 0.001$), E_{req} (F 291 ± 14 and UF 190 ± 17 W m^{-2}; $P < 0.001$), steady-state whole-body sweat rate (F 0.84 ± 0.05 and UF 0.53 ± 0.03 mg cm^{-2} min^{-1}; $P < 0.001$) and local sweat rate on the arm (F 0.75 ± 0.04 and UF 0.35 ± 0.03 mg cm^{-2} min^{-1}; $P < 0.001$) and on the forehead (F 2.92 ± 0.42 and UF 1.68 ± 0.23 mg cm^{-2} min^{-1}; $P = 0.022$) were all significantly greater in F compared with UF. Heart rate and ratings of perceived exertion were similar at all time points ($P > 0.05$). Significantly greater minute ventilation ($P < 0.001$) and end-tidal P_{CO_2} responses ($P = 0.017$) were found in F. In conclusion, aerobic fitness alters local sweating on the forehead, but not the forearm, independently of evaporative requirements for heat balance, and may be the result of differential control of sweating in these skin areas associated with the relative intensity of exercise.

(Received 30 August 2011; accepted after revision 3 January 2012; first published online 6 January 2012)
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In a recent issue of *Experimental Physiology*, Ichinose-Kuwahara *et al.* (2010) reported a greater mean local sweat rate (averaged from forehead, chest, back, forearm and thigh) in trained relative to untrained individuals at 50–65% of their maximal oxygen uptake ($\dot{V}_{O_2\,max}$). These findings have been argued to be a consequence of differences in external workload (Schwiening *et al.* 2011). However, from the point of view of heat balance, a greater sweat output in trained individuals at a fixed relative exercise intensity is theoretically better described by the greater evaporative requirements for heat balance (E_{req}) arising from the greater metabolic heat production in fit participants at a given percentage of their $\dot{V}_{O_2\,max}$ (Gagge & Gonzalez, 1996).

DOI: 10.1113/expphysiol.2011.061374

Recent evidence demonstrates that aerobic fitness *per se* does not influence whole-body sweating responses, with almost identical whole-body sweat rates in fit ($\dot{V}_{O_2\,max}$ 60 ml kg^{-1} min^{-1}) and unfit participant groups ($\dot{V}_{O_2\,max}$ 40 ml kg^{-1} min^{-1}) reported throughout 60 min of exercise at a fixed E_{req} despite substantially different relative exercise intensities (Jay *et al.* 2011). However, the independent influence of $\dot{V}_{O_2\,max}$ on local sweat distribution during exercise is not fully understood. It has been proposed that long-term aerobic training may lead to an altered distribution of sweat (Havenith & van Middendorp, 1990). It follows that such a phenomenon may contribute to the observations of Ichinose-Kuwahara *et al.* (2010), because their sweat rate measurements were determined locally.

Different local sweating responses between aerobically fit and unfit individuals may arise from non-thermoregulatory pathways (Kondo *et al.* 2010) associated with the relative intensity of exercise. Sympathetic activity is positively correlated with relative exercise intensity (Galbo *et al.* 1975) and has been shown to potentiate local sweating at the onset of dynamic exercise and during isometric hand-grip exercise (van Beaumont & Bullard, 1966; Shibasaki *et al.* 2003). Despite identical whole-body sweating in fit and unfit subjects at the same metabolic heat production and therefore different relative exercise intensities (Jay *et al.* 2011), greater forehead sweat rates have been found following manipulations of relative exercise intensity through ischaemia (Kacin *et al.* 2005) and hypoxia (Kacin *et al.* 2007) at the same absolute workloads and with significant rises in perceived exertion. The forehead is known to be responsive to both thermal and non-thermoregulatory stimuli (McGregor, 1952; Kuno, 1956; Drummond & Lance, 1987); however, whether other skin areas respond in a similar manner is unclear. Ogawa (1975) found that the palm (i.e. glabrous skin), but not forearm (i.e. non-glabrous skin), showed a greater sweat rate at the onset of cycling exercise, suggesting that exercise can elicit a differential pattern of non-thermoregulatory sudomotor activity. In contrast, more recent reports indicate that psychological stress elicits enhanced sweating of both glabrous and non-glabrous skin during normothermia (Machado-Moreira & Taylor, 2011*a*) and passive heating (Machado-Moreira & Taylor, 2011*b*).

The aim of the present investigation was to determine the influence of aerobic fitness on the sweat rate within two distinct local skin regions independently of the whole-body evaporative requirements for heat balance, determined by the rate of evaporative heat loss required for heat balance (E_{req}) and sweating efficiency, which is governed by the ratio of E_{req} relative to the maximal rate of evaporation possible in the ambient environment (E_{max}; Lustinec, 1973; Shapiro *et al.* 1982; Bain *et al.* 2011). Local sweating responses from glabrous (forehead) and non-glabrous skin (forearm) were compared between groups of high and low aerobic fitness during exercise in the following conditions: (i) a fixed heat production per unit body surface area to elicit an E_{req} of 175 W m^{-2} in all participants; and (ii) 60% $\dot{V}_{O_2\,max}$. It was hypothesized that exercise at a fixed E_{req} would produce a greater local sweat rate on the forehead (glabrous), but not the forearm (non-glabrous), in individuals of low compared with high aerobic fitness owing to the greater relative exercise intensity and associated sympathetic drive for non-thermoregulatory sweating. During exercise at 60% $\dot{V}_{O_2\,max}$, local sweat rates at both sites were hypothesized to be greater in aerobically fit individuals owing to higher rates of metabolic heat production and the greater evaporative requirements for heat balance.

Methods

Ethical approval

The experimental protocol was approved by the University of Ottawa Research Ethics Committee. Written consent and a completed Physical Activity Readiness Questionnaire were obtained from each participant prior to experimentation. All participants were informed of the risks of participation and were free to withdraw from the study at any time. This experiment conformed to the guidelines set out in the Declaration of Helsinki.

Participants

A total of 21 non-smoking, healthy men volunteered for this study. Eleven participants were assigned to an aerobically fit group (F; $\dot{V}_{O_2\,max} \geq 55$ ml kg^{-1} min^{-1}); 10 participants were assigned to an aerobically unfit group (UF; $\dot{V}_{O_2\,max} \leq 45$ ml kg^{-1} min^{-1}). Mean participant characteristics are shown in Table 1. By design, $\dot{V}_{O_2\,max}$ was significantly greater in F ($P < 0.001$). Mean age, total body mass and body surface area (BSA) were all similar between groups ($P < 0.05$). The BSA was calculated using the equation of DuBois & DuBois (1916).

Experimental design and protocol

Participants visited the laboratory on three occasions, for one preliminary incremental exercise test to exhaustion and two experimental exercise trials. The order of the experimental trials was counterbalanced. During the 24 h prior to testing, participants were asked to consume plenty of water and to avoid alcohol, caffeine and intense exercise. The preliminary test consisted of an incremental semi-recumbent cycling test for the determination of $\dot{V}_{O_2\,max}$. Following a brief warm up, the test began at 80 W and workload was increased by 20 W min^{-1} until volitional exhaustion in accordance with Canadian

Table 1. Age, body mass, height, body surface area, maximal oxygen uptake ($\dot{V}_{O_2\,max}$) and peak power output for high (F; $\dot{V}_{O_2\,max} \geq 55$ ml kg^{-1} min^{-1}) and low aerobic fitness groups (UF; $\dot{V}_{O_2\,max} \leq 45$ ml kg^{-1} min^{-1})

Group		Age (years)	Mass (kg)	Body surface area (m^2)	$\dot{V}_{O_2\,max}$ (l min^{-1})	$\dot{V}_{O_2\,max}$ (ml kg^{-1} min^{-1})	$\dot{W}_{peak}$ (W)
F	Mean ± SD	24 ± 5*	75.1 ± 7.5	1.92 ± 0.12	4.6 ± 0.5*	61.9 ± 6.0*	351 ± 33*
	Range	20–33	61.4–90.1	1.66–2.15	3.9–5.3	55.0–71.6	300–410
UF	Mean ± SD	21 ± 2	78.7 ± 5.9	1.94 ± 0.07	3.2 ± 0.4	40.4 ± 3.8	250 ± 29
	Range	19–24	71.7–89.3	1.86–2.07	2.7–3.9	33.1–44.0	210–310

Data are presented as the means ± SD for 11 aerobically fit (F) participants and 10 aerobically unfit (UF) participants. Body surface area was calculated according to the equation of DuBois & DuBois (1916). Peak external workload ($\dot{W}_{peak}$) is expressed in watts (W). *Significantly different between groups ($p < 0.05$).

Society for Exercise Physiology guidelines (CSEP, 1986). Experimental trials began at the same time of day to avoid the influence of circadian variation. Upon arrival at the laboratory, each subject voided his bladder, inserted a rectal probe and changed into a pair of light-weight running shorts, cotton socks and running shoes. Following instrumentation, the participants were seated quietly for 30 min to obtain resting values. Participants were then instructed to exercise for 60 min at either a relative exercise intensity corresponding to 60% of $\dot{V}_{O_2\,max}$ or a metabolic heat production of 275 W m^{-2} (BAL) chosen to elicit an E_{req} of ∼175 W m^{-2} with an E_{req}:E_{max} ratio of ∼0.45, thus ensuring minimal decrements in sweating efficiency (Candas *et al.* 1979), in the ambient environment, whilst maintaining a cadence of 80 r.p.m. An electrical fan situated 2.0 m in front of the participant provided constant convective air velocity ($v = 1.3$ m s^{-1}). Mean ambient temperature and humidity during all experimental trials were 24.5 ± 0.8°C and 0.9 ± 0.3 kPa, respectively.

Measurements

Heat balance calculations. Heat balance parameters were calculated using partitional calorimetry. See Appendix for the formulae used.

External workload. All exercise trials were performed on an electromagnetically braked semi-recumbent cycle ergometer (Corival Recumbent; Lode B.V., Groningen, The Netherlands). External workload (W) was regulated through a programmable control unit connected to the ergometer.

Thermometry. Rectal temperature (T_{re}) was measured using a thermocouple probe (Mon-a-therm; Mallinckrodt Medical, St Louis, MO, USA) inserted approximately 12 cm beyond the anal sphincter. Skin temperature was measured at four sites (shoulder, chest, anterior thigh and calf) using four T-type (copper–constantan) thermocouples affixed to the skin surfaces. An area-weighted mean skin temperature ($\bar{T}_{sk}$; in degrees Celsius) was then calculated as follows (Ramanathan, 1964):

$$\bar{T}_{sk} = 0.3T_{chest} + 0.3T_{shoulder} + 0.2T_{thigh} + 0.3T_{calf}$$

All temperature data were sampled every 15 s by a data acquisition unit (NI cDAQ-9172; National Instruments, Austin, TX, USA) during the experimental trials. Data were recorded using LabView software (National Instruments) and displayed in real time throughout the trial on a desktop computer.

Whole-body sweat rate. Whole-body sweat loss was estimated by measuring the change in body mass of the participant to the nearest 2 g using a digital platform scale (Combics 2; Sartorius, Mississauga, ON, Canada). Measurements were taken immediately after completing the 45th and 60th minute of exercise, with participants briefly stopping exercise for each measurement, which took ∼20 s. Participants were not towelled down prior to body mass measurements in order to ensure that mass changes better reflected the quantity of sweat that evaporated. Steady-state whole-body sweat rate ($WBSR_{ss}$) was calculated by subtracting the 60th minute value from the 45th minute measurement and subsequently dividing by BSA (in square centimetres) and the time elapsed between measurements (15 min) to yield values in milligrams per square centimetre per minute.

Local sweat rates. Technical absorbent pads (#2164, Laminated Airlaid; Technical Absorbents Ltd, Grimsby, UK) of 36 and 64 cm^2 were used to determine forehead (LSR_{head}) and forearm sweat rates (LSR_{arm}), respectively, using a modified version of the technique reported by Havenith *et al.* (2008) and Smith & Havenith (2011). Each pad was weighed on a digital scale (Denver Instrument, Bohemia, NY, USA) to the nearest 0.1 mg, and then sealed in an air-tight Ziploc® bag. Skin surfaces were towelled dry in the 10 s prior to application. Pads were placed on the glabrous skin of the forehead, which included the area above the eyebrows and below the hairline and between the temples (Cabanac & Brinnel, 1988), and on the ventral surface of the forearm. Pads were held in place by a headband (Skull Wrap, Product #8000072; Under Armour

Table 2. Heat balance parameters for high and low aerobic fitness groups between 45 and 60 min of exercise at the same E_{req} of 175 W m^{-2} (BAL trial) and 60% of $\dot{V}_{O_2\,max}$

Trial	Group	External workload (W)	Mean skin temperature (°C)	$C+R+C_{res}+E_{res}$ (W m^{-2})	H_{prod} (W m^{-2})	E_{req} (W m^{-2})	E_{max} (W m^{-2})	E_{req}:E_{max}
BAL	F	107 ± 2	31.3 ± 0.4	100 ± 4	274 ± 7	175 ± 5	406 ± 14	0.43 ± 0.01
	UF	102 ± 2	31.9 ± 0.5	103 ± 5	279 ± 9	176 ± 9	418 ± 13	0.43 ± 0.03
60% $\dot{V}_{O_2\,max}$	F	174 ± 6*	32.2 ± 0.5	126 ± 3	417 ± 13*	291 ± 14*	452 ± 11	0.65 ± 0.04*
	UF	110 ± 5	32.2 ± 0.4	115 ± 5	305 ± 15	190 ± 17	430 ± 18	0.46 ± 0.05

Data are presented as the means ± SEM for 11 aerobically fit (F) participants and 10 aerobically unfit (UF) participants. Abbreviations: E_{max}, the environmental capacity for evaporative heat exchange; E_{req}, the evaporative heat loss required for heat balance; H_{prod}, metabolic heat production; and $C+R+C_{res}+E_{res}$, the sum of dry (convective, C; radiative, R) and respiratory (convective, C_{res}; evaporative, E_{res}) heat losses. *Significantly different between groups ($P < 0.05$).

Inc., Baltimore, MD, USA) and a forearm sleeve (Forearm Shiver, Product #8000033; Under Armour Inc.). After a 5 min sampling period between 55 and 60 min of exercise, the pads were removed, placed back in the same Ziploc® bag and reweighed. Sweat rate at each site was estimated from the change in mass of the pads, and is expressed relative to the surface area of each pad.

Metabolic and ventilatory data. Expired gases were collected with a metabolic cart (Vmax® Encore; CareFusion, San Diego, CA, USA). Participants were provided with a nose-clip and mouthpiece and instructed to breathe normally. Breath-by-breath measurements were averaged over the first and last 15 min of exercise to ensure similar rates of metabolic heat per unit surface area were produced. Expired gases were also analysed for minute ventilation ($\dot{V}_E$) and the end-tidal partial pressure of carbon dioxide (P_{ET,CO_2}).

Ratings of perceived exertion. Participants provided a rating of perceived exertion (RPE) at 10 min intervals throughout each trial using Borg's scale (Borg, 1982).

Heart rate. Heart rate was recorded continuously at a sampling frequency of 5 s using a coded heart rate transmitter and wrist-watch (RS400; Polar Electro Oy, Kempele, Finland). Data were uploaded and analysed using specialized software (Polar ProTrainer 5; Polar Electro Oy).

Statistical analysis

Participant data are presented as means ± SD. All remaining data are presented as means ± SEM. Participant characteristics were compared using Student's unpaired *t* test. A two-way mixed ANOVA, using the repeated factor of time (five levels: 0, 15, 30, 45 and 60 min) and the non-repeated factor of fitness (two levels: F and UF), was performed to analyse the dependent variables of heart rate and RPE. When significant interactions were found, Student's unpaired *t* test was performed to identify individual differences. Student's unpaired *t* tests were also used to compare between-groups values for 60 min changes in T_{re} and $\bar{T}_{sk}$, metabolic heat production (H_{prod}), external workload, $\dot{V}_E$, P_{ET,CO_2}, LSR_{head}, LSR_{arm} and $WBSR_{ss}$. All comparisons were performed within each exercise condition. An α of 0.05 was set for all analyses. Statistical analysis was performed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). The data for T_{re} and whole-body sweat loss from 14 of the 21 participants in the present study were previously reported (Jay *et al.* 2011).

Results

Heat balance parameters

Heat balance parameters for both BAL and 60% $\dot{V}_{O_2\,max}$ trials are presented in Table 2. In the BAL trial, statistically similar external workloads ($P = 0.126$), $\bar{T}_{sk}$ ($P = 0.349$), combined dry and ventilatory heat losses ($P = 0.682$) and H_{prod} ($P = 0.649$) were produced between groups. Additionally, no significant differences were found for either E_{req} ($P = 0.855$) or E_{max} ($P = 0.540$) between groups in the BAL trial. As a result, the E_{req}:E_{max} ratio was not significantly different ($P = 0.854$).

At 60% of $\dot{V}_{O_2\,max}$, the external workload was significantly greater in the F group ($P < 0.001$); therefore, H_{prod} and E_{req} were also significantly greater in the F group ($P < 0.001$). Similar E_{max} values were produced ($P = 0.288$); thus, the E_{req}:E_{max} ratio was significantly different between groups during the 60% $\dot{V}_{O_2\,max}$ trial ($P < 0.001$). Although $\bar{T}_{sk}$ was statistically equivalent between groups ($P = 0.997$), the significantly greater H_{prod} in the F group resulted in a trend towards a greater sum of dry and ventilatory heat losses ($P = 0.081$).

Rectal and mean skin temperatures

In the BAL trial, pre-exercise resting T_{re} was 37.43 ± 0.08°C in the UF group and 37.14 ± 0.07°C in

the F group ($P = 0.009$). Following 60 min of exercise, T_{re} was 38.36 ± 0.10°C in the UF group and 38.09 ± 0.07°C in the F group ($P = 0.047$). In the 60% $\dot{V}_{O_2\,max}$ trial, pre-exercise resting T_{re} was 37.40 ± 0.07°C in the UF group and 37.09 ± 0.06°C in the F group ($P = 0.003$). Following 60 min of exercise T_{re} was 38.32 ± 0.08°C in the UF group and 38.67 ± 0.07°C in the F group ($P = 0.005$). The 60 min changes in rectal temperature (ΔT_{re}) are shown in Fig. 1. Values for ΔT_{re} were not different between groups during the BAL trial ($P = 0.767$). In contrast, the ΔT_{re} was significantly greater in the F group at 60% $\dot{V}_{O_2\,max}$ ($P < 0.001$). Values for T_{sk}, which were not different between F and UF groups, are shown in Table 2.

Sweat rates

No differences were found between groups for $WBSR_{ss}$ in the BAL trial (F 0.44 ± 0.02 and UF 0.47 ± 0.02 mg cm^{-2} min^{-1}; $P = 0.385$), but $WBSR_{ss}$ was significantly greater in the F (0.84 ± 0.05 mg cm^{-2} min^{-1}) than in the UF group (0.53 ± 0.03 mg cm^{-2} min^{-1}) at 60% $\dot{V}_{O_2\,max}$ ($P < 0.001$). The LSR data are presented in Fig. 2. In the BAL trial, no differences between groups were found for LSR_{arm} ($P = 0.129$); however, LSR_{head} was significantly greater ($P = 0.002$) in the UF group relative to the F group. At 60% V_{O2max}, significantly greater local sweating responses were found in the F compared with the UF group for LSR_{head} ($P = 0.022$) and LSR_{arm} ($P < 0.001$).

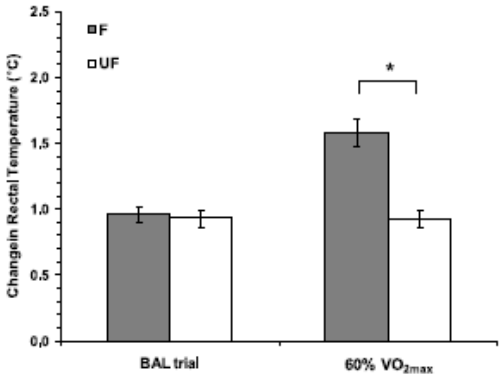

Figure 1. Changes in rectal temperature from rest (ΔT_{re}) in high [F; maximal oxygen uptake ($\dot{V}_{O_2\,max}$) ≥ 55 ml kg^{-1} min^{-1}] and low aerobic fitness groups (UF; $\dot{V}_{O_2\,max}$ ≤ 45 ml kg^{-1} min^{-1}) during exercise at the same evaporative requirement for heat balance (E_{req}) of 175 W m^{-2} (BAL trial) and 60% of $\dot{V}_{O_2\,max}$
Values are means ± SEM. *Significantly different between groups ($P < 0.05$).

Table 3. Ventilatory parameters for high and low aerobic fitness groups between 45 and 60 min of exercise at the same E_{req} of 175 W m^{-2} (BAL trial) and 60% of $\dot{V}_{O_2\,max}$

Trial	Group	Minute ventilation (l min^{-1})	End-tidal P_{CO_2} (mmHg)
BAL	F	41.1 ± 0.9	42.5 ± 0.5*
	UF	46.4 ± 2.4	40.0 ± 0.9
60% $\dot{V}_{O_2\,max}$	F	64.0 ± 1.7*	42.7 ± 0.6*
	UF	48.0 ± 2.9	40.0 ± 0.9

Data are presented as the means ± SEM for 10 aerobically fit (F) participants and 10 aerobically unfit (UF) participants in the BAL trial and 11 F and 10 UF participants at 60% $\dot{V}_{O_2\,max}$. *Significantly different between groups ($P < 0.05$).

Ratings of perceived exertion

The RPE data are presented in Fig. 3. During the BAL trial, a significant interaction between time and fitness was found ($P = 0.044$), with RPE progressively greater in the UF compared with F group throughout exercise. At 60% $\dot{V}_{O_2\,max}$, RPE increased from 10 min of exercise and remained elevated throughout; however, there was no significant effect of fitness ($P = 0.179$).

Heart rate

Heart rate data were obtained for seven F and seven UF participants in each set of conditions (Fig. 3). A significant main effect of time was found for heart rate in both the BAL ($P = 0.002$) and the 60% $\dot{V}_{O_2\,max}$ trials ($P < 0.001$). Heart rate was significantly elevated in the UF compared with the F group at all time points during the BAL trial. In contrast, no influence of fitness on heart rate was found at any time point at 60% $\dot{V}_{O_2\,max}$.

Ventilatory parameters

Steady-state $\dot{V}_E$ and P_{ET,CO_2} values are presented in Table 3. In the BAL trial, there was a trend towards a greater steady-state $\dot{V}_E$ in the UF group ($P = 0.052$), and P_{ET,CO_2} was significantly greater in the F group ($P = 0.028$). At 60% $\dot{V}_{O_2\,max}$, $\dot{V}_E$ was significantly greater in the F group ($P < 0.001$), as was P_{ET,CO_2} ($P = 0.017$).

Discussion

In the present study, individuals of high and low aerobic fitness exercised at a similar external workload of ∼105 W (Table 2), corresponding to a fixed evaporative requirement for heat balance (E_{req}) of 175 W m^{-2} (BAL trial), and at 60% of $\dot{V}_{O_2\,max}$. Our main finding is that while exercise at a fixed percentage of $\dot{V}_{O_2\,max}$ elicits local and whole-body sweat rates that are all greater in individuals with a high aerobic fitness, primarily due to their

greater metabolic heat production and therefore greater evaporative requirement for heat balance, exercise at a fixed E_{req} elicits a forehead (glabrous) sweat rate in unfit individuals that is almost double that of fit participants, despite similar whole-body and forearm (non-glabrous) sweat rates between groups. This observation at a fixed E_{req} is paralleled by significantly greater levels of cardiovascular and respiratory strain, as well as RPE, with no differences in thermal strain.

Previous research has clearly demonstrated that steady-state whole-body sweating responses during exercise in a physiologically compensable environment are greatly dependent upon the evaporative requirements for heat balance (Lustinec, 1973; Shapiro *et al.* 1982; Bain *et al.* 2011). Whole-body sweating responses have conventionally been related to relative exercise intensity (Saltin & Hermansen, 1966; Gant *et al.* 2004). However, when controlling for body mass, body surface area and ambient conditions, core temperature and whole-body sweat rate are in fact determined by heat balance requirements independently of aerobic fitness (Jay *et al.* 2011). The present study extends these findings to demonstrate that while whole-body sweat rate at the same E_{req} is similar between aerobically fit and unfit participant groups, the local distribution of sweat production is apparently different (Fig. 2).

Ichinose-Kuwahara *et al.* (2010) recently reported a greater average local sweat rate (using simultaneous measurements taken on the forehead, chest, back, forearm and thigh) in aerobically fit individuals during exercise at 50 and 65% of $\dot{V}_{O_2\,max}$. In response, Schwiening *et al.* (2011) argued that the greater absolute power in fit participants was the underlying reason for the observed differences in sweating. In the BAL trial of the present study, absolute power (external workload) was similar between F and UF participants (Table 2), because there was no appreciable difference in mechanical efficiency (F 16.9 and UF 15.9%) on the cycle ergometer and both groups had similar body surface areas. However, a significant difference between F and UF groups was still observed in the local sweat rate of the glabrous skin region (forehead) despite the same E_{req}, albeit in the opposite direction to those reported by Ichinose-Kuwahara *et al.* (2010).

While the present study did not measure local sweat rates on the chest and thigh, the different sweat rates in the 60% $\dot{V}_{O_2\,max}$ trial indicate that greater sweat rates previously reported by fit participants at a fixed relative exercise intensity are probably due to differences in E_{req} and do not represent an independent influence of aerobic fitness. In contrast, the potentiated forehead sweat rate in the UF group in the BAL trial indicates that sudomotor activity in this skin region may be mediated by non-thermoregulatory variables differing between F and UF groups.

Following a period of physical training or heat acclimation, numerous reports have demonstrated enhanced local sweating on the forearm in response to exogenous sudorific agonists (Buono & Sjoholm, 1988; Buono *et al.* 1992; Lorenzo & Minson, 2010). However, when fixing the evaporative requirements for heat balance in the present study (BAL trial) the sweat rate on the forearm was the same between the UF and F group, whereas a greater local sweat rate on the forehead was observed in the UF group, not the F group. This observation suggests that any differences in sweat gland sensitivity to neural stimulation as a function of aerobic

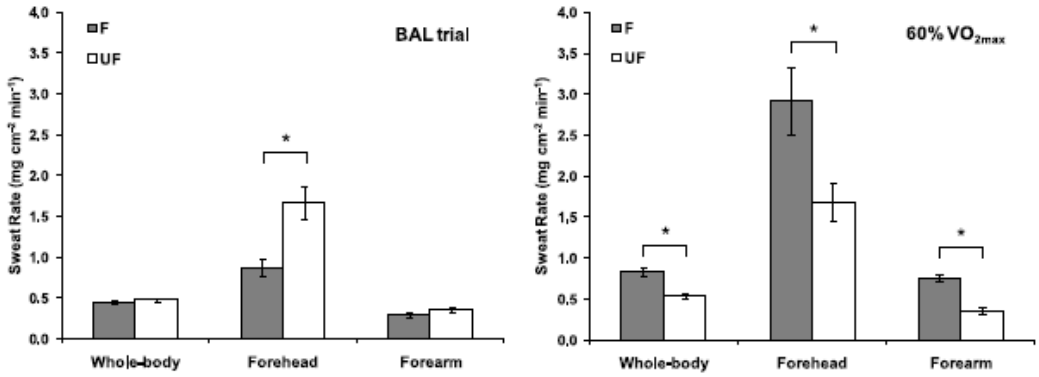

Figure 2. Steady-state whole-body ($WBSR_{ss}$) and local sweat rates on the forehead (LSR_{head}) and forearm (LSR_{arm}) in F and UF groups during exercise at the same E_{req} of 175 W m^{-2} (BAL; left panel) and 60% $\dot{V}_{O_2\,max}$ (right panel)

The $WBSR_{ss}$ was estimated from changes in body mass between 45 and 60 min of exercise. The LSR_{head} and LSR_{arm} were measured with technical absorbents between 55 and 60 min. Values are means ± SEM. * Significantly different between groups ($P < 0.05$).

fitness did not contribute to the observed differences in LSR_{head}.

A greater level of central command increases sympathetic activity to the skin (Vissing & Hjortsø, 1996) and has been associated with augmented local sweating (Shibasaki *et al.* 2003). In the BAL trial, central command would have been greater in the UF group as evidenced by their greater percentage $\dot{V}_{O_2\,max}$, heart rate and RPE (Fig. 3); however, only LSR_{head} was greater in the UF group (Fig. 2). The lack of difference in LSR_{arm} is in accordance with the greatly diminished relative influence of central command upon forearm sweating previously reported with elevations in core temperature similar (~1.0°C) to those observed in the BAL trial (Shibasaki *et al.* 2003). Whether a greater central command is responsible for the greater LSR_{head} in the UF group in the BAL trial is unclear, because the isolated role of central command on sudomotor activity using a partial neuromuscular blockade has only been examined for the local sweating response of the forearm (Shibasaki *et al.* 2003). A similar examination of the independent influence of central command on forehead and other glabrous skin regions would therefore merit further research.

It is well established that cardiovascular, perceptual and ventilatory responses are associated with sympatho-adrenal activity, which itself is a function of the relative intensity of exercise (Galbo *et al.* 1975; Kjaer *et al.* 1988) and is considerably reduced in aerobically trained individuals at the same absolute workload (Galbo *et al.* 1975; Winder *et al.* 1978). Therefore, it is possible that the enhanced sympathetic response to a greater relative exercise intensity in the UF group in the BAL trial elicited a significantly greater LSR_{head}. The mechanism by which this would occur is not clear, but may involve separate pathways to the glabrous forehead and non-glabrous forearm. Eccrine sweat glands, which are predominantly responsive to cholinergic stimulation, can also respond to adrenergic stimulation (Sato & Sato, 1981).

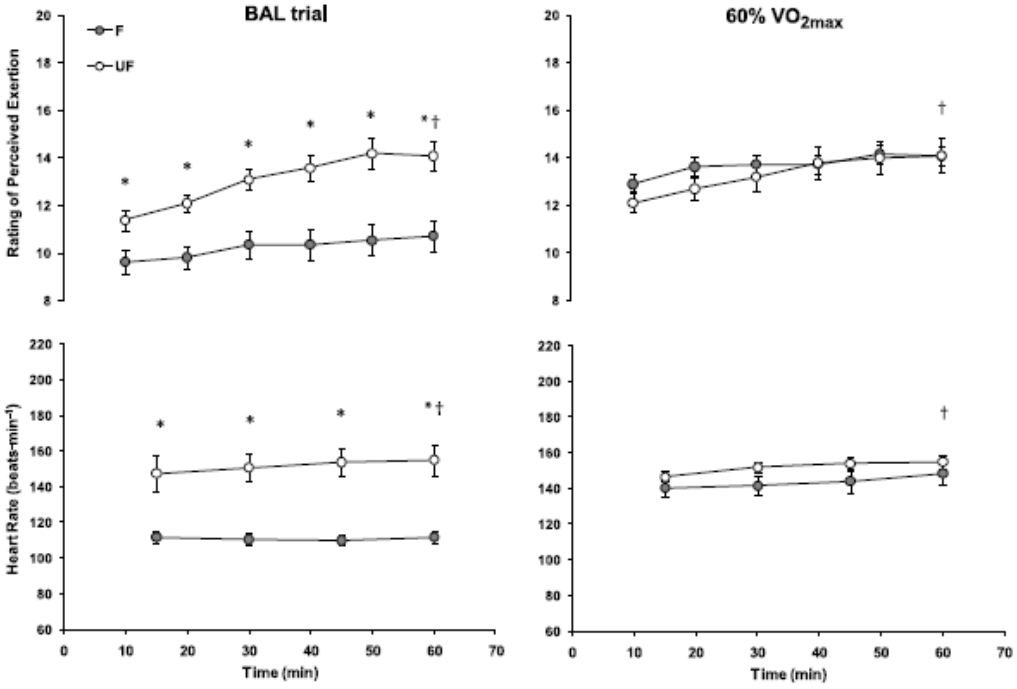

Figure 3. Ratings of perceived exertion and heart rate for F and UF groups during exercise at the same E_{req} of 175 W m^{-2} (BAL; left panel) and 60% $\dot{V}_{O_2\,max}$ (right panel)
Values are means ± SEM. *Significantly different between groups ($P < 0.05$). † Main effect of time.

While numerous studies have reported that adrenergic stimulation of sweat glands within the forearm produces minimal or no changes in local sweating (Morgan *et al.* 2006; Buono *et al.* 2010), the local sweating response to the administration of adrenergic agonists has not been investigated in the forehead. According to this hypothesis, cholinergic stimulation of whole-body and local forearm (i.e. non-glabrous) sweating responses would be mediated to achieve an elevated steady-state core temperature, and therefore elicit a rate of sweat production sufficient to attain the evaporative requirements for heat balance, whilst local forehead (i.e. glabrous) sweating would be further potentiated by a heightened sympathetic response due to an elevation in relative exercise intensity. Such a mechanism would explain the observations of Kacin *et al.* (2005, 2007), who demonstrated increases in forehead sweating through manipulations of relative exercise intensity via ischaemia and hypoxia despite similar external work rates.

Conflicting evidence currently exists regarding whether sudomotor activity is differentially controlled in glabrous and non-glabrous skin areas. Differential sympathetic nerve activity has been reported in response to mental arithmetic (Iwase *et al.* 1997) and passive heating (Okamoto *et al.* 1994). Additionally, patients suffering from primary hyperhidrosis, which is thought by some to occur at least partly in response to emotional distress (Cerfolio *et al.* 2011), primarily experience excessive sweating from glabrous skin (de Campos *et al.* 2003). Moreover, Ogawa (1975) reported augmented palmar (i.e. glabrous), but not forearm, sweating in response to a mental arithmetic task and exercise; however, pain and loud noise induced sweating in both regions. On the contrary, recent reports show that psychological stress, irrespective of its nature (cognitive challenge and pain), elicits greater sweating across the body during both passive heating (Machado-Moreira & Taylor, 2011*b*) and normothermia (Machado-Moreira & Taylor, 2011*a*). The greater LSR_{head} in the BAL trial of the present study suggests that exercise and psychological (or mental) stimuli represent unique stressors, resulting in different patterns of local sweating. Whether changes in relative exercise intensity inflict psychological stress and whether psychological stimuli can affect sweating during exercise is not known (Kondo *et al.* 2010) and deserves further investigation.

It is important to clarify that, from a theoretical point of view, the independent comparison of sweat rates between fit and unfit groups requires the same evaporative requirement for heat balance (E_{req}) and not necessarily the same absolute power as suggested by Schwiening *et al.* (2011). This distinction is pertinent to identify the circumstances in which the relationship between absolute power and sweating no longer holds. For example, a difference in mechanical efficiency between independent groups would result in divergent rates of oxygen consumption and therefore heat production at the same absolute power, leading to greater evaporative requirement for heat balance in the group with a lower mechanical efficiency. Any subsequent difference in sweating between the two groups would therefore not be exclusively of a physiological origin, because the biophysical factors determining sweat production would be different. Likewise, a comparison of local sweat rates between groups of different body surface areas performing the same absolute power would also theoretically lead to potentially erroneous conclusions. A fixed workload would generate a similar amount of metabolic heat in all participants (assuming no differences in mechanical efficiency); thus, the same absolute rate of evaporation is required for heat balance. Given no differences in evaporative efficiency, the same absolute amount of sweat production (e.g. in milligrams per minute) would be required to achieve the required evaporative rate. An equal total volume of sweat would be spread over a smaller surface area in smaller individuals and, as local sweat rate is measured over a fixed area of the skin surface in all participants, the rate of local sweat production per unit surface area (milligrams per square centimetre per minute) would be correspondingly higher with a lower BSA at a fixed workload. According to the analyses of Schwiening *et al.* (2011), the modest difference in BSA between sexes (~10%) in the study of Ichinose-Kuwahara *et al.* (2010) was not sufficient to greatly alter the relationship of absolute power with local sweat rate between men and women. However, when comparing independent groups with vastly different BSA, such as children at various stages of development (e.g. prepubertal *versus* late pubertal) or groups of lean *versus* obese individuals, a completely independent comparison of local sweat rates between groups should not be performed unless E_{req} per unit surface area (i.e. in watts per square metre) is the same.

The influence of a high $\dot{V}_{O_2\,max}$ on individual sweating responses has previously been attributed to a more even distribution of sweat, serving to reduce local skin wettedness and improve sweating efficiency (Havenith & van Middendorp, 1990). An increase in forehead sweating in unfit individuals would produce greater local skin wettedness and reduced sweating efficiency (i.e. more dripping). Thus, aerobic fitness may seemingly confer some thermoregulatory advantage. However, assuming a forehead surface area of ~150 cm^2 (Cabanac & Brinnel, 1988), LSR_{head} would have contributed approximately 1.5 and 2.7% to $WBSR_{ss}$ in F and UF subjects, respectively, during 60 min of exercise in the BAL trial; therefore, the role of forehead sweating relative to whole-body sweating may be considered negligible. On the contrary, if other glabrous sites respond in a similar manner to the forehead, $WBSR_{ss}$ in the UF group would be greater while sweating

efficiency would be lower. The results of the BAL trial also demonstrate that the use of forehead sweating as an index of whole-body sweating responses may lead to erroneous conclusions regarding the influence of aerobic fitness on whole-body sudomotor responses. Moreover, calculating average local sweat rate as an equally weighted average of numerous sites (Ichinose-Kuwahara *et al.* 2010; Amano *et al.* 2011) may allow forehead sweat rate (or, if included, other glabrous sites affected by relative exercise intensity) to influence the average local sweat rate disproportionately in aerobically unfit individuals.

The observation that LSR_{head} was significantly greater in UF subjects during the BAL trial despite a lack of difference in $WBSR_{ss}$ may appear contradictory. However, the 0.8 mg cm^{-2} min^{-1} greater LSR_{head} in the UF group would only equate to ~1.8 g of extra total sweat production during the final 15 min of exercise; a difference that would have probably been obscured by the sensitivity of our scale (±1 g). This consideration assumes that the elevation in local sweat rate would have been confined to the forehead only, whereas if local sweating was potentiated in all glabrous skin areas one would potentially expect an observable difference in whole-body sweat rates between F and UF groups. Whether local sweating at other glabrous skin regions was influenced in a similar manner by $\dot{V}_{O_2\,max}$, and/or whether elevations in sudomotor activity in some skin regions were balanced by concurrent reductions in other regions, is unclear from the present data. As local sweat rates were only measured at the forearm and forehead, local sweating may have been reduced proportionally in other skin regions. As such, further research is needed to compare steady-state local sweat rates on other glabrous and non-glabrous skin regions between fit and unfit participant groups during exercise that elicits the same E_{req}. The technical absorbent method for measuring local sweat rate is relatively new, and the influence of the absorbent material on skin saturation is not known. However, the highest average sweat rate observed during the present study (forehead sweat rate of the F group in the 60% $\dot{V}_{O_2\,max}$ trial) equated to less than 1% of the absorbent capacity of a 36 cm^2 patch (57,175 mg). The saturation point of the absorbent material was therefore not close to being approached during any of our measurements, and the notion that local skin humidity was disproportionately increased by the sweat patch method therefore seems highly unlikely. The method employed in the present study was slightly modified relative to previous studies by other research groups. As the local sweat rate of specific isolated regions was required, a separate 2-cm-wide frame surrounding each absorbent patch was used with each measurement. The frame, which was discarded after each individual measurement, ensured that dripping sweat from surrounding skin regions did not contaminate the sweat rate measurement of the patch itself.

In conclusion, aerobic fitness alters local sweating on the forehead, but not the forearm, independently of evaporative requirements for heat balance, and may be the result of a greater sympathetic drive associated with a higher relative exercise intensity.

Appendix

Calculations

The rate of metabolic energy expenditure ($\dot{M}$) was calculated from the rate of oxygen consumption ($\dot{V}_{O_2}$) and respiratory exchange ratio (RER) using eqn (A1) (Nishi, 1981):

$$\dot{M}(\text{in watts per square metre}) = \dot{V}_{O_2}\frac{\left[\left(\frac{RER-0.7}{0.3}\right)e_c\right]+\left[\left(\frac{1-RER}{0.3}\right)e_f\right]}{60BSA}\times 1000 \quad (A1)$$

The energy equivalent of carbohydrate (21.13 kJ) and fat (19.62 kJ) are denoted by e_c and e_f, respectively, and BSA is the body surface area.

Convective (C) and radiative (R) heat losses were calculated using eqns (A2) and (A3), respectively (Parsons, 2003):

$$C(\text{in watts per square metre}) = f_{cl}h_c(t_{cl}-t_a) \quad (A2)$$

$$R(\text{in watts per square metre}) = f_{cl}h_r(t_{cl}-t_a) \quad (A3)$$

where f_{cl} is the clothing area factor (assumed to be 1.0 due to the minimal amount of clothing worn by the participants); h_c is the convective heat transfer coefficient (in watts per square metre per degree kelvin), calculated as $h_c = 8.3v^{0.6}$ with an air velocity (v) of 1.3 m s^{-1} covering 70% of body surface area; $(t_{cl}-t_a)$ is the temperature gradient between the clothed skin (assumed to be equal to $\bar{T}_{sk}$) and the environment; and h_r (in watts per square metre per degree kelvin) is the linear radiative heat transfer coefficient, calculated using eqn (A4) (Parsons, 2003), as follows:

$$h_r = 4\varepsilon\sigma\left(\frac{A_r}{BSA}\right)\left[273.2+\frac{(t_{cl}+t_r)}{2}\right]^3 \quad (A4)$$

where ε is the area-weighted emissivity of the clothed skin, estimated as 0.95; σ is the Stefan-Boltzmann constant (5.67×10^{-8} W m^{-2} K^{-4}); A_r is the effective radiative surface area (in square metres), estimated as 0.7 for a seated individual (Fanger, 1970); and t_r is the mean radiant temperature (in degrees Celsius), assumed to be equal to t_a.

Convective (C_{res}) and evaporative respiratory heat losses (E_{res}) were calculated together (in watts per square

metre) using eqn (A5) (Parsons, 2003), as follows:

$$C_{res} + E_{res} = 0.0014(H_{prod})(34 - t_a) + 0.0173(H_{prod})(5.87 - P_a) \quad \text{(A5)}$$

where H_{prod} is the rate of metabolic heat production in Watts per square metre, calculated as the difference between $\dot{M}$ and external workload ($\dot{W}$), and P_a is the ambient vapour pressure of water.

Using the terms defined above, the required evaporative heat loss to achieve heat balance (E_{req}) was calculated as follows using eqn (A6):

$$E_{req}(\text{in watts per square metre}) = H_{prod} - (C + R + C_{res} + E_{res}) \quad \text{(A6)}$$

The environmental capacity for evaporative heat loss (E_{max}) was calculated (in watts per square metre) using eqn (A7) (ASHRAE, 2009):

$$E_{max} = \frac{\omega(P_{sks} - P_a)}{(1/h_e)} \quad \text{(A7)}$$

where skin wettedness is denoted as ω, which is equal to 1.0 at maximal evaporation; $(P_{sks} - P_a)$ is the water vapour pressure gradient between the skin surface (assumed to be saturated at a given T_{sk}) and the environment (in kilopascals); and h_e is the evaporative heat transfer coefficient (in watts per square metre per kilopascal) calculated as the product of h_c and the Lewis number (16.5 K kPa^{-1}; Parsons, 2003).

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Acknowledgements

This research was supported by a Natural Sciences and Engineering Research Council (NSERC) of Canada Discovery Grant (grant holder O.J.). A.R.B. was supported by a University of Ottawa Master's Scholarship and an Ontario Graduate Scholarship. The authors wish to thank the volunteers for their co-operation, Christopher Bell for his assistance with data collection and Dr Simon Hodder for his guidance with the local sweat rate measurement technique.

APPENDIX I Published article investigating the role of the rate of heat storage on endurance exercise performance

Eur J Appl Physiol (2014) 114:2399–2410
DOI 10.1007/s00421-014-2958-y

ORIGINAL ARTICLE

Do greater rates of body heat storage precede the accelerated reduction of self-paced exercise intensity in the heat?

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Received: 8 April 2014 / Accepted: 14 July 2014 / Published online: 5 August 2014

Abstract

Aim To reevaluate the previous hypothesis that greater reductions in self-paced exercise intensity in the heat are mediated by early differences in the rate of body heat storage (S).

Methods Eight trained volunteers cycled in 19 °C/1.8 kPa (COOL), 25 °C/1.2 kPa (NORM), and 34 °C/1.6 kPa (HOT), while maintaining an RPE of 16. Potential differences in S following the onset of exercise were assessed by comparing rates of esophageal temperature change ($\Delta T_{es}/\Delta t$); and estimated S values using a traditional two-compartment thermometric model (S_{therm}) of changes in rectal (T_{re}) and skin (T_{sk}) temperature, and partitional calorimetry (S_{cal}).

Results After 15 min of exercise, workload decreased more in HOT vs. COOL ($P = 0.03$), resulting in a shorter time (HOT: 40.7 ± 14.9 min; COOL: 53.5 ± 18.7 min; $P = 0.04$) to 70 % of initial workload. However, there were no preceding differences in $\Delta T_{es}/\Delta t$ between conditions ($P = 0.18$). S_{therm} values were different between HOT and COOL during the first 5 min of exercise ($P < 0.05$), primarily due to negative S_{therm} values (−32 ± 15 kJ min^{-1}) in COOL, which according to partitional calorimetric measurements, required improbably high (~56 kJ min^{-1}) rates of evaporation when no sweating on the back and thigh was observed until after 7.6 ± 1.5 min and 4.8 ± 1.7 min of exercise, respectively. S_{cal} values in the first 5 min of exercise confirmed S was actually positive in COOL (+21 ± 8 kJ min^{-1}) and not negative. Different S_{therm} values following the onset of exercise at different environmental temperatures are simply due to transient differences in the rate of change in T_{sk}.

Conclusion Reductions in self-paced exercise intensity in the heat are not mediated by early differences in S following the onset of exercise.

Keywords Core temperature · Exercise performance · Partitional calorimetry · Rating of perceived exertion · Thermoregulation

Abbreviations

A_r/A_D	Effective radiant surface area (ND)
BF	Biceps femoris
A_D	Body surface area (m^2)
C	Convective heat exchange (W m^{-2})
C_{res}	Convective heat exchange via respiration (W m^{-2})
E_{sk}	Evaporative heat loss from the skin (W m^{-2})
E_{res}	Evaporative heat loss via respiration (W m^{-2})
E_C	Caloric equivalent of carbohydrates (kJ LO^{-2})
E_F	Caloric equivalent of lipids (kJ LO^{-2})
EMG	Electromyography (% of initial EMG)
ε	Area-weighted emissivity of the skin (ND)

Communicated by Narihiko Kondo.

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f_{cl}	Area-weighted clothing factor (ND)
GM	Gluteus maximus
h	Combined heat transfer coefficient (W m^{-2} °C^{-1})
h_c	Convective heat transfer coefficient (W m^{-2} °C^{-1})
h_r	Radiative heat transfer coefficient (W m^{-2} °C^{-1})
H_{prod}	Rate of metabolic heat production (W m^{-2})
iEMG	Integrated electromyography (% of initial iEMG)
LG	Lateral gastrocnemius
LSR_{back}	Local sweat rate on the lower back (mg cm^{-2} min^{-1})
LSR_{thigh}	Local sweat rate on the thigh (mg cm^{-2} min^{-1})
M	Metabolic energy expenditure (W m^{-2})
PAR-Q	Physical Activity Readiness Questionnaire
P_a	Ambient water vapor pressure (kPa)
R	Radiant Heat exchange (W m^{-2})
R_{cl}	Thermal resistance of clothing (m^2 °C W^{-1})
RER	Respiratory exchange ratio (ND)
RPE	Rating of perceived exertion
S	Rate of body heat storage (kJ min^{-1})
S_{cal}	Rate of body heat storage measured with partitional calorimetry (kJ min^{-1})
S_{therm}	Rate of body heat storage estimated with a traditional 2-compartment thermometry model (kJ min^{-1})
σ	Stefan-Boltzmann constant (5.67×10^{-8}W m^{-2} °C^{-4})
T_a	Ambient air temperature (°C)
ΔT_b	Change in mean body temperature (°C)
T_{cl}	Temperature of the clothing (°C)
T_{es}	Esophageal temperature (°C)
$\Delta T_{es}/\Delta t$	Rate of oesophageal temperature change (°C min^{-1})
T_o	Operative temperature (°C)
T_r	Mean radiant temperature (°C)
T_{re}	Rectal temperature (°C)
T_{sk}	Mean skin temperature (°C)
VO_{2peak}	Peak rate of oxygen consumption (L min^{-1})
VO_2	Rate of oxygen consumption (L min^{-1})
v	Air velocity (m s^{-1})
VL	Vastus lateralis
W	Rate of external work (W m^{-2})
W_{peak}	Peak rate of external work (W)

Introduction

It has been proposed that catastrophic levels of hyperthermia may be avoided during self-paced exercise in the heat via an anticipatory (i.e. feed forward) reduction of power output, motor unit recruitment (and therefore metabolic heat production), which are subconsciously mediated by the rate of body heat storage (S) during the first 4 min of exercise (Tucker et al. 2006). This interpretation was subsequently challenged using a theoretical heat balance assessment that demonstrated that the observed S values following the onset of exercise were potentially incorrect (Jay and Kenny 2009). It was further proposed that the underlying reason for these inaccurate S values was the erroneous nature of the two-compartment thermometric model employed that uses minute-by-minute changes in rectal temperature (T_{re}) and mean skin temperature (T_{sk}) to estimate S (Stolwijk and Hardy 1966; Horstman and Horvath 1972; Vallerand 1992; Snellen 2000; Jay et al. 2007). Specifically, early changes in T_{sk}, which represent the body "shell", seem to exaggerate any potential differences in S during the early stages of exercise between hot and cold environments; and changes in T_{re}, which represent the body "core", do not seem to reflect any changes in S following the start of exercise due to its well documented time lag (Jay and Kenny 2009). If this is the case, then the original conclusion—that differences in S between hot and cool conditions only occur during the first 4 min of exercise, with no differences observed thereafter (when changes in self-regulated power output then occur)—may be greatly dependent upon the "core" to "shell" weightings used to estimate S.

In the absence of whole-body direct calorimetry, a different thermometric approach is required to re-evaluate whether S plays a potential role in a feed-forward regulatory model of self-paced exercise. Firstly, any early changes in T_{sk} can likely be discounted since they do not contribute to the description of changes in heat storage during the first 10 min of exercise (Jay et al. 2007). Secondly, a temperature probe placed in the esophagus (T_{es}) should provide a more responsive indicator of early changes in S than T_{re}. Since the tissue temperature changes occurring in the body as a consequence of the large rates of initial heat storage will primarily be centralized around the main source of exercise-induced thermogenesis—the active musculature (Jay et al. 2007)—temperature of out-flowing blood from active muscle and returning to the heart should therefore closely resemble T_{es}, which has been shown to approach aortic blood temperature with only a minor lag of 80–160 s during high rates of changing blood temperature (Cooper and Kenyon 1957; Shiraki et al. 1986). Therefore, while replacing T_{re} with T_{es} as a representative of the body "core" in the conventional two-compartment thermometry model probably does not yield precise absolute values for S during the early stages of exercise, it stands to reason that different rates of change of T_{es} ($\Delta T_{es}/\Delta t$) will occur in parallel to proportional physiologically significant differences in S with a minimal time delay.

The primary purpose of the present study was to reevaluate the potential role of early changes in S in an anticipatory feed-forward regulatory model of self-paced exercise (Tucker et al. 2006). Previous procedures were replicated and S was assessed using a range of methods in subjects self-regulating their cycling power output at a fixed rating of perceived exertion (RPE) (Borg 1982) in cool, neutral, and warm environments. Specifically, we sought to determine if subjects only show different $\Delta T_{es}/\Delta t$ during the early stages of exercise, indicative of different S, with similar $\Delta T_{es}/\Delta t$ occurring thereafter irrespective of environmental conditions due to a reduction in power output that is greatest in the hottest environment. A secondary purpose of the present study was to assess whether previous conclusions related to the role of S were dependent upon the weighting coefficients of the "core" and "shell" components of the two-compartment thermometry model used to estimate S, and to determine how the S values previously reported in cooler environments using thermometry during the early stages of exercise compare to S values measured using partitional calorimetry. It was hypothesized that: (1) $\Delta T_{es}/\Delta t$ would be similar between cool, neutral, and hot conditions throughout self-regulated exercise at a fixed RPE; (2) different "core" and "shell" weighting coefficients employed in the two-compartment thermometry model alter the conclusion of different S values between conditions during the early stages of exercise; and (3) S values measured with partitional calorimetry during the early stages of self-regulated exercise in cooler environments are positive and not negative.

Methods

Participants

A power calculation using esophageal temperature data from pilot studies was performed using the calculated effect size of 1.2, $\alpha = 0.05$, and $\beta = 0.2$ which determined that eight participants were required to demonstrate a difference in $\Delta T_{es}/\Delta t$. Therefore, 8 endurance-trained volunteers (seven males, one female) participated in this study (VO_{2peak} 59.3 ± 6.3 ml kg^{-1} min^{-1}; W_{peak} 355 ± 49 W, 5.0 ± 0.6 W kg^{-1}; Age 26.0 ± 5.5 years; Mass 72.0 ± 7.3 kg; Height 1.88 ± 0.12 m^2). Prior to experimentation, all participants provided written informed consent, and completed a Physical Activity Readiness Questionnaire (PAR-Q) 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 to the guidelines set forth in the Declaration of Helsinki.

Preliminary trials

During the first visit to the laboratory, each participant performed an incremental exercise test to exhaustion on an upright cycle ergometer to determine their peak rate of oxygen consumption (VO_{2peak}) and peak external workload (W_{peak}): Following a 10 min warmup the incremental protocol began at an external workload of 80 W, which was then increased by 20 W min^{-1} until volitional exhaustion. This test was conducted in accordance with the guidelines of the Canadian Society for Exercise Physiology (CSEP 1996). The second visit involved familiarization with the fixed RPE protocol: In the familiarization trial, participants commenced cycling at a workload of 100 W, which was subsequently increased by 10 W every 5 min until an RPE of 16 (corresponding to a rating between 'hard' and 'very hard' on the Borg scale) was reached. The participants were then instructed to adjust their workload to maintain this sensation for an additional 10 min. This approach allowed the participants to become familiar with the Borg scale and the sensation associated with the target RPE. Thus for each participant the initial workload for each experimental trial was established as the average workload during the final 10 min of the familiarization trial.

Experimental protocol

In separate sessions, experimental trials were performed in hot (HOT: 33.7 ± 0.8 °C, 1.6 ± 0.5 kPa), thermo neutral (NORM: 25.2 ± 0.7 °C, 1.2 ± 0.5 kPa), and cool (COOL: 19.3 ± 1.4 °C, 1.8 ± 0.5 kPa) conditions, with trial order counterbalanced across participants. Levels of humidity were chosen to elicit a similar absolute skin-air vapor pressure gradient at each ambient air temperature, and to thereby produce a similar drive for evaporation. In the 24 h prior to each experimental trial, participants were asked to avoid alcohol, caffeine, and strenuous exercise. Additionally, they were asked to consume a light meal and 500 ml of water ~2 h prior to arrival at the laboratory. Upon arrival, the participants voided their bladders providing a urine sample to ensure hydration and changed into a standardized clothing ensemble consisting of cotton shorts, cotton socks, and cycling shoes. Trials would be postponed and rescheduled if urine specific gravity measured using a clinical refractometer (Reichert TS 400, Depew, NY, USA) was greater than 1.020. Following a 45 min instrumentation period, a 10 min warmup with the cycle ergometer set at 125 W was performed. Following this, the participants entered the laboratory and rested quietly in a seated position on the ergometer while instrumentation was completed. A 20 min baseline data collection period preceded exercise, during which time a body mass measurement was taken 5 min before exercise with a platform scale accurate

to the nearest ± 2 g (Combics 2; Sartorius, Mississauga, ON, Canada) with sensor cables secured to an adjacent table. Immediately prior to the start of exercise participants were reminded to maintain a RPE of 16 by adjusting the workload. The ergometer was set to a cadence-independent mode, so that a preferred cadence could be maintained for any self-selected workload. The participants then began cycling, facing a mechanized fan providing an air velocity of 1.7 ± 0.4 m s^{-1}. Participants were blinded to physiological and performance feedback throughout all trials. Exercise continued until workload declined to <70 % of the initial 5 min average. A final body mass measurement was taken immediately upon the completion of exercise, prior to the subject drying off, and with sensor cables secured to an adjacent table at exactly the same point as during the pre-exercise body mass measurement.

Measurements

Ambient conditions: Dry-bulb temperature and absolute humidity were measured every 5 s using a dew point mirror (473 RH Systems, Albuquerque, NM, USA). Air velocity was measured with a hot wire anemometer (HHF42, Omega Engineering, Stamford, CT, USA).

Indirect calorimetry: Participants were equipped with a mouthpiece and nose clip, and were instructed to breathe normally at all times. Expired gases were analyzed breath-by-breath throughout exercise using a metabolic cart (V_{max} Encore, CareFusion, Yorba Linda, CA, USA).

Thermometry: Core temperature was measured continuously in the rectum and the esophagus using general purpose pediatric T-type (copper/constantan) thermocouple probes (Mon-a-therm®, Mallinckrodt Medical, St. Louis, MO, USA). Rectal temperature (T_{re}) was measured at a depth of 12 cm beyond the anal sphincter. Esophageal temperature (T_{es}) was measured at a maximum depth of 40 cm, estimated to be at the level of the left ventricle (Mekjavic and Rempel 1990). Skin temperature was measured at four sites on the left side of the body using T-type thermocouples integrated into heat flux sensors (Concept Engineering, Old Saybrook, CT, USA), which were secured to the skin with surgical tape (Transpore®, 3M, London, ON, Canada). Mean skin temperature (T_{sk}) was estimated using a weighted average of four sites in accordance with Ramanathan (1964): chest 30 %, triceps 30 %, thigh 20 %, and calf 20 %. Thermometric measurements were sampled every 5 s (NI cDAQ-91722 module, National Instruments, Austin, TX, USA) and displayed in real-time on a desktop computer using customized LabView software (v7.0, National Instruments, Austin, TX, USA).

Local sweat rates were measured on the lower back (LSR_{back}) and thigh (LSR_{thigh}) on the right side of the body using the ventilated capsule technique. These sites were chosen as they demonstrate the relatively early onset times for thermoregulatory sweating (Cotter and Taylor 2005). Anhydrous air was supplied to each 4.1 cm^2 capsule at a constant flow rate of 1.80 L min^{-1} (Omega FMA-A2307, Omega Engineering, Stamford, CT, USA). Capsules were secured using skin glue (Collodion USP MD0002, Mavidon, Lake Worth, FL, USA) and surgical tape. The temperature and humidity of effluent air were measured every 5 s using factory-calibrated capacitance hygrometers (HMT333, Vaisala, Vantaa, Finland). Local sweat rate was 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 cm^{-2} min^{-1}).

Electromyography (EMG): Surface EMG data were collected from the right vastus lateralis (VL), gluteus maximus (GM), biceps femoris (BF), and lateral gastrocnemius (LG) using bipolar, pre-amplified surface electrodes connected to an external amplifier system (Delsys Bagnoli-8, Natick, MA, USA). The recording sites were prepared and the electrodes were attached using double-sided adhesive strips, and secured using surgical tape. A grounding electrode (Kendall Q-Trace 5400, Covidien Inc., Mansfield, MA, USA) was placed over the participant's right anterior superior iliac spine.

Unfiltered raw EMG was digitally sampled at 1 kHz (National Instruments PCI-6052E, Austin, TX, USA) for the first 10 s of each minute during cycling and EMG values for all four muscles were calculated from a time window corresponding to 10 cycles within each 10 s time block irrespective of cadence. The magnitude of the integrated EMG (iEMG) was calculated for each muscle by numerically integrating the rectified EMG signal within the 10-cycle window on each trial. To quantify muscle output for the whole leg (LEG) in a more holistic manner, LEG weighted average iEMG was calculated from the normalized iEMG and expressed as a percentage of initial LEG. The weightings used were: *V*L, 41 %; GM, 28 %; BF, 10 %; LG, 21 % (Ericson 1986). To normalize between testing sessions, iEMG was expressed as a value per unit of work (W) by dividing iEMG by the cycle ergometer power output observed at minute 5 in each session (see above). Initial iEMG was then calculated as the mean of iEMG at minutes 4, 5, and 6. For minutes 10, 15 and 20, iEMG values were calculated as the mean iEMG values from the preceding 5 min (i.e., 6–10, 11–15, 16–20), and expressed as a percentage of initial iEMG.

Calculations

Rate of heat storage (partitional calorimetry): Calorimetric estimates of the rates of heat storage (S_{cal}) were calculated for NORM and COOL conditions according to the conceptual heat balance equation:

$$S_{cal} = M - W - (C + R + E_{sk} + C_{res} + E_{res}) \left(\mathrm{W\ m^{-2}}\right)$$

Metabolic rate (M) was calculated as:

$$M = VO_2 \frac{\left(\left(\frac{RER-0.7}{0.3}\right)e_c\right) + \left(\left(\frac{1.0-RER}{0.3}\right)e_f\right)}{(60)(A_D)} \times 1000 \left(\mathrm{W\ m^{-2}}\right)$$

where: VO_2 is the rate of oxygen consumption (L min^{-1}); RER is the non-dimensional respiratory exchange ratio; e_c and e_f are the energetic equivalents of carbohydrate (21.13 kJ L^{-1} O_2) and fat (19.62 kJ L^{-1} O_2), respectively; A_D is body surface area in m^2, estimated using the equation of DuBois and Dubois (1916). External workload (W) was regulated using an electromagnetically-braked upright cycle ergometer (Ergo Race, Kettler, Ense-Parsit, Germany). The rate of metabolic heat production (H_{prod}) was calculated as the difference between metabolic rate and external workload (in W m^{-2}).

Combined respiratory heat exchange (H_{res}) via convection (C_{res}) and evaporation (E_{res}) was calculated as:

$$C_{res} + E_{res} = \left[0.0014 \times (H_{prod}) \times (34 - T_a)\right] + \left[0.0173\ (H_{prod}) \times (5.87 - P_a)\right] \left(\mathrm{W\ m^{-2}}\right)$$

where: P_a is the ambient vapor pressure in kilopascals (kPa).

Heat exchange via convection (C) and radiation (R) was calculated as:

$$C + R = \frac{(T_{sk} - T_o)}{R_{cl} + \frac{1}{f_{cl} \cdot h}} \left(\mathrm{W\ m^{-2}}\right)$$

where: R_{cl} is the thermal resistance of clothing (m^2 °C W^{-1}), but was assumed to be negligible in the present study due to a minimal clothing ensemble; f_{cl} is the non-dimensional area-weighted clothing factor (assumed to be 1.0 with minimal clothing); h is the combined heat transfer coefficient (W m^{-2} °C^{-1}), which is the sum of the convective (h_c) and radiant (h_r) heat transfer coefficients (see below).

Operative temperature (T_o) was estimated as:

$$T_o = \frac{(h_c T_a) + (h_r T_r)}{h_r + h_c} \left(^\circ\mathrm{C}\right)$$

where: T_a is ambient temperature (°C) and T_r is the radiant temperature (°C), assumed to be equal to T_a.

Values for h_c and h_r were calculated as:

$$h_c = 8.3 v^{0.6} \left[\mathrm{W\ m^{-2}\ ^\circ C^{-1}}\right]$$

$$h_r = 4 \varepsilon \sigma \frac{A_r}{A_D} \left[273.15 + \left(\frac{T_{cl} + T_r}{2}\right)\right]^3 \left(\mathrm{W\ m^{-2}\ ^\circ C^{-1}}\right)$$

where: v is air velocity (m s^{-1}); ε is the area-weighted emissivity of the skin, taken as 0.95; σ is the Stefan-Boltzmann constant (5.67 × 10^{-8}W m^{-2} °C^{-4}); A_r/A_D is the effective radiant surface area (ND), estimated to be 0.7 for a seated individual (Fanger 1970); and T_{cl} is the temperature of the clothing (°C), assumed to be equal to T_{sk}.

Evaporative heat loss was assumed to be negligible in NORM and COOL conditions until the onset of sweating. No estimate of evaporative heat loss and therefore S_{cal} was made in HOT since sweating was evident prior to exercise.

Although estimated in W m^{-2}, all heat balance parameters were converted to kJ min^{-1} (1 W = 0.06 kJ min^{-1}) to compare the present results to those of previous studies.

Rate of heat storage (thermometry): Minute-by-minute changes in mean body temperature (ΔT_b) were estimated using four different two-compartment thermometric models: T_{re}/T_{sk} (A) 0.66/0.34, (B) 0.79/0.21, (C) 0.90/0.10, and (D) 1.00/0.00. Thermometric estimates of heat storage (S_{therm}) were calculated as the product of body mass, an estimated average-specific heat capacity of 3.47 kJ kg^{-1} °C^{-1} for body tissue (Gephart and DuBois 1915), and ΔT_b. Values of S_{therm} using T_{re}/T_{sk} weighting coefficients of 0.79/0.21 were compared directly to S_{cal} during the first 5 min of exercise in COOL and NORM.

Statistical analysis

All data are reported as the mean ± standard deviation (SD) for each variable. Mean trial duration was analyzed using a one-way analysis of variance (ANOVA) employing the independent variable of ambient temperature (three levels: HOT, NORM, COOL). Since trial duration varied between subjects, analyzes were performed for the first 20 min of exercise, which was the minimum trial duration for all participants. A two-way repeated measures ANOVA, with the independent factors of ambient temperature and time (four levels: Baseline, 10, 15, 20 min) were used to analyze the dependent variables of percentage change in workload, $\Delta T_{es}/\Delta t$, $\Delta T_{sk}/\Delta t$, H_{prod}, S_{threm}, LSR_{back}, LSR_{thigh}, individual muscle iEMG, and whole-leg iEMG. S_{cal} values in each of the first 5 min of exercise were compared between NORM and COOL using a two-way ANOVA. A Greenhouse-Geisser correction was applied if assumptions of sphericity were not met. When a significant main effect was detected, individual differences were compared using the Holm–Bonferonni method. The probability of a Type I error was set at the 0.05 level. All statistical analyzes were performed with SPSS 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Trial duration

Mean trial duration was 53.5 ± 18.7, 54.5 ± 18.5, and 40.7 ± 14.9 min for COOL, NORM, and HOT, respectively

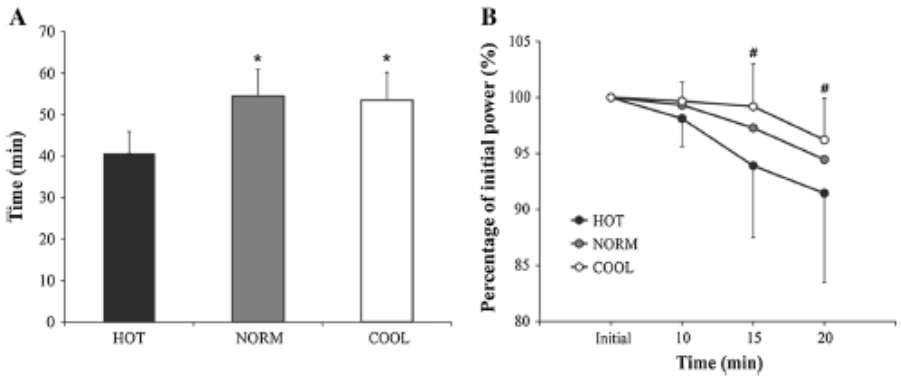


Fig. 1 Mean trial duration (**a**) and self-selected power output expressed as a percentage of the absolute workload at 5 min of exercise (**b**) for HOT, NORM, and COOL. *Significantly higher than HOT ($P < 0.05$). #Significantly lower in HOT compared to COOL ($P < 0.05$)

(Fig. 1a). Mean trial duration was significantly shorter in the HOT compared to the NORM and COOL condition ($P < 0.05$).

External workload

Changes in workload expressed as a percentage of the initial workload (i.e., at 5 min) are depicted in Fig. 1b. Initial workloads were not different between the COOL, NORM, and HOT (219 ± 27, 224 ± 35, and 219 ± 35 W, respectively; $P > 0.05$). However, the reduction in workload was significantly greater in HOT compared to COOL after 15 min ($P < 0.05$; Fig. 1b).

Rates of change of esophageal and skin temperatures

The rate of change of esophageal temperature ($\Delta T_{es}/\Delta t$) is shown in Fig. 2. $\Delta T_{es}/\Delta t$ changed significantly with exercise time ($P < 0.001$); however, there was no difference between HOT, NORM and COOL ($P = 0.18$) (Fig. 2).

The rates of change of rectal temperature ($\Delta T_{re}/\Delta t$) and mean skin temperature ($\Delta T_{sk}/\Delta t$) are shown in Fig. 3a, b. No differences were observed between conditions for $\Delta T_{re}/\Delta t$ during the first 20 min of exercise. $\Delta T_{sk}/\Delta t$ declined rapidly following the onset of exercise, with the highest rates of skin cooling observed at 2 min in all conditions. While $\Delta T_{sk}/\Delta t$ changed significantly with exercise time ($P < 0.001$), there was also a significant interaction between time and environmental temperature ($P < 0.001$) showing that the change in $\Delta T_{sk}/\Delta t$ with exercise time was most negative and greatest in magnitude in the COOL (Fig. 3b).

Differences in absolute T_{sk} were evident between conditions ($P < 0.001$), with the highest values observed in

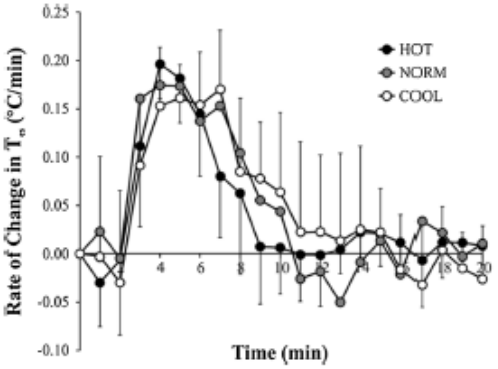


Fig. 2 Rate of change in T_{es} during the first 20 min of exercise

HOT (33.89 ± 0.20 °C) and the lowest values in COOL (28.30 ± 0.57 °C) during the first 20 min.

Rate of heat storage estimated using thermometry (S_{therm})

Compared to HOT, S_{therm} in NORM and COOL was negative and significantly lower during the first 4 min of exercise using model A (core/shell: 0.66/0.34) and B (core/shell: 0.79/0.21), and between 2–4 min of exercise using model C (core/shell: 0.90/0.10). In models A, B, and C, S_{therm} reached a nadir after 2 min (Fig. 4a–c). However, as the proportion of the "shell" compartment became progressively smaller (from 0.34 to 0.10), the estimated values of S_{therm} became less negative in the COOL and NORM conditions and became increasingly similar to the HOT condition. When the "shell" compartment was completely

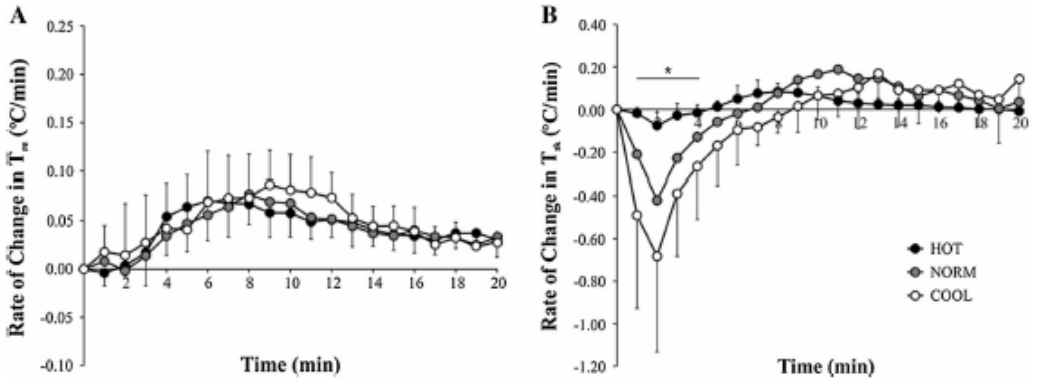


Fig. 3 Rate of change in T_{re} (**a**) and $\bar{T}_{sk}$ (**b**) during the first 20 min of exercise. *Significantly greater in HOT compared to NORM and COOL ($P < 0.05$)

eliminated in model D (core/shell: 1.00/0.00) (Fig. 4b), no difference in S_{therm} was observed between conditions.

Rate of heat storage estimated in COOL and NORM conditions using partitional calorimetry (S_{cal})

S_{cal} in the HOT condition could not be estimated using partitional calorimetry because sweating had already begun and minute-by-minute rates of evaporation could not be measured (see "Methods"). The average of the first 5 min of exercise heat balance parameters for NORM and COOL condition are detailed in Fig. 5. While H_{prod} increased significantly with exercise time ($P < 0.001$), this change was not altered by environmental temperature ($P = 0.98$). In both COOL and NORM, S_{cal} was positive (i.e. heat energy was stored in the body), and increased during the first 5 min of exercise while the first 5-minute average was negative and significantly lower for S_{therm} ($P < 0.001$). While the rate of evaporation could not be measured, when compared to the values estimated in the COOL and NORM using thermometry (S_{therm}), rates of evaporation needed for these S_{therm} values to be correct would have been between 30 and 56 kJ min^{-1}, respectively.

Local sweat rates

Significantly greater LSR_{back} was observed in the HOT compared to the COOL during the first 20 min ($P < 0.05$), while LSR_{thigh} was significantly greater in the HOT compared to the COOL during the first 11 min ($P < 0.05$). The onset of sweating at LSR_{back} and LSR_{thigh} in COOL and NORM occurred after 7.6 ± 1.5 and 4.8 ± 1.7 min of exercise, respectively. Sweating on both the back and thigh had already initiated prior to the onset of exercise in the HOT condition.

Integrated EMG (iEMG)

For iEMG values, a main effect of time was found for all four muscles (Fig. 6; $P < 0.05$). There were no other main effects or interactions. Pre-planned comparisons showed that for BF and GM, iEMG was significantly lower than initial iEMG at 10, 15, and 20 min ($P < 0.05$). For VL, iEMG was significantly lower than initial iEMG at the 15 and 20 min ($P < 0.05$), and for LG, iEMG was only significantly lower than initial iEMG at 20 min ($P < 0.05$).

LEG weighted average iEMG data are presented in Fig. 6. Similar to the individual muscles, for LEG there was a main effect of time on iEMG ($P = 0.001$). Pre-planned comparisons showed that for LEG, iEMG was significantly lower at all time points compared to initial iEMG ($P < 0.05$). There was no main effect for temperature ($P = 0.387$) and no interaction between the variables ($P = 0.497$).

Discussion

In the present study an ambient temperature-dependent reduction in power output occurred after 15–20 min of self-paced fixed-RPE exercise, a result similar to that reported by Tucker et al. (2006). However, in contrast to their conclusions, we did not observe any difference in $\Delta T_{es}/\Delta t$ between COOL, NORM and HOT conditions in advance of these changes in power output, or thereafter, suggesting a similar S in all conditions. The negative S estimated by Tucker et al. (2006) during the first 4 min of exercise using

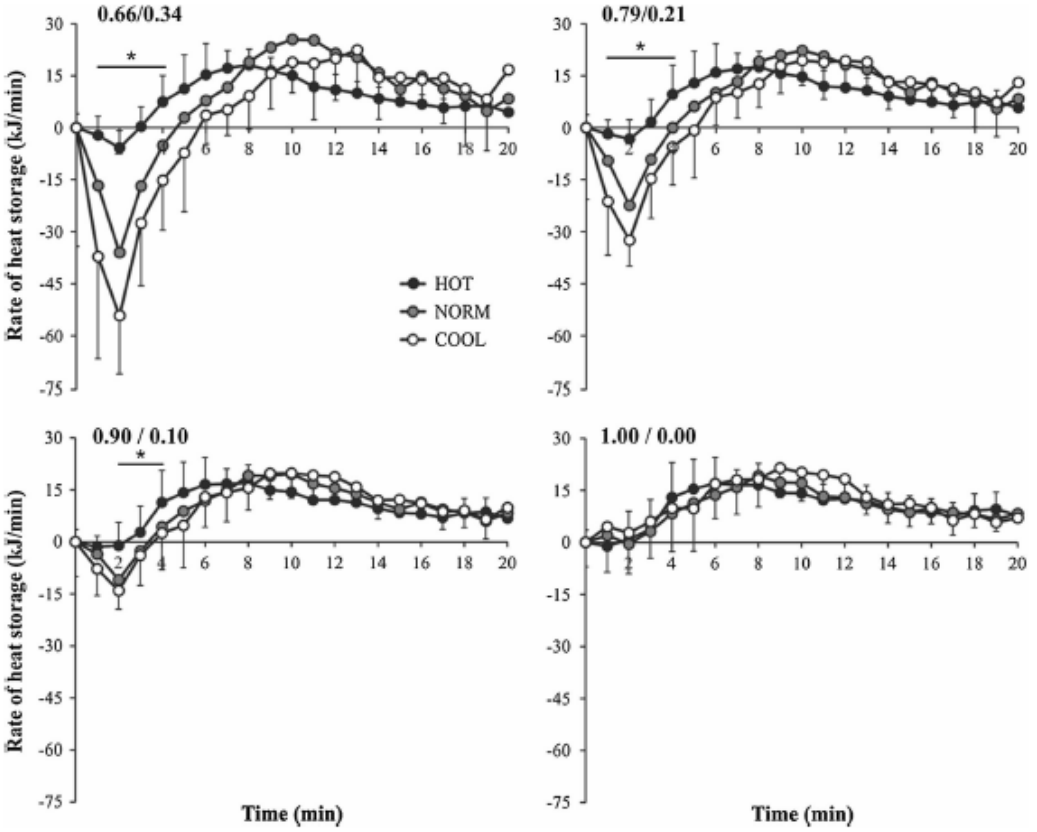


Fig. 4 Thermometric estimates of the rate of heat storage, using four different T_{re}/T_{sk} weighting coefficients for T_b: **a** 0.66/0.34, **b** 0.79/0.21, **c** 0.90/0.10 and **d** 1.00/0.00. *Significantly greater in HOT compared to NORM and COOL ($P < 0.05$)

the traditional two-compartment thermometry model in the COOL and NORM conditions, were also obtained with the S_{therm} thermometry model in the present study, but it is clear that these negative values are the result of a disproportionate influence of negative rates of skin temperature change during the first 5 min of exercise arising from an increased self-generated air velocity across the legs (Nishi and Gagge 1970). Taken together our findings do not support the hypothesis that S during the early minutes of exercise mediates subsequent changes in self-selected exercise intensity.

It has been previously argued that T_{es} may not provide an accurate absolute estimation of changes in body heat content when incorporated within a two-compartment thermometry model (Jay et al. 2007). However, while an accurate absolute S value can probably not be derived, considering the responsiveness of this core temperature measurement to changes in arterial blood temperature, it stands to reason that physiologically significant differences in the rate of body heat storage will be paralleled by different rates of change of T_{es}. Theoretically, differences in S will be best detected by measuring rates of temperature change at a site that is well perfused with blood, and serves as a major conduit for heat transfer from the working muscles to the skin. Despite its close proximity to the working muscles, the pelvic region has a high tissue density and relatively low blood perfusion, therefore the rate of change in rectal temperature is unsuitable to assess rapid changes in S such as those seen during the early stages of exercise (Blight 1957; Jay and Kenny 2009). In contrast, T_{es} is measured at the level of the right atrium/aorta (Mekjavic and Rempel 1990); therefore, rapid changes in blood temperature due to changes in heat storage are adequately reflected in the change in T_{es} (Cooper and Kenyon 1957;

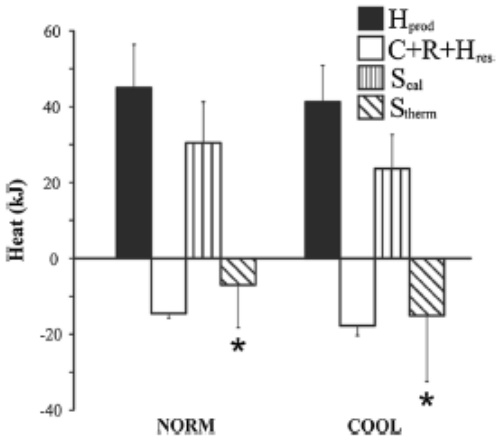


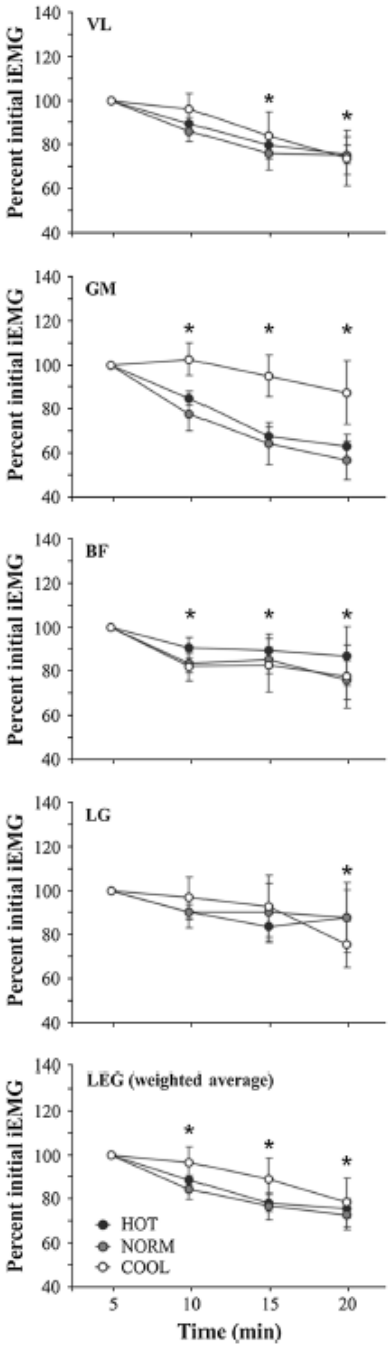
Fig. 5 Heat balance parameters averaged over the first 5 min of exercise for COOL and NORM conditions. H_{prod}, rate of metabolic heat production (i.e. M−W); $C + R + H_{res}$, rates of convective, radiant, and respiratory heat exchange, respectively; S_{cal}, rate of heat storage estimated via partitional calorimetry; S_{therm}, core/shell weighting of 0.79/0.21, respectively. *Significantly lower in S_{therm} compared to S_{cal} ($P < 0.001$)

Molnar and Read 1974; Shiraki et al. 1986). Indeed, heat production within the muscle begins almost immediately at the onset of dynamic exercise, followed by heat transfer to the blood (with a rise in blood temperature) and a rise in T_{es} (González-Alonso et al. 2000). Therefore, based on the time course for heat exchange between muscle and blood, as well as the regional differences between the esophagus and rectum, it would be expected that only a slight delay between the rise in H_{prod} and $\Delta T_{es}/\Delta t$ should be observed, while $\Delta T_{re}/\Delta t$ would be delayed. Accordingly, H_{prod} reached its peak between 2 and 4 min into exercise; meanwhile T_{es} and T_{re} reached their peak after 4 and 8 min of exercise, respectively (Fig. 2, 3a).

Large differences in S_{therm} between conditions during the first 5 min of exercise are clearly the result of a disproportionate influence of early and marked differences in the rate of skin temperature change ($\Delta T_{sk}/\Delta t$) (Fig. 3b). In both COOL and NORM conditions, the greatest (negative) $\Delta T_{sk}/\Delta t$ occurred after 2 min, coinciding with the most negative S_{therm} values when T_{sk} was included in the thermometry model (Fig. 4a–c). Moreover, the thermometry models with the greatest weighting of T_{sk} yielded the most negative S_{therm} values during the first 5 min of exercise. Notably, when T_{sk} was eliminated from the thermometry model, no differences in S_{therm} were observed between COOL, NORM and HOT conditions (Fig. 4).

While the rate of metabolic heat production rises rapidly at the start of exercise, the increase in the rate of total heat dissipation lags considerably, resulting in heat imbalance and a positive S. Based on this well-established pattern of thermogenesis and thermolysis, Jay and Kenny (2009) argued that the negative S values estimated using the traditional two-compartment thermometric model in cold environments would require rates of heat dissipation that were impossible based on the characteristics of the environment (i.e., ambient temperature, humidity, air velocity) and the lag in thermoeffector onset (i.e., thermoregulatory sweating). Indeed, given the H_{prod}, C+R, and H_{res} values measured in the present study, for the S_{therm} values estimated in the COOL and NORM conditions after 2 min of exercise to be correct, rates of whole-body sweating (and subsequent evaporation) equivalent to 1.39 and 1.31 L h^{-1}, respectively, would have been required when in fact local sweat rate on the back and thigh had not changed from baseline pre-exercise levels. Assuming little evaporation from the skin was occurring, S_{cal} in COOL and NORM conditions actually increased rapidly in a positive direction during the first 3 min of exercise, as would be expected (Jay and Kenny 2009), suggesting early positive whole-body heat storage—which is also supported by the positive change in T_{es} by ~0.4 °C from rest to 5 min. In the absence of any means to measure dynamic rates of whole-body evaporation, and since sweating had already begun prior to exercise, S_{cal} could not be determined in the HOT condition. Nevertheless, since H_{prod} (Fig. 5) and $\Delta T_{es}/dt$ (Fig. 2) were similar during the first 5 min of exercise it is likely that S_{cal} would have also been similar in all three environmental conditions. As such, higher evaporation in HOT during this time would have likely been counterbalanced by smaller dry heat losses via convection and radiation.

A unique feature of the fixed-RPE protocol is the ability to isolate the physiological factor(*s*) that affects RPE-mediated changes in work rate, and therefore performance (Tucker 2004). As in previous studies, exercise duration (i.e., the time to reach 70 % of initial work rate) was shorter in HOT compared to NORM and COOL (Fig. 1a) with similar variability as previously reported (Tucker et al. 2006; Crewe et al. 2008) due to an accelerated decline in self-selected work rate (Fig. 1b), suggesting some factor related to a high ambient temperature influenced the selection of work rate for a RPE of 16. The present findings do not support any influence of S on the decline in exercise performance; however, this does not discount the possibility of other thermally-mediated effects. While a reduction in force production has been shown following hyperthermia (Nybo and Nielsen 2001), absolute core temperature responses were not different between conditions. However, large differences in skin temperature were observed. A high T_{sk} or thermal sensation alters RPE and performance (Schlader et al. 2011a, b, c; Flouris 2011), and therefore may have been the primary stimulus for the reduction in



◀**Fig. 6** iEMG during the first 20 min of exercise. *VL* vastus lateralis, *GM* gluteus medius, *BF* biceps femoris; *LG* lateral gastrocnemius. *Significantly different from initial for all conditions ($P < 0.05$)

work rate during the early minutes of exercise in the present study. Yet, since a high T_{sk} was present before the onset of exercise, one might expect that the initial self-selected workload would have been lower in the HOT condition due to a higher T_{sk}. Although this was not the case, a high T_{sk} coupled with a rising core temperature may have precipitated the subsequent reduction in self-selected work rate (Ely et al. 2009). Future studies should investigate the independent role of T_{sk} on exercise performance through acute mean or local T_{sk} manipulations as recent work has suggested afferent feedback from skin thermoreceptors could mediate differences in self-paced work rate (Schlader et al. 2011a).

Another important unresolved issue regarding exercise performance is whether the accelerated decline in work rate during the HOT condition occurred in an anticipatory fashion. That is, it may be that neuromuscular activation (and therefore exercise intensity) was regulated to prevent deleterious homeostatic disturbances. However, it is unclear whether this was the case in the present study. Exercise performance in the HOT condition was impaired (Fig. 1), with a more accelerated decline in self-selected work rate resulting in a shorter time to reach 70 % of the initial work rate (the condition for terminating exercise). An anticipatory reduction in exercise intensity is argued to be mediated through a subconsciously altered pattern of neuromuscular activation (Tucker et al. 2006). In the present study, iEMG declined similarly over the first 20 min of exercise in HOT, NORM, and COOL conditions (Fig. 6), yet the reduction in work rate was significantly greater in the HOT condition when expressed as a percentage of the initial work rate (Fig. 1). It is possible that greater reductions in work rate in the HOT condition, while significant relative to NORM and COOL condition, in terms of the percentage decline from the initial work rate, were not large enough in absolute terms to yield significantly different iEMG signals between conditions. These iEMG results are similar to those previously presented by Tucker et al. (2006), even though the methods for normalizing iEMG varied. In fact, our normalization method (averaging over the first 5 min of dynamic exercise) led to a decrease in variability compared to normalizing to MVC, a static contraction. Importantly, however, in the present study the observed decrease in iEMG did not seem to occur in an anticipatory manner but rather in response to changes in core temperature.

The main limitation of the present study was the inability to measure S_{cal} in the HOT condition. The

determination of S_{cal} depends on the ability to measure (1) the rate of metabolic heat production and (2) the estimation of all avenues of heat exchange. This latter condition is complicated by the inability to measure minute-by-minute changes in evaporative heat loss from the skin (E_{sk}) that would have required a direct calorimeter or continuous body mass measurements while accounting for dripping sweat (if necessary). No sweating was evident until 3 and 5 min of exercise in NORM and COOL, respectively; therefore, there was no need to account for E_{sk} in the estimation of S_{cal} in those conditions (see "Methods"). However, sweating was apparent in the HOT condition during the baseline period, preventing an accurate determination of E_{sk} and S_{cal}. Nevertheless, since the rates of change of both T_{es} and T_{re} were similar in all conditions, it seems reasonable that a higher E_{sk} counterbalanced the negligible dry heat loss in the HOT condition to elicit similar S_{cal} values as the COOL and NORM conditions. Another minor limitation of the present study was that the ambient temperature of the COOL condition was slightly higher (~19 °C) than the COOL condition (~15 °C) in the main comparator study (Tucker et al. 2006). However, air temperature was still sufficiently low to recreate the performance differences previously observed between environmental conditions, and the two-compartment thermometric estimates of heat storage were similarly negative in our COOL condition to those previously reported (Tucker et al. 2006; Crewe et al. 2008).

In conclusion, despite a greater decline in self-paced exercise intensity in the HOT condition after ~15 min of exercise as previously reported (Tucker et al. 2006), $\Delta T_{es}/\Delta t$ was similar in COOL, NORM and HOT conditions suggesting no early differences in the rate of body heat storage, thus apparently ruling this factor out as a potential mediator of the subsequent changes in power output. The accelerated decline in power output in the HOT condition occurred in parallel with a lower neuromuscular activation but in the absence of any evidence of neuromuscular fatigue, which may indicate an anticipatory regulation of exercise intensity based on factors unrelated to S, such as a high mean skin temperature.

Acknowledgments The authors thank the volunteers for their participation and effort. This research was supported by a Discovery Grant from the Natural Sciences and Engineering Research Council (NSERC) of Canada (#386143-2010, held by O. Jay). Funding for the metabolic cart and dew point sensor were provided by a Canadian Foundation for Innovation (CFI) Infrastructure grant (co-applicant: O. Jay). N.M. Ravanelli was supported by a University of Ottawa Faculty of Health Sciences Research Bursary. M.N. Cramer is supported by a Postgraduate Scholarship (doctoral) from NSERC and an Excellence Scholarship from the University of Ottawa. Y. Molgat-Seon was supported by a University of Ottawa Master's Scholarship. A.N. Carlsen is supported by NSERC and the University of Ottawa, Faculty of Health Sciences.

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