

Sex modulates whole-body sudomotor thermosensitivity during exercise

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Non-technical summary The human body controls its temperature through coordinated physiological processes. Prior to the current study, it remained unknown if differences between males and females existed in these processes. The results from the current study show that females have a lower whole-body sweat response during exercise in the heat compared to males, which results in a greater increase in body temperature. The physiological process responsible for the lower whole-body sweat rate was a lower thermosensitivity of the response, meaning a lower increase in sweat production for a given increase in body temperature. Knowledge of sex-related differences in the physiology of temperature regulation may lead to better improvements in heat exposure guidelines for industrial, military and athletic settings.

Abstract It is unclear whether true physiological differences exist in temperature regulation between males and females during exercise, independently of differences in physical characteristics and metabolic heat production. Therefore, we examined differences in the onset threshold and thermosensitivity of whole-body sudomotor activity and cutaneous vascular conductance between males and females matched for body mass and surface area. Nine males and nine females performed 90 min of exercise at each of the following intensities in a warm/dry environment: 50% of maximum oxygen consumption ($\dot{V}_{O_{2,max}}$) and at a fixed rate of metabolic heat production equal to 500 W. Evaporative heat loss (EHL, direct calorimetry) and cutaneous vascular conductance (CVC, laser-Doppler) were measured continuously. Mean body temperature was calculated from the measurements of oesophageal and mean skin temperatures. During exercise at 50% $\dot{V}_{O_{2,max}}$, a lower rate of sudomotor activity was observed in females (385 ± 12 vs. 512 ± 24 W, $P < 0.001$). However, irrespective of sex, individual EHL values were strongly associated with metabolic heat production ($R^2 = 0.82$, $P < 0.001$). Nonetheless, a lower rate of EHL was observed in females when exercise was performed at 500 W of metabolic heat production (419 ± 7 vs. 454 ± 11 W, $P = 0.032$). Furthermore, a lower increase in EHL per increase in mean body temperature was observed in females (553 ± 77 vs. 795 ± 85 W °C⁻¹, $P = 0.051$), with no differences in the onset threshold (36.77 ± 0.06 vs. 36.61 ± 0.11 °C, $P = 0.242$). In contrast, no differences were observed in CVC. Collectively, these findings demonstrate that females have a lower thermosensitivity of the whole-body sudomotor response compared to males during exercise in the heat performed at a fixed rate of metabolic heat production.

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Introduction

The physiological variables of temperature regulation, consisting of the body temperature at onset of effector responses (onset threshold) and the increase in effector output per unit increase in body temperature (thermosensitivity), dictate the capacity of the human body to regulate its temperature. When comparing these variables between populations, however, all other environmental (e.g. air temperature and humidity, heat production) and physical (e.g. body mass/surface area) factors must remain constant. This is particularly relevant when comparing temperature regulation between males and females, since both have unique physical characteristics which make it difficult to discern whether differences in temperature regulation are attributed to either physiological or physical/environmental variables (Nunneley, 1978; Burse, 1979; Kenney, 1985).

Most studies examining differences in temperature regulation between males and females have focused on core temperature responses (Wyndham *et al.* 1965; Morimoto *et al.* 1967; Weinman *et al.* 1967; Shapiro *et al.* 1980, 1981; McLellan, 1998). Although sex differences in core temperature might intuitively suggest differences in the physiology of temperature regulation, core temperature alone does not provide an accurate assessment of thermoregulatory function when differences in physical characteristics between sexes are not taken into account (Gagnon *et al.* 2009). Furthermore, studies that have examined sex differences in heat loss responses during exercise have exclusively done so during weight-bearing exercise (i.e. treadmill) at a fixed external workload (Davies, 1979; Avellini *et al.* 1980a,b; Moran *et al.* 1999), or during exercise at a fixed percentage of maximum oxygen consumption (Paolone *et al.* 1978; Frye & Kamon, 1981; Horstman & Christensen, 1982; Keatisuwan *et al.* 1996; Ichinose-Kuwahara *et al.* 2010). Although a consistent finding from these studies is a lower sweat rate in females, this observation is proportional to the variations in metabolic heat production elicited by such experimental protocols (Havenith, 2001a; Gagnon *et al.* 2008). Since previous studies have not fully accounted for differences in physical and/or environmental variables, differential core temperature and/or sweating responses between sexes during exercise may not necessarily indicate a true sex-related difference in temperature regulation, but may rather be attributed to simple differences in physical characteristics and rate of metabolic heat production. As such, conclusions about whether sex can modulate the physiology of temperature regulation remain limited, a matter which has recently gained interest within this field of research (Schwiening *et al.* 2011).

Determining whether sex can modulate the physiology of temperature regulation has important mechanistic and practical implications. Sex has traditionally not been

considered an independent modulator of temperature regulation (Sawka *et al.* 1996). It therefore often remains unknown if and/or how changes in thermoregulatory function differ between males and females, as a function of age, chronic disease and various physiological states. Such findings could lead to sex-specific improvements in public health, particularly in the improvement of heat exposure guidelines for industrial, military and sport settings which currently do not consider sex as a potential factor affecting heat stress and strain during work in the heat (United States Army Center for Health Promotion and Preventive Medicine, 2003; American Conference of Industrial Hygienists, 2007).

Therefore, the purpose of this study was to examine whether sex can modulate the physiological variables of human temperature regulation independently of physical and environmental factors. To achieve this objective, males and females were matched for body mass and surface area, while exercise at a fixed percentage of maximum oxygen consumption was compared to a condition of fixed metabolic heat production. The physiological variables of temperature regulation consisted of the onset threshold and thermosensitivity of the evaporative heat loss and cutaneous vascular conductance responses. We hypothesised that no sex-related differences in the onset threshold and thermosensitivity of the evaporative heat loss and cutaneous vascular conductance responses would be observed during exercise at a fixed rate of metabolic heat production. A secondary objective was to contrast the results from this condition with exercise performed at a fixed percentage of maximum oxygen consumption, which we hypothesised would result in a lower evaporative heat loss response in females, proportional to a lower rate of metabolic heat production.

Methods

Ethical approval

The current experimental protocol was approved by the University of Ottawa Health Sciences and Science Research Ethics Board, in accordance with the *Declaration of Helsinki*. Written informed consent was obtained from all volunteers prior to their participation in the study.

Participants

An effect size of 10% and standard deviation of 5%, estimated from previous publications (Gagnon *et al.* 2008, 2009), resulted in a minimum calculated ($\beta = 0.9$, $\alpha = 0.05$) sample size of six participants in each group. Eighteen participants, nine males and nine females, were recruited within the University community and volunteered for the study. To eliminate

Table 1. Participant characteristics

Sex	Age (years)	Body mass (kg)	Height (cm)	A_D (m^2)	Fat mass (kg)	Lean mass (kg)	Bone mass (kg)	\dot{V}_{O_2max} ($l\ min^{-1}$)	\dot{V}_{O_2max} ($ml\ kg^{-1}\ min^{-1}$)	\dot{V}_{O_2max} ($ml\ kg_{LBM}^{-1}\ min^{-1}$)
Males	24 ± 4	66.4 ± 4.6	173 ± 6	1.79 ± 0.08	6.1 ± 2.2*	57.2 ± 4.6*	3.1 ± 0.3*	3.83 ± 0.48*	57.8 ± 6.3*	66.9 ± 6.1
Females	27 ± 4	66.8 ± 5.0	168 ± 5	1.76 ± 0.08	17.1 ± 6.5	46.9 ± 4.8	2.7 ± 0.3	3.09 ± 0.31	46.7 ± 6.4	66.0 ± 6.5

A_D , body surface area; \dot{V}_{O_2max} , maximum oxygen consumption; LBM, lean body mass. *Significantly different from females ($P \leq 0.05$). Values are mean ± standard deviation.

the confounding influence of differences in physical characteristics between sexes, males and females were matched in pairs for body mass. Furthermore, to eliminate the influence of differences in hormonal status across the menstrual cycle, female participants performed each experimental session within the first and tenth day after the onset of their self-reported menses. Female participants taking oral contraceptives ($n = 6$) performed the experimental sessions during the no pill/placebo phase of oral contraceptive use. Hormonal status was confirmed by taking a venous blood sample on the day of each experimental session. None of the experimental sessions for female participants had to be withdrawn or repeated based on blood sample results. Participants were healthy, non-smoking and free of any known cardiovascular, metabolic or respiratory diseases. Participant characteristics are presented in Table 1.

Experimental design

Participants volunteered for one screening visit and two experimental sessions. During the screening visit, measurements of body height and mass, as well as maximum oxygen uptake were determined. Body height was determined using a stadiometer (Detecto, model 2391, Webb City, MO, USA), while body mass was calculated as the sum of fat tissue mass, lean tissue mass and bone mass as determined using dual-energy X-ray absorpsiometry. Body surface area was calculated from the measurements of body height and mass (DuBois & DuBois, 1916). Maximum oxygen uptake was determined by an automated indirect calorimetry system (MOXUS system, Applied Electrochemistry, Pittsburgh, PA, USA) during a progressive incremental cycling protocol performed on an upright seated constant-load cycle ergometer (Corival, Lode B.V., Groningen, the Netherlands). The participants were asked to cycle continuously at 80 rpm, at a starting work rate of 80 W for 2 min. The work rate was then increased by 20 W increments every minute thereafter until the subject could not maintain a pedaling cadence of at least 60 rpm (Canadian Society for Exercise Physiology, 1986).

For each experimental session, participants reported to the laboratory between 07.00 and 09.00, after eating

a small breakfast (i.e. toast and juice), but consuming no tea or coffee that morning. The participants were also asked to drink 500 ml of water the night prior to, as well as the morning of, each experimental session and to refrain from alcohol and exercise for 24 h prior to experimentation. Upon arrival at the laboratory, the participants voided their bladder and provided a urine sample before weighing themselves nude. Subsequently, the participants changed into shorts and sandals (as well as a sports bra for female participants), and sat quietly for a 30 min instrumentation period at an ambient room temperature of 24°C. Following instrumentation, the participant entered the calorimeter regulated to an ambient air temperature of $35.21 \pm 0.24^\circ\text{C}$, a specific humidity of $4.27 \pm 1.51\ \text{g}\ \text{kg}^{-1}$ (~12% relative humidity) and an air mass flow of $5.75 \pm 0.28\ \text{kg}\ \text{air}\ \text{min}^{-1}$. The participant, seated in the upright position, rested for a 45 min habituation period. Subsequently, the participant performed 90 min of continuous cycling exercise at either 50% of maximum oxygen consumption, or a rate of metabolic heat production equal to 500 W. A fixed percentage of maximum oxygen consumption (50%) was selected since it is a widely used approach to study sex-related differences in thermoregulation during exercise. In contrast, a fixed rate of absolute heat production (500 W) was chosen to provide the same requirement for heat loss for males and females. At the end of the exercise period, all instrumentation was removed except for the laser-Doppler probe, and participants remained seated for a 45 min local heating period to determine maximum skin blood flow (see details below). At the end of the local heating period, the participants exited the calorimeter and a final nude body mass measurement was obtained.

The two experimental sessions were performed on separate days, separated by a minimum of 48 h. For all experimentation, clothing was standardized to cotton underwear, running shorts, sandals and sports bra for female participants. Possible differences in acclimation status between males and females were not taken into account. However, since all experimentation occurred between the months of October and May, it was assumed that all participants were not heat acclimated.

Measurements

The main thermoeffector responses during exercise in the heat consist of whole-body sudomotor activity and cutaneous vasodilatation. Therefore, the current study focused on differences between sexes in evaporative heat loss and local skin blood flow.

Whole-body sudomotor activity was estimated from measurements of evaporative heat loss using the modified Snellen direct air calorimeter (Reardon *et al.* 2006). In order for evaporative heat loss to be a valid measure of whole-body sudomotor activity, we ensured that the environmental conditions provided a high vapour pressure gradient between the skin surface and the surrounding air. Furthermore, we continually maintained this vapour pressure gradient by continuously providing a high air mass flow of dry air through the calorimeter. Calorimeter outflow to inflow differences in absolute humidity were collected at 8 s intervals throughout the trials. The real-time data were displayed and recorded on a personal computer with LabVIEW software (Version 7.0, National Instruments, TX, USA). Evaporative heat loss was subsequently calculated using the following equation:

$$\frac{\text{Mass flow}(\text{Humidity}_{\text{out}} - \text{Humidity}_{\text{in}}) \times 2426}{60} \text{ W} \quad (1)$$

where mass flow is the rate of flow of air mass (kg air s⁻¹); (Humidity_{out} – Humidity_{in}) is the calorimeter inflow–outflow difference in absolute humidity (g of water (kg of air)⁻¹); and 2426 is the latent heat of vaporization of sweat (J (g of sweat)⁻¹) at 30°C (Wenger, 1972).

Cutaneous vasodilatation was estimated using laser-Doppler velocimetry (PeriFlux System 5000, Perimed AB, Stockholm, Sweden). Prior to the start of the experimental trial, the laser-Doppler flow probe (PR 401 Angled Probe, Perimed AB) was affixed with an adhesive ring to the upper back in a site without superficial veins that demonstrated pulsatile activity. Upper back skin blood flow responses have been shown to be similar to those observed on the forearm and chest (Ichinose *et al.* 2009). The probe was not moved from its location throughout the experimental trial. To determine maximum skin blood flow, a local heating period to 42°C for 30 min and then to 44°C for an additional 15 min was performed at the end of each experimental trial. Cutaneous vascular conductance was subsequently calculated as laser-Doppler velocimetry output in arbitrary perfusion units (PU) divided by mean arterial pressure and expressed as a percentage of maximum.

Indirect calorimetry was used for the concurrent measurement of metabolic energy expenditure (Nishi, 1981). Expired gas was analysed for O₂ (error of ±0.01%)

and CO₂ (error of ±0.02%) concentrations using electrochemical gas analysers located outside of the calorimeter chamber (AMETEK model S-3A/1 and CD 3A, Applied Electrochemistry). Expired air was recycled back into the calorimeter chamber in order to account for respiratory heat exchange. Prior to each session, gas mixtures of 4% CO₂, 17% O₂ and balance nitrogen were used to calibrate the gas analysers and a 3 l syringe was used to calibrate the turbine ventilometer (error ± 3%, typically <1%).

Mean arterial pressure was measured using a Finometer (Finapres Medical Systems, Amsterdam, the Netherlands) from the beat-to-beat recording of the right middle finger arterial pressure waveform with the volume-clamp method (Penaz, 1973) and physical criteria (Wesseling *et al.* 1995). Prior to beginning the measurement period, a level calibration was performed and brachial artery pressure reconstruction (Gizdulich *et al.* 1996, 1997) was calibrated with an upper arm return-to-flow systolic pressure detection (Bos *et al.* 1996).

Heart rate was monitored using a Polar coded transmitter, recorded continuously and stored with a Polar Advantage interface and Polar Precision Performance software (Polar Electro, Oy, Finland).

Oesophageal and rectal temperatures were measured with general purpose thermocouple temperature probes (Mallinckrodt Medical Inc., St Louis, MO, USA). The oesophageal probe was inserted 40 cm past the entrance of the nostril while the participants sipped water (250–500 ml) through a straw. The rectal probe was inserted to a depth of 15 cm past the anal sphincter. Skin temperature was measured at 10 sites using thermocouples (Concept Engineering, Old Saybrook, CT, USA) attached to the skin with surgical tape. Mean skin temperature was subsequently calculated using a 10-point weighting of the regional proportions determined by Hardy & DuBois (1938). Temperature data were collected using a HP Agilent data acquisition module (model 3497A) at a rate of one sample every 15 s and simultaneously displayed and recorded in spreadsheet format on a personal computer with LabVIEW software (Version 7.0, National Instruments, TX, USA).

Whole-body sweat production was calculated as the difference in pre- to post-measurements of body mass to the nearest 0.01 kg using a digital high-performance weighing terminal (model CBU150X, Mettler Toledo Inc., Mississauga, ON, Canada). Urine specific gravity was determined in duplicate using a handheld total solids refractometer (model TS400, Reichter Inc., Depew, NY, USA).

On the day of each experimental session, a venous blood sample (10 ml) was obtained from female participants to confirm that the session occurred in the follicular/low hormone phase of the menstrual cycle. The blood samples were collected with a SST vacutainer (BD Vacutainer, Franklin Lakes, NJ, USA) for the determination of plasma

17 β -oestradiol and progesterone. Plasma concentrations of 17 β -oestradiol and progesterone were quantified using automated chemiluminescent microparticle immunoassays (ARCHITECT system; Abbott Diagnostics, Abbott Park, IL, USA) by an independent external laboratory (Gamma-Dynacare Medical Laboratories, Ottawa, ON, Canada) using appropriate monoclonal antibody-coated microparticles and acridium-labelled conjugates. The plasma concentrations representative of the follicular phase of the menstrual cycle for 17 β -oestradiol and progesterone are 46–604 pmol l⁻¹ and 0.6–4.7 nmol l⁻¹, respectively.

Statistical analyses

For all variables, minute averages were performed to carry out the statistical analyses. To examine sex-related differences in the thermal control of the evaporative heat loss and cutaneous vascular conductance responses, the visually determined linear portion of each response against mean body temperature was analysed using a simple linear regression. The onset threshold was defined as the intercept of the regression line with the evaporative heat loss and cutaneous vascular conductance values at rest, while the thermosensitivity was defined as the slope of the regression line (Cheuvront *et al.* 2009). To account for the relative influence of core and skin temperatures on the activation of heat loss responses (Hertzman *et al.* 1952; Nadel *et al.* 1971a,b), mean body temperature was calculated as: $0.9 \times$ oesophageal temperature + $0.1 \times$ mean skin temperature (Shibasaki *et al.* 2006).

All dependent variables were compared between groups (males *vs.* females) within each experimental condition (50% and 500 W). Independent samples *t* tests were used for single comparisons between groups, while a two-way mixed model analysis of variance was used for multiple comparisons using the repeated factor of time and the non-repeated factor of group. When a significant main effect was observed, *post hoc* comparisons were carried out with independent samples *t* tests. Furthermore, a simple linear correlation was performed to assess the relationship between end-exercise evaporative heat loss and rate of metabolic heat production values during exercise at a fixed percentage of maximum oxygen consumption. The level of significance for all analyses was set at an alpha level of $P \leq 0.05$, corrected for multiple comparisons using the Holm–Bonferroni approach. Analyses were performed using commercially available statistical software (SPSS 18.0 for Windows, SPSS Inc., Chicago, IL, USA). All values for sample parameters are reported as mean \pm standard deviation, while those for variables are reported as mean \pm standard error of the mean.

Results

Participant characteristics

By design, there were no differences in body mass between groups ($P = 0.873$). Furthermore, there were no differences in height between groups ($P = 0.104$), such that both sexes had a similar body surface area ($P = 0.504$). In contrast, males had a lower absolute fat mass ($P < 0.001$), as well as a greater absolute lean ($P < 0.001$) and bone ($P = 0.021$) mass compared to females. Finally, males had a higher maximum oxygen consumption both in absolute values ($P = 0.001$) and relative to body mass ($P = 0.002$). However, there were no sex differences in maximum oxygen consumption expressed as a function of lean body mass ($P = 0.767$).

Exercise at a fixed percentage (50%) of maximum oxygen consumption

On the day of the experimental session, plasma concentrations of 17 β -oestradiol and progesterone for the female participants averaged 139 ± 28 pmol l⁻¹ and 1.2 ± 0.2 nmol l⁻¹, respectively. Baseline urine specific gravity did not differ between groups (males: 1.015 ± 0.002 *vs.* females: 1.015 ± 0.003 , $P = 0.816$). Furthermore, there were no differences between groups in baseline oesophageal ($P = 0.786$, Table 2), rectal ($P = 0.555$, Table 2), mean skin (males: $34.72 \pm 0.11^\circ\text{C}$ *vs.* females: $34.54 \pm 0.19^\circ\text{C}$, $P = 0.432$) and mean body (males: $36.68 \pm 0.08^\circ\text{C}$ *vs.* females: $36.67 \pm 0.10^\circ\text{C}$, $P = 0.936$) temperatures. Similarly, heart rate ($P = 0.409$), metabolic heat production ($P = 0.328$), whole-body evaporative heat loss ($P = 0.110$) and cutaneous vascular conductance ($P = 0.469$) did not differ between males and females prior to the beginning of exercise.

Based on the participants pre-determined absolute maximum oxygen consumption, the target oxygen consumption during exercise averaged 1917 ± 239 ml min⁻¹ for males and 1544 ± 153 ml min⁻¹ for females ($P \leq 0.001$). Consequently, rate of metabolic heat production was significantly greater in males during exercise ($P < 0.001$), which was paralleled by a greater rate of whole-body evaporative heat loss ($P < 0.001$, see Fig. 1A). However, the level of evaporative heat loss achieved during exercise significantly correlated ($P < 0.001$) with rate of metabolic heat production. In fact, differences in metabolic heat production between sexes explained more than 80% of the variance in evaporative heat loss (Fig. 2). The differences in whole-body evaporative heat loss were reflected by a greater whole-body sweat production in males (1.69 ± 0.06 kg *vs.* 1.29 ± 0.08 kg, $P = 0.002$). In contrast, there were no differences between sexes in cutaneous

Table 2. Baseline and end-exercise oesophageal and rectal temperatures for males and females during exercise at a fixed percentage of $\dot{V}_{O_{2max}}$ (50%) and a fixed rate of absolute heat production (500 W)

Condition	Sex	Baseline T_{Oes} ($^{\circ}C$)	End-ex T_{Oes} ($^{\circ}C$)	Baseline T_{re} ($^{\circ}C$)	End-ex T_{re} ($^{\circ}C$)
50%	Males	36.90 ± 0.07	37.81 ± 0.08	36.90 ± 0.07	38.10 ± 0.09
	Females	36.93 ± 0.09	37.80 ± 0.11	36.97 ± 0.08	38.19 ± 0.07
500 W	Males	36.65 ± 0.11	$37.54 \pm 0.08^*$	36.78 ± 0.10	$37.89 \pm 0.07^*$
	Females	36.83 ± 0.09	38.13 ± 0.19	36.86 ± 0.08	38.35 ± 0.17

End-ex, end-exercise, T_{Oes} , oesophageal temperature; T_{re} , rectal temperature. *Significantly different from females ($P \leq 0.05$). Values are mean \pm standard error of the mean.

vascular conductance during exercise ($P = 0.221$, see Fig. 3A), as well as the maximum cutaneous vascular conductance values reached during the local heating period (males: 1.02 ± 0.18 PU mmHg $^{-1}$ vs. females: 1.23 ± 0.25 PU mmHg $^{-1}$, $P = 0.500$). Overall, the differences in whole-body evaporative heat loss between sexes were proportional to the differences in metabolic heat production such that no differences in both oesophageal ($P = 0.953$) and rectal ($P = 0.433$) temperatures were observed at the end of exercise (see Table 2). Furthermore, there were no significant differences in mean skin temperature throughout exercise ($P = 0.117$), which averaged $35.36 \pm 0.08^{\circ}C$ and $34.96 \pm 0.16^{\circ}C$ for males and females, respectively, at the end of exercise.

The mean body temperature onset threshold for evaporative heat loss (males: $36.67 \pm 0.09^{\circ}C$ vs. females: $36.76 \pm 0.09^{\circ}C$, $P = 0.518$) and cutaneous vasodilatation (males: $36.70 \pm 0.09^{\circ}C$ vs. females: $36.76 \pm 0.09^{\circ}C$, $P = 0.617$) did not differ between groups. However, the thermosensitivity of the whole-body evaporative heat

loss (762 ± 56 W $^{\circ}C^{-1}$ vs. 559 ± 75 W $^{\circ}C^{-1}$, $P = 0.049$, see Fig. 4A) and cutaneous vascular conductance responses ($52 \pm 5\%$ CVC $^{\circ}C^{-1}$ vs. $30 \pm 4\%$ CVC $^{\circ}C^{-1}$, $P = 0.002$, see Fig. 5A) were significantly greater in males compared to females.

Exercise at a fixed rate of absolute metabolic heat production (500 W)

On the day of the experimental session, plasma concentrations of 17β -oestradiol and progesterone for the female participants averaged 233 ± 66 pmol l $^{-1}$ and 1.1 ± 0.3 nmol l $^{-1}$, respectively. Baseline urine specific gravity did not differ between groups (males: 1.020 ± 0.003 vs. females: 1.014 ± 0.002 , $P = 0.249$). Furthermore, there were no differences between groups in baseline oesophageal ($P = 0.261$, Table 2), rectal ($P = 0.550$, Table 2), mean skin (males: $34.83 \pm 0.13^{\circ}C$ vs. females: $34.83 \pm 0.10^{\circ}C$, $P = 0.962$) and mean body (males: $36.45 \pm 0.12^{\circ}C$ vs. females: $36.60 \pm 0.08^{\circ}C$, $P = 0.353$) temperatures. Similarly, heart rate ($P = 0.226$),

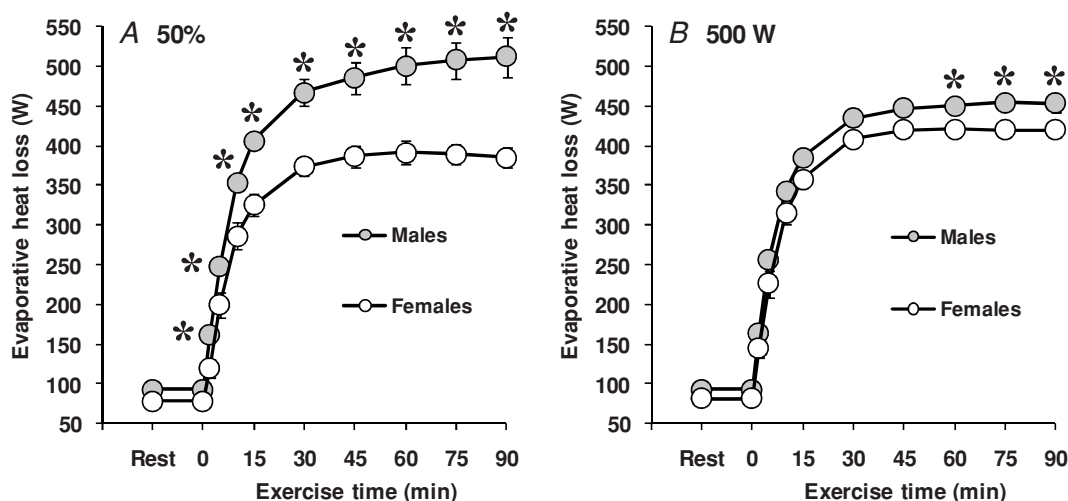


Figure 1. Sex-related differences in evaporative heat loss during exercise performed at either a fixed percentage of maximum oxygen consumption (50%, A) or a fixed rate of metabolic heat production (500 W, B)

Values are mean \pm standard error. *Significantly different from females ($P \leq 0.05$).

metabolic heat production ($P = 0.147$), whole-body evaporative heat loss ($P = 0.196$) and cutaneous vascular conductance ($P = 0.919$) did not differ between males and females prior to the beginning of exercise.

By experimental design, rate of metabolic heat production during exercise did not differ between sexes (males: 508 ± 5 W vs. females: 504 ± 6 W, $P = 0.573$). Nonetheless, a greater rate of whole-body evaporative heat loss was observed in males ($P = 0.028$, see Fig. 1B). The greater rate of whole-body evaporative heat loss was paralleled by a greater whole-body sweat production in males (1.63 ± 0.07 kg vs. 1.38 ± 0.06 kg, $P = 0.029$). In contrast, there were no differences in cutaneous vascular conductance during exercise ($P = 0.899$, see Fig. 3B), as well as the maximum cutaneous vascular conductance values reached during local heating (males: 1.24 ± 0.34 PU mmHg⁻¹ vs. females: 0.97 ± 0.20 PU mmHg⁻¹, $P = 0.362$). The net consequence of the lower evaporative heat loss in females was a greater end-exercise oesophageal ($P = 0.019$) and rectal ($P = 0.026$) temperature (Table 2). In contrast, there were no significant differences between groups in mean skin temperature during exercise ($P = 0.486$), which averaged $35.38 \pm 0.07^\circ\text{C}$ and $35.58 \pm 0.21^\circ\text{C}$ for males and females, respectively, at the end of exercise.

The mean body temperature onset threshold for whole-body evaporative heat loss (males: $36.61 \pm 0.11^\circ\text{C}$ vs. females: $36.77 \pm 0.06^\circ\text{C}$, $P = 0.242$) and cutaneous vasodilatation (males: $36.65 \pm 0.11^\circ\text{C}$ vs. females: $36.77 \pm 0.08^\circ\text{C}$, $P = 0.363$) did not differ between groups. However, the thermosensitivity of the whole-body evaporative heat loss response was significantly greater in males compared to females (795 ± 85 W °C⁻¹ vs. 553 ± 77 W °C⁻¹, $P = 0.051$, see Fig. 4B). In contrast, there were no significant differences in the thermosensitivity of the cutaneous vascular conductance response ($48 \pm 13\%$ CVC °C⁻¹ vs. $38 \pm 5\%$ CVC °C⁻¹, $P = 0.447$, see Fig. 5B).

Discussion

This is the first study to examine the independent effect of sex on the thermoeffector responses of whole-body sudomotor activity and cutaneous vasodilatation during exercise. The findings confirm previous observations that differences in sudomotor activity between males and females during exercise at a fixed percentage of maximum oxygen consumption are proportional to variations in metabolic heat production. However, contrary to our hypothesis, females demonstrate a lower whole-body sudomotor activity during exercise at a fixed rate of metabolic heat production (500 W). The physiological variable responsible for the lower sudomotor activity is a lower thermosensitivity of the response to changes in mean

body temperature. In contrast, no differences in cutaneous vascular conductance were observed during exercise at a fixed rate of metabolic heat production. Collectively, these findings demonstrate that sex modulates the thermosensitivity of whole-body sudomotor activity during exercise, independently of differences in body mass, surface area and metabolic heat production.

Similar to previous studies which have examined sweating responses between males and females during exercise (Paolone *et al.* 1978; Frye & Kamon, 1981; Horstman & Christensen, 1982; Keatisuwan *et al.* 1996; Ichinose *et al.* 2009; Ichinose-Kuwahara *et al.* 2010), a lower rate of whole-body evaporative heat loss was observed in females when exercise was performed at a fixed percentage of maximum oxygen consumption. However, this response was paralleled by a lower rate of metabolic heat production (Fig. 2). These findings confirm previous observations that a lower sudomotor response in females during exercise at a fixed percentage of maximum oxygen consumption is proportional to a lower rate of metabolic heat production, and not necessarily due to physiological differences in temperature regulation (Gagnon *et al.* 2008). Nonetheless, the lower thermosensitivity of both the evaporative heat loss and cutaneous vascular conductance responses in females may suggest a physiological difference in the control of heat loss responses. However, greater exercise intensities (and therefore rates of metabolic heat production) are generally paralleled by a greater thermosensitivity of the sweating response (Montain *et al.* 1995; Kondo *et al.* 1998). In contrast, the thermosensitivity of the cutaneous vascular conductance response has generally been found to be unaffected by exercise intensity (Kondo *et al.* 2010). Yet, no

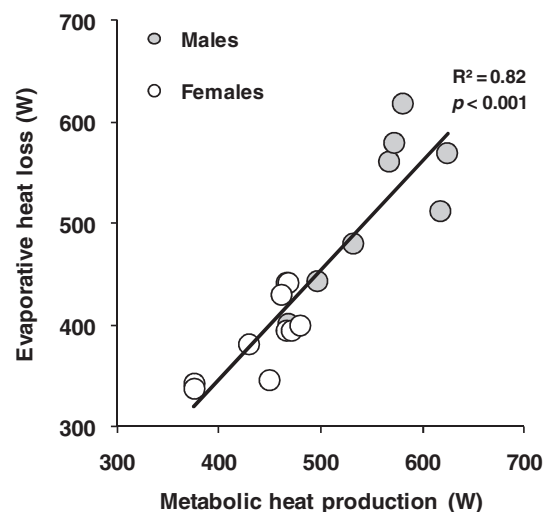


Figure 2. Relationship between evaporative heat loss and rate of metabolic heat production for males and females during exercise performed at a fixed percentage of maximum oxygen consumption

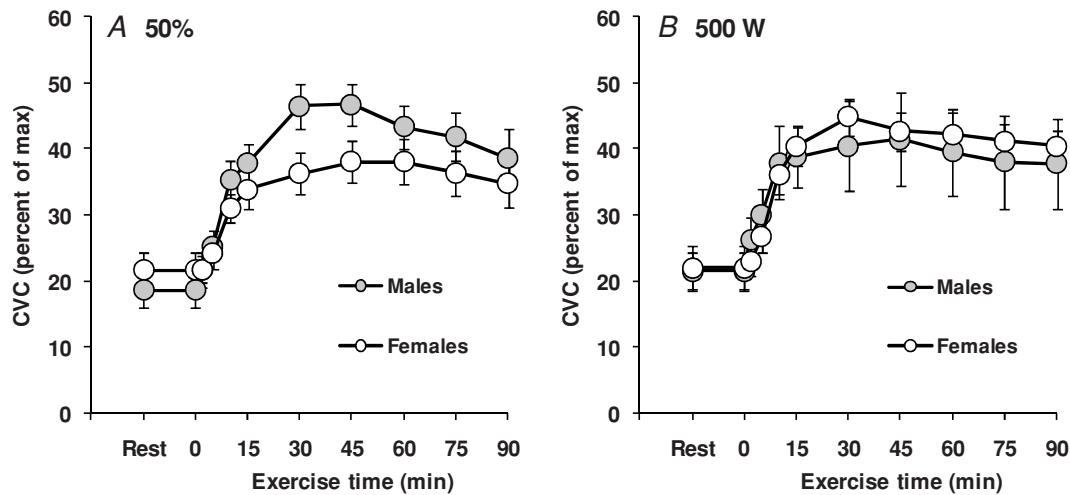


Figure 3. Sex-related differences in the cutaneous vascular response (CVC) during exercise performed at either a fixed percentage of maximum oxygen consumption (50%, *A*) or a fixed rate of metabolic heat production (500 W, *B*)

Values are mean \pm standard error.

differences between males and females were observed in the onset threshold and thermosensitivity of the cutaneous vascular response when exercise was performed at a fixed rate of metabolic heat production. Together, these observations suggest that the greater thermosensitivities observed in males during exercise at a fixed percentage of maximum oxygen consumption were due to a greater rate of metabolic heat production.

In order to isolate the physiological variables of temperature regulation, consisting of the onset threshold

and thermosensitivity of thermoeffector responses, males and females were matched for body mass and surface area to account for the main physical characteristics which determine the individual heat stress response (Havenith *et al.* 1995, 1998; del Coso *et al.* 2011). As such, the use of a fixed absolute heat production in constant environmental conditions provided a similar requirement for heat loss in both groups. Yet, females nonetheless exhibited a lower whole-body evaporative heat loss response compared to males, due to a lower thermosensitivity of the response,

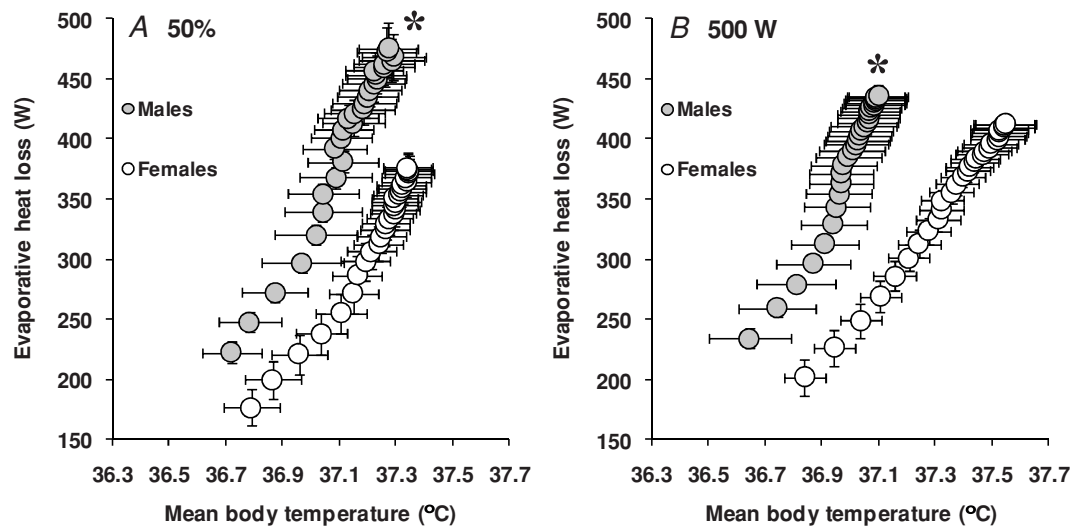


Figure 4. Sex-related differences in the sensitivity of the evaporative heat loss response to changes in mean body temperature during exercise performed at either a fixed percentage of maximum oxygen consumption (50%, *A*) or a fixed rate of metabolic heat production (500 W, *B*)

The data represent the average slopes of the linear portion of the response. Values are mean \pm standard error. *Significantly different slope from females ($P \leq 0.05$).

with no significant differences in the onset threshold. Consequently, these observations provide conclusive and novel evidence that sex can independently modulate whole-body sudomotor activity during exercise. A lower whole-body evaporative heat loss response for a given increase in mean body temperature suggests either: (1) altered afferent neural activity from peripheral (i.e. skin) and central (i.e. core) thermoreceptors causing a different integration of thermal information; (2) altered efferent neural activity for a given level of afferent input; and/or (3) an altered effector response (i.e. sweat production) for a given level of efferent neural activity.

Ichinose-Kuwahara *et al.* (2010) recently suggested that sex differences in sweat gland function improvements elicited by exercise training are intensity dependent. They reported a greater thermosensitivity of the sweating response in trained males compared to trained females. In contrast, no differences in thermosensitivity of the sweating response were observed between untrained males and untrained females. It should be noted, however, that these observations were made during exercise at fixed percentages (i.e. 35%, 50% and 65%) of maximum oxygen consumption. Since males and females of various training status were compared, both sexes exercised at different external workloads (and therefore rates of metabolic heat production), which may have confounded their results (Gagnon *et al.* 2008; Schwiening *et al.* 2011). Nonetheless, their observations, combined with the results of the current study, may provide important insight into the mechanisms responsible for the lower

evaporative heat loss and thermosensitivity of the response observed in females at a fixed rate of metabolic heat production.

The study by Ichinose-Kuwahara *et al.* (2010) suggests that sex can modulate human temperature regulation in an intensity-dependent manner, such that differences are only observed above a certain requirement for heat loss. If sex modulates the level of thermal afferent and/or efferent neural activity during exercise, it would be expected that the differences in thermosensitivity of the sweating response reported by Ichinose-Kuwahara *et al.* (2010) would not only be limited to trained males and females, but would also be seen between the untrained males and females. Since they only observed differences in thermosensitivity of the sweating response between the males and females who exercised at the highest external workloads (and therefore metabolic heat production), there must be a point at which the requirement for heat loss exceeds the capacity of the sweat gland to contribute to temperature regulation which, as evidenced from the current study, is lower in females compared to males. Consequently, it can be hypothesized that thermal integration and subsequent efferent neural activity is similar between sexes during exercise in the heat, with sex modulating the effector organ (i.e. sweat gland) and its response (i.e. sweat rate). This modulation may not be seen at lower rates of metabolic heat production (or external workloads), since the requirement for heat loss would not exceed the ability of the sweat gland to contribute to temperature regulation. This would explain the lack of differences in

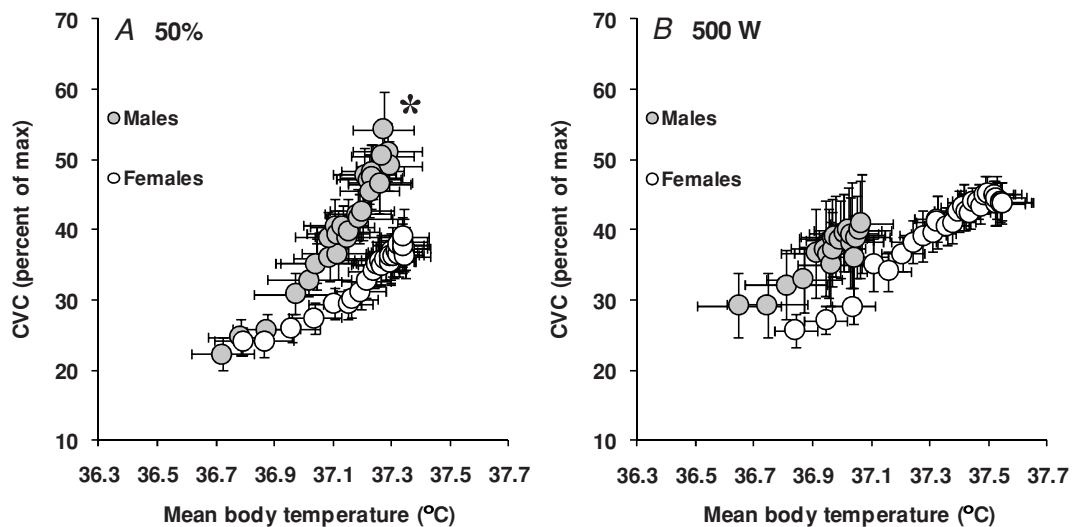


Figure 5. Sex-related differences in the sensitivity of the cutaneous vascular conductance (CVC) response to changes in mean body temperature during exercise performed at either a fixed percentage of maximum oxygen consumption (50%, *A*) or a fixed rate of metabolic heat production (500 W, *B*)

The data represent the average slopes of the linear portion of the response. Values are mean \pm standard error.

*Significantly different slope from females ($P \leq 0.05$).

sweat rate and thermosensitivity of the sweating response between untrained males and females, while a difference was observed between trained males and females in the study by Ichinose-Kuwahara *et al.* (2010).

In contrast, the rate of metabolic heat production chosen in the current study (500 W) evidently exceeded the capacity of the sweat gland to contribute to temperature regulation in females, since the greater end-exercise oesophageal and rectal temperatures could only be ascribed to differences in whole-body evaporative heat loss. Furthermore, a given level of thermal afferent and/or efferent activity would only be expected to result in a lower thermosensitivity of the effector response if a maximal effector output could not offset the overall requirement for heat loss. In this situation, the combination of a lower maximal effector output and a greater increase in body temperature would result in a lower thermosensitivity of the response, as observed for evaporative heat loss in females during the 500 W condition of the current study. This hypothesis is further supported by previous observations of a lower sweat output per gland, despite a greater number of active sweat glands in females during passive heating (Bar-Or *et al.* 1968; Inoue *et al.* 2005), as well as a lower eccrine sweat gland response to given doses of acetylcholine (Kahn & Rothman, 1942; Gibson & Shelley, 1948) and pilocarpine (Madeira *et al.* 2010). However, since these observations were made during passive heat stress or in the absence of heat stress, future studies are needed to directly assess the specific mechanism mediating the lower whole-body evaporative heat loss response observed during exercise in the current study. Furthermore, we are unable to determine at which rate of metabolic heat production this modulation occurs since we did not compare responses between males and females at progressively increasing rates of metabolic heat production. Future studies are warranted to address this hypothesis.

While whole-body sudomotor activity represents the main thermoeffector response, particularly during exercise in the heat, increases in skin blood flow also represent an important avenue for heat exchange. In contrast to the observed differences in sudomotor activity, no sex differences in cutaneous vascular conductance were observed. To our knowledge, only Inoue *et al.* (2005) have specifically examined sex-related differences in skin blood flow during heat stress. Although their observations were made during passive heating, they observed similar skin blood flow responses between males and females on the forehead, chest, back and forearm. As such, the observations in the current study support these findings and extend them to exercise in the heat. However, Inoue *et al.* (2005) did note a greater skin blood flow response on the thigh in females. Furthermore, Hodges *et al.* (2010) have recently reported lower peak blood flow responses in females following a period of

forearm occlusion. As such, future studies should consider examining potential sex differences in regional skin blood flow during exercise at greater combinations of exercise intensity and/or environmental temperatures.

Perspectives

The net outcome of the lower whole-body sudomotor thermosensitivity in females was shown as a greater oesophageal and rectal temperature at the end of exercise performed at a fixed rate of metabolic heat production. Prior to the current study, it was generally thought that sex differences in temperature regulation were associated with differences in physical characteristics and not with physiological differences in heat loss responses (Sawka *et al.* 1996; Havenith, 2001*b*). The findings of the current study therefore have important implications. They warrant considering sex as an independent factor in modulating human temperature regulation, particularly when examining the effects of age, chronic disease and various physiological states (e.g. dehydration, orthostatic stress, etc.). Since the majority of human temperature regulation studies focus on male participants only, or do not include enough female participants to analyse potential sex differences, it is often unknown if and/or how changes in temperature regulation differ between males and females as a function of such factors. Considering sex as a modulator of human temperature regulation could lead to improvements in public health, particularly for heat exposure guidelines which do not currently provide sex-specific exposure limits for safe work in the heat (United States Army Center for Health Promotion and Preventive Medicine, 2003; American Conference of Industrial Hygienists, 2007).

Considerations

The current study employed whole-body direct calorimetry to assess sex-related differences in sudomotor activity, the main thermoeffector during exercise in the heat. The design of the calorimeter (high air mass flow), as well as the environmental conditions employed (low specific humidity) ensure that our measurements of whole-body evaporative heat loss reflect local changes in sweat rate. In fact, the lower whole-body evaporative heat loss observed in females was paralleled by a lower whole-body sweat production. It is also interesting to note that the onset thresholds for evaporative heat loss, expressed as a change from baseline rest, were generally lower than those reported for local measurements of sweat rate, which may be due to the sensitivity of whole-body calorimetry. Nonetheless, we acknowledge that measurements of local sweat rate and/or the number of active sweat glands would provide insight into

the specific mechanisms (number of glands *vs.* sweat output per gland) responsible for the lower whole-body evaporative heat loss response observed in females. It is possible that differences in absolute maximum oxygen consumption ('fitness') between males and females may explain the observed results. Several observations argue against this reasoning, however. First, the differences in absolute maximum oxygen consumption between sexes in the current study are due to differences in the amount of metabolically active tissue and not necessarily to differences in training status, since no differences were observed when maximum oxygen consumption was expressed as a function of lean body mass. Second, resting heart rates and core temperatures, a strong indication of training status, did not differ between groups. Third, recent evidence suggests that maximum oxygen consumption itself does not modulate sweat production, nor the thermosensitivity of the response (Jay *et al.* 2011). Finally, female participants performed the experimental trials between the first and tenth day after the onset of menses, or during the no pill/placebo period of oral contraceptive use. These time periods were primarily chosen to ensure low levels of progesterone, which has been associated with an elevated resting core temperature and parallel increases in thermoeffector onset thresholds (Stephenson & Kolka, 1985). However, it is possible that elevations in oestrogen, which have been shown to decrease resting core temperature and onset thresholds of thermoeffector responses (Stephenson & Kolka, 1999), may have occurred by the tenth day after the onset of menses. It is equally possible that progestin exposure may not have completely subsided during the no pill/placebo period. Nonetheless, baseline oesophageal temperature and onset thresholds of thermoeffector responses did not differ between sexes.

Conclusion

The current study examined the effect of sex on whole-body sudomotor activity and cutaneous vascular conductance during exercise in the heat. When exercise was performed at a fixed rate of absolute metabolic heat production, females demonstrated a lower evaporative heat loss, and lower thermosensitivity of the response, despite a similar requirement for heat loss compared to males. Importantly, these results were not due to differences in physical characteristics, as both sexes were matched for body mass and surface area. In contrast, no differences in cutaneous vascular conductance were observed. These results demonstrate that sex modulates whole-body sudomotor activity during exercise in the heat, independently of differences in body mass, surface area and rate of metabolic heat production.

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Author contributions

All authors contributed to the conception and design of the experiments, to the collection, analysis and interpretation of

data, as well as to the drafting and critical revising of the manuscript. All authors have approved the final version of the manuscript. All experiments were performed at the University of Ottawa.

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