PULMONARY VENTILATION FOLLOWING ACCLIMATION TO A HOT ENVIRONMENT

by

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ABSTRACT

Human pulmonary ventilation and the hyperoxic-centrally mediated ventilatory response to CO_2 were studied before and after a 10-day passive heat acclimation (HA). It was hypothesized pulmonary ventilation during a passively- or actively-induced hyperthermia would adapt similarly to thermolytic heat loss responses and that chemosensitivity would be increased following HA. Following HA, onset of increased cutaneous vasodilatation, eccrine sweating and ventilation in both passively- and actively-induced hyperthermia were at significantly lower esophageal temperature thresholds ($p<0.05$). Addtitionally, following HA the breathing pattern during passively-induced hyperthermia adapted to promote respiratory heat loss and actively-induced hyperthermia gave a significantly ($p<0.05$) greater ventilation. Irrespective of acclimation state, hyperthermia significantly increased chemosensitivity ($p=0.027$) across all levels of end-tidal partial pressures of CO_2. HA did not modify the normo- or hyperthermic ventilatory recruitment thresholds (VRT) or the supra-VRT chemosensitivity. In conclusion, pulmonary ventilation adapted similarly to thermolytic heat loss responses and chemosensitivity was unmodified following HA.

Keywords: hyperthermia; thermoregulation; ventilation; heat acclimation; core temperature; threshold.

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ABBREVIATIONS AND ACRONYMS

ATP.....adenosine triphosphate

ATPS.....ambient temperature, pressure saturated

AVA.....arteriovenous anastomoses

BTPS.....body temperature, pressure saturated

$\dot{C}$ .....rate of convective heat exchange

°C.....degrees Celsius

CBV.....cutaneous blood cell velocity

CO_2.....carbon dioxide

$\dot{C}_{res}$ .....rate of convective respiratory heat loss

CSF.....cerebral spinal fluid

$\dot{E}_{res}$ .....rate of evaporative respiratory heat loss

$\dot{E}_{sk}$ .....rate of evaporative heat loss from the skin

FBF.....forearm blood flow

F_ICO_2.....inspired fraction of CO_2

f.....breathing frequency

$[H^+]$.....hydrogen ion concentration

HCO_3^-.....bicarbonate

HCVR.....hypercapnic ventilatory response

HR.....heart rate

HVR.....hypoxic ventilatory response

$\dot{K}$ .....rate of conductive heat exchange

kPa.....kiloPascal

$\dot{M}$ .....rate of metabolic heat production

min.....minute

mm Hg.....millimetres of mercury

O_2.....oxygen

P_ACO_2.....alveolar CO_2 partial pressure

P_AO_2.....alveolar O_2 partial pressure

P_aCO_2.....arterial CO_2 partial pressure

P_aO_2.....arterial partial pressure of O_2

P_{CO2}.....partial pressure of CO_2

$P_{ET}CO_2$..end-tidal partial pressure of CO_2

pH_a.....arterial pH

POAH.....preoptic anterior hypothalamus

PV.....plasma volume

$\dot{Q}$ .....rate of cardiac output

Q_{10}.....thermal coefficient

$\dot{R}$ .....rate of radiative heat exchange

RER.....respiratory exchange ratio

RH.....relative humidity

$\dot{S}$ .....rate of heat storage

SBC.....selective brain cooling

s.....seconds

SkBF.....skin blood flow

$\dot{E}_{sw}$.....sweat rate

STPD.....standard temperature, pressure desaturated.

T_a.....ambient temperature

$\overline{T}_b$ .....mean body temperature

T_c.....core temperature

T_{es}.....esophageal temperature

$\dot{T}_{es}$.....rate of T_{es} change

T_{hypo}.....hypothalamus temperature

TNZ.....thermoneutral zone

T_{re}.....rectal temperature

T_{sk}.....skin temperature

$\overline{T}_{sk}$.....mean skin temperature

T_{ty}.....tympanic temperature

μ.....energies of apparent activation

$\dot{V}_A$ .....rate of alveolar ventilation

$\dot{V}CO_2$ ...rate of carbon dioxide production

$\dot{V}_D$ .....rate of dead space ventilation

$\dot{V}e$ .....rate of minute ventilation

$\dot{V}O_2$ .....rate of oxygen consumption

$\dot{V}O_{2max}$....rate of maximal O_2 consumption

$\dot{W}$ .....rate of work

V_t.....tidal volume

W.....watts

DEFINITIONS

Acclimation – physiological or behavioural changes occurring within the lifetime of an organism (i.e., phenotypic adaptation) which reduces the strain caused by experimentally induced changes in climatic factors such as ambient temperature and relative humidity in a controlled environment (1).

Acclimatization – physiological or behavioural changes occurring within the lifetime of an organism which reduces strain caused by changes in the natural climate (1).

Adaptation – physiological changes that reduce the physiological strain produced by stressful environmental components of the total environment within the lifetime of an organism (phenotypic adaptation) or through genetic selection in a species or subspecies (genotypic adaptation) (1).

Alveolar ventilation – the volume of fresh gas entering the respiratory zone in the lungs available for gas exchange (178).

Ambient temperature – the average temperature of a gaseous or liquid environment surrounding a body as measured outside the thermal and hydrodynamic boundary layers that overlay the body (1).

Arteriovenous anastomoses – large direct vascular shunts between arterioles and venules within the cutaneous vascular system (22).

Body temperature, mean – the sum of the products of the heat capacity and temperature of all tissues of the body divided by the total heat capacity of the organism. Usually estimated from measurements of a representative core temperature and mean skin temperature according to: $\overline{T}_b = a_1 \cdot T_c + a_2 + \overline{T}_{sk}$, where a_1 and a_2 represent the empirically determined contributions of thermal core and shell to mean body temperature (1).

Breathing frequency – the number of breathes per minute (117).

Conductive heat exchange – the net rate of heat transfer by a solid material or a non-moving gas or fluid down a thermal gradient within an organism or between an organism an its external environment (1).

Control – refers to the action of a system on the responses that oppose perturbations (i.e., body temperature is regulated through the control of heat loss and heat production responses) (31).

Convective heat exchange – the rate of net heat transfer per unit area between a surface and a moving fluidic medium per unit temperature difference between the surface and the medium (1).

Core temperature – the mean temperature of the inner tissues of the body whose temperatures are not changed in their relationship to each other by circulatory adjustments and changes in heat dissipation to the environment that affect the thermal shell of the body (1).

Cutaneous blood flow – the flow of blood through the skin vasculature (1).

Dead space ventilation – the volume of gas entering the respiratory system not involved is gas exchange (includes both anatomic and physiologic dead space) (178).

Eccrine sweating – a response of the eccrine sweat glands to a thermal stimulus (1).

Evaporative heat loss – the rate of net heat transfer per unit vapour pressure gradient caused by the evaporation of water from a unit area of wet surface or by the condensation of water vapour on a unit area of body surface (1).

Heat balance equation – a mathematical equation describing the net rate at which a subject generates, gains, loses and exchanges heat with its environment (1).

Heat loss mechanism – physiological response to increase the rate at which heat energy is transferred from an organism to the environment (1).

Heat production mechanism – an increase in metabolic heat production in excess of basal metabolic rate via shivering and non-shivering thermogenesis(1).

Heat storage – the rate of gain or loss of heat associated with changes in body temperature or mass (1).

Homeotherm – a tachymetabolic species in which cyclic variation in core temperature is maintained within arbitrarily defined limits (± 2°C) despite much larger variations in ambient temperature (1).

Hypercapnia – a condition of high arterial partial pressure of carbon dioxide (22).

Hypercapnic ventilatory response (HCVR) – the hyperventilation associated with increasing levels of arterial partial pressure of carbon dioxide (13).

Hyperoxia – a condition of high arterial partial pressure of oxygen (117).

Hyperpnea – abnormal increases in the rate and depth of respiration (117).

Hyperpnea, thermal – an increase in tidal volume associated with an increase in alveolar ventilation occurring during severe heat stress, which has caused a large rise in core temperature. Deep breathing is also named second phase panting since it is usually preceded by a phase of typical panting (rapid shallow breathing) (1).

Hyperthermia – the condition of a temperature regulator when core temperature is above its set-range specified for the normal active state of the species (1).

Hyperventilation – an increase in the rate of ventilation greater than that required for metabolic needs resulting in a decrease in arterial partial pressure of carbon dioxide (117).

Hypocapnia – a condition of low arterial pressure of carbon dioxide (117).

Hypothermia – the condition of a temperature regulator when core temperature is below its set-range specified for the normal active state of the species (1).

Hypoxia – a condition of low arterial partial pressure of oxygen resulting in low tissue oxygen levels within the body (117).

Hypoxic ventilatory response (HVR) – the hyperventilation response associated with decreasing levels of arterial partial pressure of oxygen (13).

Insensible heat loss – evaporative heat loss (1).

Insulation – the reciprocal of thermal conductance (1)

Interthreshold zone – the temperature range between two threshold (body) temperatures, for activation of any thermoeffector responses, particularly metabolic heat production and of evaporative heat loss when no thermal load is present (1).

Mechanical efficiency – work done on an external system per unit of energy expended by an organism in the performance of that work (1).

Metabolic heat production – rate of transformation of chemical energy into heat in an organism (1).

Metabolic rate – the rate of transformation of chemical energy into heat and mechanical work by aerobic and anaerobic metabolic activities within an organism (1).

Normothermia – the condition of a temperature regulator when its core temperature is within ± 1 SD of the range associated with the normal post-absorptive resting condition of the species in a thermoneutral environment (1).

Null zone – a range of core temperature between the thresholds for shivering thermogenesis and sweating within which vasomotor responses to thermal stress are the prominent means of maintaining heat balance (120).

Radiative heat exchange – the net rate of heat transfer per unit area by the exchange of thermal radiation between two surfaces, per unit temperature difference between the surfaces (1).

Regulation – the maintaining constant of a variable in the *milieu intérieur* (31).

Respiratory exchange ratio (RER) – the ratio of volume of CO_2 produced to the volume of O_2 consumed (i.e., $R = \dot{V}CO_2 \cdot \dot{V}O_2^{-1}$) (22).

Selective brain cooling – the lowering of brain temperature, either locally or as a whole, below aortic (arterial blood) temperature (1).

Sensible heat loss – the sum of heat flows or heat fluxes by radiation, convection and conduction from a body to the environment (1).

Set-point – the value of a regulated variable which a healthy organism tends to stabilize by the process of regulation. Found in a situation when external or internal interferences tending to alter the regulated variable and the resulting effector activities tending to counteract these alterations (1).

Shivering – the involuntary tremor of skeletal muscles as a thermoeffector activity for increasing metabolic heat production in response to a decrease in mean body temperature and core temperature away from the regulated set-range specified for the normal active state of the species (1).

Sweat rate – the quantity of eccrine sweat secreted from an area of skin during a given time (i.e., $mg \cdot m^{-2} \cdot s^{-1}$) (1).

Sweat sensitivity – the increase in sweat rate relative to an increase in core temperature (i.e., $\Delta \dot{E}_{sw} \cdot \Delta T_c^{-1}$) (163).

Temperature sensitive neurons – neural elements that change their activity in responses to changes in their own temperature (1).

Thermal hyperpnea – an increase in tidal volume associated with an increase in alveolar ventilation occurring during severe heat stress which has caused a large rise in core temperature (1).

Thermoeffector – an organ system and its action, respectively, that affects heat balance in a *controlled* manner as part of the process of temperature regulation (1).

Thermogenesis, non-shivering – heat production due to metabolic energy transformation by processes that do not involve contractions of skeletal muscles (1).

Thermogenesis, shivering – an increase in the rate of heat production during cold exposure due to increased contractile activity of skeletal muscles not involving voluntary movements and external work (1).

Thermoneutral zone (TNZ) – the range of ambient temperatures in which temperature regulation is achieved only by control of sensible heat loss (i.e., without regulatory changes in metabolic heat production or evaporative heat loss) (1).

Thermoregulation – the maintenance of the temperature or temperatures of a body within a restricted range under conditions involving variable internal and/or external heat loads by autonomic or behavioural means (1).

Thermosensor – neural elements or circuitry of neural elements that transduce temperature in such a way that thermal sensation is elicited and/or temperature regulation is adequately stimulated (1).

Tidal volume – volume of air entering and leaving the lungs with each breathe (117).

Vasomotion – alterations in the pattern of blood flow through a capillary bed in response to changes in the local environment (117).

Ventilation – the amount of air inspired and expired each minute, calculated as a product of tidal volume and breathing frequency; a common measurement of pulmonary ventilation (22). Expressed as BTPS.

Ventilatory acclimatization - time-dependent changes in ventilatory magnitude resulting from exposure to a changed environment or biological process over hours, days, weeks and years (57).

Water vapour pressure – the pressure exerted by water vapour in the air (91).

Work, negative – the rate of work done **on** an organism by an external force (1).

Work, positive – the rate of work done **by** an organism on an external system (1).

Chapter 1 – Thesis Overview

For over a century, an increase in core temperature has been known to stimulate human pulmonary ventilation at rest (6). Hyperthermia has also been shown to contribute to increases in ventilation during exercise (3, 8, 13), but the mechanism(s) through which an increased core temperature stimulates ventilation are still unresolved (12). One hypothesis is that the increased ventilation is a result of a greater sensitivity to normal levels of chemical stimuli since hyperthermia augments the ventilatory response to hypoxia and hypercapnia (1, 3-5, 7, 9, 10, 12). A more recent hypothesis is that the hyperthermic-induced increase in ventilation in humans is a thermoregulatory heat loss response important in cranial temperature regulation (2, 13). When humans acclimate to a hot environment, the thermoregulatory heat loss responses of cutaneous vasodilatation and eccrine sweating both adapt to increase heat loss and help prevent a rise in core temperature during subsequent heat exposures (11). The effect of heat acclimation on the human ventilatory response during hyperthermia is the focus of this thesis.

The second chapter in this thesis is a review of literature on the topics of human and non-human temperature regulation. This is followed by a review of literature on the description of thermoregulatory adaptations acquired when humans are acclimated to either a hot or cold environment. Subsequently, the literature on the regulation of human pulmonary ventilation and its responses to chemical and thermal stimuli, along with the ventilatory adaptations occurring with chronic exposure to hypoxia, eucapnic

hypercapnia and eucapnic hypocapnia is reviewed. Chapter 2 concludes with an outline of the thesis rationale, research hypotheses and testable questions.

Chapter 3 is the first of three studies performed to assess adaptations of pulmonary ventilation following acclimation to a hot environment. It explores the relationship between ventilation and esophageal temperature during a passively-induced hyperthermia prior to and following a 10-day passive heat acclimation. It investigates whether the esophageal temperature threshold for an increase in ventilation and the ventilatory response adapt similarly to that for cutaneous vasodilatation and eccrine sweating following the passive heat acclimation protocol. Chapter 4 follows up by determining whether the relationships between exercise ventilation and its components with esophageal temperature during an actively-induced hyperthermia adapt similarly as during a passively-induced hyperthermia, following the same 10-day heat acclimation protocol. Finally, Chapter 5 examines whether the hyperoxic central chemoreflex ventilatory response at a normothermic and hyperthermic esophageal temperatures is altered by a 10-day passive heat acclimation.

Chapter 6 concludes the thesis with responses to the research hypotheses and testable questions as given at the end of Chapter 2.

Individual reference lists are given for each chapter, with an overall reference list contained in Chapter 7.

Following Chapter 7, Appendix A contains the calibration record for the esophageal thermocouples and rectal thermistors used to measure core temperature within the individual studies and the acclimation protocol, respectively. Finally, Appendix B outlines the response time of the capacitance hygrometry method used to measure eccrine sweat rate.

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Chapter 2 - Review of Literature

Humans are homeotherms and they defend their body core temperature within a restricted range (33). This is achieved via a balance between the rate of heat gained by the body and the rate of heat lost from the body to the environment and may be expressed through the following equation: (19)

$$\dot{S} = \dot{M} \pm \dot{W} \pm \dot{C} \pm \dot{R} \pm \dot{K} \pm \dot{C}_{res} - \dot{E}_{res} - \dot{E}_{sk} \quad (2.1)$$

Where:

$\dot{S}$ = rate of heat stored in or lost from the body;

$\dot{M}$ = rate of internal heat produced by metabolism;

$\dot{W}$ = rate of work;

$\dot{C}$ = rate of non-respiratory heat exchanged through convection;

$\dot{R}$ = rate of heat exchanged through radiation;

$\dot{K}$ = rate of heat exchanged through conduction;

$\dot{C}_{res}$ = rate of respiratory convective heat loss;

$\dot{E}_{res}$ = rate of respiratory evaporative heat loss;

$\dot{E}_{sk}$ = rate of heat lost by evaporation from the skin.

Humans utilize both behavioural and autonomic responses in order to regulate core temperature. The following review of literature examines the human autonomic

thermoregulatory system and the thermolytic responses employed during periods of heat stress, cold stress and exercise. It also examines how these responses adapt to repeated or extended exposure to heat or cold stress. The thermoregulatory mechanism of panting is also reviewed. Additionally, the regulation of human ventilation is examined in detail. The review concludes with a statement of the research hypotheses and a list of testable questions examined.

2.1 Human Thermoregulation

The human autonomic thermoregulatory system consists of a set of temperature sensitive neurons that sense changes in skin and core temperature, a branch of the central nervous system which receives, integrates and coordinates afferent sensory information into a thermoeffector response and a set of effectors through which the body makes the appropriate thermoregulatory response (169).

There are both peripheral and central temperature sensitive neurons involved in temperature regulation. Peripheral sensors are located in the skin and monitor absolute and rate of change of skin temperature (T_{sk} and $\dot{T}_{sk}$, respectively) in order to activate or inhibit thermoregulatory effector responses (48, 88). Within the cutaneous thermoreceptors, there are specific populations of neurons sensitive to warm or cold stimuli and both include dynamic and static responses (22). Central thermosensitive sites are found in the pre-optic anterior hypothalamus (POAH), the medulla and the spinal cord. Within these areas, there are three distinct populations of temperature sensitive neurons (22, 141). Within the POAH, ~30% of temperature sensitive neurons are warm-sensitive, 5% are cold-sensitive and the remainder (~65 %) are temperature insensitive

(23). In addition to its role as a temperature sensor, the POAH is also the major integrating sensor for human thermoregulation (33). Afferent signals from peripheral and central temperature sensitive neurons are sent to the POAH where they are integrated and the appropriate autonomic heat loss or heat gain effector responses are initiated (156). Thermoregulatory autonomic effector responses involve physiological systems that subserve or compete with other regulatory functions responsible for maintaining osmolarity, gas pressures and blood pressure (48, 88).

Autonomic thermoregulatory effector responses are initiated when the thermal environment produces a change in T_{sk} or core temperature (T_c) or both. The thermoneutral ambient temperature (T_a) range, where heat balance is achieved via $\dot{C}$, $\dot{R}$ and $\dot{K}$differs with the environmental medium. The thermoneutral zone (TNZ) for humans within air is approximately 23°C to 26°C while within water the TNZ zone is raised to 34°C to 36°C (171). The width of the TNZ varies within species according to basal metabolic rate, individual body size, level of insulation or posture (1, 190). When the thermal environment is outside the TNZ, above or below, it may result in an increase or decrease in skin and core temperatures and stimulation of heat loss or heat production responses.

There are two main models on how the thermoregulatory system responds to T_{sk} and T_c stimuli in order to initiate appropriate heat loss or heat production responses. In one model, T_{sk} and T_c are compared to a neuronally represented reference or 'set-point'. If T_c increases or decreases to above or below the 'set-point' level, heat loss or heat production mechanisms are stimulated (Figure 2.1) (36, 48, 75). The other emerging

model is based on the neurophysiological properties of temperature sensitive neurons. It asserts there is a T_c range between the T_c thresholds for the initiation of sweating and shivering that does not elicit either of these two thermoregulatory effector responses. That is, there is a "null zone" or "interthreshold range" of core temperatures where there is neither shivering nor sweating and T_c is maintained through vasomotion (118).

2.1.1 Heat Stress

Heat stress occurs when the thermal environment is above the critical level of the TNZ thus promoting an increase in heat storage ($\dot{S}$) and a subsequent increases in T_{sk} and/or T_c. During such periods, peripheral and central temperature sensitive neurons detect the temperature increase and send afferent signals to the POAH. When T_c rises above a 'set-point' or above the "null zone", the appropriate heat loss mechanisms are activated through the sympathetic nervous system (Figure 2.1). In humans, traditional thermolytic responses include cutaneous vasodilatation to increase blood flow to the skin in order to increase $\dot{C}$, $\dot{R}$, and $\dot{K}$ heat loss and stimulation of eccrine sweating. The effectiveness of $\dot{E}_{sk}$ in enhancing heat loss is dependent upon the size of the vapour pressure gradient from the skin surface to the environment (141).

2.1.1.1 Vasodilatation

Convective heat exchange is an important contributor to heat transfer in humans. Extracellular heat is absorbed and carried by the blood to the peripheral capillary networks where it is transferred to the surface of the skin and upper respiratory tract through a combination of convective and conductive processes (18). Cutaneous blood

flow is enhanced in acral parts of the body such as the hands, feet, ears, nose and lips as a result of the presence of arteriovenous anastomoses that are under control of the the sympathetic nervous system. Arteriovenous anastomoses are vascular shunts from arterioles to venules whose specific role is to enhance or diminish heat loss. The difference between T_{sk} and T_a along with the difference between the temperature of the mucous membrane of the respiratory system and the inhaled air are main determinants of the rate of convective and radiative heat loss to the environment (88). During periods of heat stress, cutaneous blood flow is initially increased via a release of sympathetic vasoconstrictor tone when T_{sk} and T_c begin to increase (85, 97). If T_c continues to rise, there is a further and progressive increase in cutaneous blood flow via an incompletely understood actively mediated vasodilatation (93, 95).

Both T_{sk} and T_c influence cutaneous blood flow during a heat stress. The relation between T_{sk} and T_c on the rate of increase of cutaneous blood flow during a heat stress was studied by Brengelmann, Wyss, and Rowell (26). They observed that T_{sk} had a minor role in the regulation of forearm blood flow (FBF; representative of cutaneous blood flow) in resting humans when T_{sk} was controlled at various temperatures within the 34 to 40°C range, whereas T_c appeared to be the dominant stimulus in the regulation of FBF. These findings are supported by Wyss et al (187) who observed a 50 to 100 % increase in FBF as T_{sk} started to rise at the beginning of a square wave heating protocol, but when T_c surpassed a threshold temperature, FBF increased proportionally to T_c and at the conclusion of the heating protocol, had increased by ~400 % above resting levels. They concluded T_c has an average influence on FBF more than twenty times that of T_{sk}. These studies served to show the predominant role of an increase in T_c as compared to an

increase in T_{sk} in the stimulation of an increase in cutaneous blood flow during heat stress.

2.1.1.2 Evaporative Heat Loss

Two avenues of evaporative heat loss are through the skin ($\dot{E}_{sk}$) and via the respiratory tract ($\dot{E}_{res}$). For humans, $\dot{E}_{res}$ plays a large role in total cephalic heat loss (see section below on selective brain cooling in humans), but plays a minor role in whole body cooling (144). On the other hand, heat loss via the evaporation of eccrine sweat from the skin is considered to be, quantitatively, the most important method of heat loss for humans during hyperthermia.

If T_a is greater than T_{sk}, T_{sk} will be raised and as it approaches T_c, the thermal gradient from the core of the body to the periphery is decreased, thereby reducing or nullifying the ability to lose heat by means of $\dot{C}$, $\dot{R}$ and $\dot{K}$ via increased cutaneous blood flow. Therefore, an additional response is required in such circumstances to increase heat loss in order to minimize $\dot{S}$ and the subsequent rise in T_c. In humans, that mechanism is eccrine sweating and an attempt to increase evaporative heat loss from the skin.

The evaporation of sweat depends on the difference between the water vapour pressure on the skin and in the air. In order for sweat to evaporate, the water vapour pressure on the skin must be greater than in the surrounding air. The rate at which sweat is evaporated from the skin surface is proportional to the difference between the water vapour pressure on the skin and in the air (88). The water vapour pressure of air

increases exponentially as a function of dry bulb temperatures and a maximum saturated water vapour pressure for a given dry bulb temperature is denoted as 100 % relative humidity (RH). An environment with a RH greater than on the skin surface hinders the evaporation of sweat. The evaporation of sweat in such an environment is still possible as long as the T_a is lower than the elevated T_{sk} (88, 177). As a result, sweating is most effective within hot-dry environments where the water vapour pressure gradient between the fully wetted skin and the environment may be the greatest.

Similar to cutaneous blood flow, sweat rate ($\dot{E}_{sw}$) is influenced by changes in T_{sk} and T_c. The difficulty in determining the individual effects of T_{sk} and T_c on $\dot{E}_{sw}$ is that it is hard to distinguish between the individual roles of the peripheral and central temperature sensitive neurons in the thermal drive for activation and augmentation of $\dot{E}_{sw}$ (77, 172).

The influence T_a has on T_{sk} plays a large role in the sweating response of humans. At rest, sweating can be stimulated via an increase in T_{sk} prior to an increase in T_c (184), and conversely, sweating may be inhibited by a rapid cooling of the skin while T_c continues to rise while at rest (116, 185).

Wurster & McCook (184) employing step changes in T_a found that a positive $\dot{T}_{sk}$ does not greatly impact on sweat gland recruitment while participants rested on a copper screen bed, but a rapid decline in T_{sk} inhibited sweating while T_c was still rising. Similarly, Banjeree, Elizondo & Bullard (7) observed a direct relationship between a

negative $\dot{T}_{sk}$ and the rate at which $\dot{E}_{sw}$ declined in resting conditions. Therefore, it appears a positive $\dot{T}_{sk}$ while T_c is stable at normothermic levels, does not impact greatly on the recruitment of eccrine sweat glands. Rather, a negative $\dot{T}_{sk}$ greatly contributes to the inhibition of sweating since sweating may be inhibited, even though T_c is at hyperthermic levels.

On the other hand, T_c has been shown to have a greater importance on the stimulation and escalation of $\dot{E}_{sw}$. Wyss et al (187), assumed if a positive $\dot{T}_{sk}$ was an important influence on sweating, then there should be an increase in $\dot{E}_{sw}$ at the onset of passive heating when T_c was still at normal resting levels. Similar to Wurster & McCook (184) during the period of increasing T_{sk} they showed there was no significant increase in $\dot{E}_{sw}$. Subsequently, they showed that $\dot{E}_{sw}$ increased in proportion to the rise in T_c while T_{sk} remained virtually constant. They concluded T_{sk} had an influence on $\dot{E}_{sw}$ of less than one-tenth as important to that of T_c (187).

Nadel, Bullard & Stolwijk (127) looked at the independent influences of mean T_{sk} ($\overline{T}_{sk}$), T_c, local T_{sk} and $\dot{T}_{sk}$ on $\dot{E}_{sw}$ after the sweating response had been stimulated while at rest. They found $\dot{E}_{sw}$ was directly related to $\overline{T}_{sk}$ and independent of a positive $\dot{T}_{sk}$. When a participant's T_{sk} was cooled, the decline in $\dot{E}_{sw}$ was greater than the decline in $\overline{T}_{sk}$. This relationship was minimized and became more linear when T_c was elevated above resting levels indicating local $\dot{E}_{sw}$ is directly related to T_c with $\overline{T}_{sk}$ working as a modifier affecting the relationship in the appropriate direction.

In summary of human thermolytic responses, an increase in cutaneous blood flow and eccrine sweating are initiated within thermal environments promoting heat storage and a subsequent rise in T_{sk} and T_c. Both increases in cutaneous blood flow and eccrine sweating can be stimulated by an increase in T_{sk}, however the most important stimulus for the onset of both thermolytic events is a rise in T_c. Additionally, both heat loss responses, once stimulated, may be modified by input from peripheral temperature sensitive neurons.

2.1.2 Cold Stress

An environment may be described as cold when the T_a promotes a negative $\dot{S}$ resulting in a decrease in T_{sk} and T_c plus stimulation of heat production mechanisms (141, 190). In addition to behavioural modifications during acute periods of cold stress the autonomic nervous system responds to prevent heat loss and maintain T_c at optimal levels. Effector responses employed include vasoconstriction of peripheral vasculature and shivering.

2.1.2.1 Vasoconstriction

During periods of cold stress, cutaneous blood flow is reduced, thereby helping to produce an increase in insulation between the cold environment and the warm body core. By varying cutaneous blood flow, humans are capable of varying the depth of the insulative tissue layer between the environment and the body core consisting of the skin, subcutaneous fat, and skeletal muscle. With increasing tissue insulation, T_{sk} is permitted to drop closer to T_a resulting in reduced heat loss through $\dot{C}$, $\dot{R}$ and $\dot{K}$ thus slowing the rate of decline in T_c and helping to prevent T_c dropping to dangerous levels.

Similar to acute periods of heat stress, modifying the peripheral vascular tone is the initial response during an acute cold stress. The resulting increased tone of the cutaneous vasculature is a result of the direct action of lowering T_{sk} on vessel diameter along with an active vasoconstriction that includes the release of norepinephrine from sympathetic nerve terminals stimulated by augmented cutaneous cold sensitive neuron activity (171, 190). Cutaneous vasoconstriction is maximal within an ambient air temperature of ~10°C (17). The reduction in cutaneous blood flow is, in part, due to shunting of blood to deeper vessesls in acral regions of the body, including the hands, feet, nose, lips and ears after the sympathetically controlled arteriovenous anastomoses constrict. As cooling at rest progresses, total body insulation is further improved by decreasing blood flow to subcutaneous fat and skeletal muscle (39, 140). When shivering is not induced, skeletal muscle may provide as much as 75% of the total body insulation for participants resting in water at a temperature below the critical level of the TNZ with subcutaneous fat and skin providing the remaining 25% (140).

2.1.2.2 Shivering

The subsequent response to an acute cold stress is to increase metabolic heat production ($\dot{M}$). The metabolic process through which the chemically stored energy of adenosine tri-phospate (ATP) is produced and converted into mechanical energy is only 20 to 25% efficient, with the remainder being released as heat (18, 88, 108, 141). Therefore, during periods of cold stress, an increase in $\dot{M}$ via shivering is employed to increase heat production when there is a drop in either T_{sk} or T_c or both.

Shivering is initiated in response to augmented activity of cutaneous temperature sensitive neurons as T_{sk} is lowered due to ambient temperatures below the critical level of the TNZ. Once shivering is initiated, its intensity is determined, in part, by further decreases in T_{sk}. If heat loss is greater than thermogenesis, T_c will decrease below the regulated set-point or out of the null zone resulting in stimulation of the central temperature sensitive neurons and shivering intensity increases in proportion to the magnitude of T_c depression (171).

Apart from individual influences, T_{sk} and T_c interact to modify the shivering response. Downey, Miller and Darling (56) showed an earlier initiation of metabolic heat production (i.e., shivering) when participants' T_c were lowered while resting within a room with an T_a of between 22 to 24°C that decreased skin temperature (no mean T_{sk} given) when compared to an alternate condition where T_c was decreased while participants rested in a warm room ($T_a > 32$°C) and $\overline{T}_{sk}$ remained greater than 35°C. Additionally, in a group of humans with high spinal cord transactions, the shivering thresholds was dependent on the amount of sentient skin exposed to the environment. The threshold for the onset of shivering was at a higher T_c in participants with a greater amount of sentient skin (i.e., greater cutaneous thermal afferent inputs when exposed to the cool T_a) than the participants with a smaller sentient portion of the body (i.e., less cutaneous afferent thermal input) exposed to the same cool environment (56). In skin with normal functioning temperature sensitive neurons, when T_{sk} is maintained at a high level, the threshold for shivering onset is delayed to a lower T_c (99). In addition to modifying the shivering threshold, the rate at which $\dot{M}$ increases is modified by T_{sk} so there is an increased sensitivity to declines in T_c when T_{sk} is low and vice versa (130).

Specifically, there is an inverse relationship between metabolic thermogenesis and T_c so that thermogenesis is initiated at a higher T_c and increases at a faster rate when T_{sk} is low (9, 10).

In summary for human thermoregulation during periods of cold stress, the first autonomic thermoregulatory response to acute cold stress is to decrease blood flow to the skin, subcutaneous fat and underlying skeletal muscle in order to increase the amount of thermal insulation surrounding the body core. If T_{sk} continues to decrease out of the TNZ, shivering is stimulated to help maintain T_c within normal levels. If heat loss exceeds thermogenesis resulting in a drop in T_c, there is greater stimulation of $\dot{M}$ via central temperature sensitive neurons. Skin temperature and T_c sensory information interact to modify the T_c threshold for the onset of shivering (10) and the intensity of the shivering response (171).

2.2 Additional Thermogregulatory Responses

Non-human homeothermic animals deal with thermal stresses in a similar way to humans. They make alterations to increases or decreases in body temperature through adjustments in behaviour and via autonomic nervous system responses (48). In general, the neurophysiology of the thermoregulatory system is similar between other homeotherms and humans. Both contain peripheral and central temperature sensitive neurons and a central integrator that receives and integrates afferent sensory stimuli to coordinate effector responses. One difference between other homeotherms and humans is

they have a greater dependence on pulmonary ventilation as an effector response during periods of heat stress.

2.2.1 Panting

Many mammalian species have an insulative layer of fur that minimizes $\dot{C}$, $\dot{R}$ and $\dot{K}$ heat loss via the skin with increases in cutaneous blood flow and also have few eccrine sweat glands (88). As a result, they rely on the alternate avenue of convective and evaporative heat loss through the respiratory system in a 2 phase panting response after an increase in their body temperature.

The first phase of panting is characterized by a thermal tachypnea as the increase in pulmonary ventilation ($\dot{V}_E$) is accomplished by an increase in functional residual capacity via rapid, shallow breaths. This increase in $\dot{V}_E$ is restricted almost entirely to an increase in respiratory dead space ($\dot{V}_D$) with $\dot{V}_D$ contributing up to ~90 % of total $\dot{V}_E$ during an acute heat stress, thus minimizing changes to the acid-base balance of the blood (74). During prolonged, severe heat stress, producing elevations in T_c, the acid-base balance of the blood is compromised for greater respiratory heat loss with $\dot{V}_E$ being increased further by an increase in alveolar ventilation ($\dot{V}_A$) via a shift to a secondary phase of panting or thermal hyperpnea, characterized by a decrease in breathing frequency and an increase in depth (74). The biphasic pattern of the panting response has been shown to occur in dogs, cats, sheep, cattle (148) and humans appear to have only a second phase panting response (37, 180).

In addition to the increased $\dot{V}_E$, there is an increased secretion of mucous in the nasal cavity, an increased secretion of saliva in the mouth and in animals such as dogs, an increased blood flow to the tongue (30). On inhalation, air is moistened and warmed to T_c by passing over the moist mucosal lining of the nose and/or mouth, taking heat from the blood flowing through the nasal region and the tongue. When this warmed, humidified air is then exhaled it results in marked evaporation taking place in the upper airway resulting in powerful cooling of the nose and mouth area (30, 47, 88).

In order to modify heat loss, animals such as the dog, vary inhalation and exhalation patterns. In resting animals, inhalation occurs through the nose with the bulk of the exhalation occurring through the mouth (160). If passive hyperthermia is allowed to continue or if there is an increased $\dot{S}$ producing an increase in body temperature because of increased physical activity, this pattern changes to inhalation through both the nose and mouth with the majority of exhalation still occurring through the mouth in an attempt to maximize $\dot{C}_{res}$ and $\dot{E}_{res}$ (160).

2.2.2 Control of Panting

The main focus on the regulation of panting has been to study the participation of central and peripheral thermal stimuli in the initiation and modification of the panting response. Similar to human thermoregulatory effector responses, both peripheral and central thermal stimuli are involved in the control of panting (20). Solely heating the hypothalamus can increase the respiratory frequency of some animals (19, 110). On the

other hand, panting can be initiated exclusively through peripheral thermal stimuli (20, 111).

Lim & Grodins (107) performed a series of experiments on anaesthetized dogs to determine whether peripheral and central temperatures interact to initiate panting. They observed during whole body heating that all dogs panted when peripheral (T_{sk}) and central (hypothalamic and rectal) temperatures were ~41°C. Maintaining hypothalamic temperature (T_{hypo}) at a normothermic level and increasing T_{sk} (i.e., peripheral heating alone), no panting was observed in any of the dogs. In a series of central heating experiments, T_{hypo} of the dogs that panted were in the region of 42.8°C while subcutaneous and rectal temperature (T_{re}) remained at low levels. Comparing whole body heating experiments with elevations in both T_{sk} and T_{hypo} versus central heating experiments with elevations in only T_{hypo}, the mean T_{hypo} threshold for the initiation of panting during whole body heating was lower than during central heating. It was concluded both peripheral and central temperatures contribute to the initiation and control of panting in anaesthetized dogs. It must be noted, these findings may be of limited value because anaesthesia influences the thermoregulatory system in such a way that panting, a reflex response to peripheral stimulus in the conscious animal, does not occur until there is a considerable deviation from normal body temperature (20, 188). Lim and Grodins (107) assumed since peripheral mechanisms operated in the anaesthetized dog there was a strong argument they would also function in unanaesthetized dogs. This assumption was corroborated by Chatonnet et al (41) when they looked at the relationship of T_{sk} and T_{hypo} in the control of panting in unanaesthetized dogs. Plotting the relationship between T_{sk}, T_c and panting, they observed the hypothalamic T_c at which panting occured was lowered

when T_{sk} was higher during a heating protocol. Therefore, it appears the initiation and control of panting is a function of T_{sk} as well as T_c.

The literature on the control of panting in mammals gives a vast amount of conflicting data (148, 167), but it has been shown peripheral and central temperatures are integrative in the initiation and control of panting. Presently, it is accepted that both peripheral and central temperature sensitive neurons participate in the initiation and control of panting, similar to human control of cutaneous blood flow and sweating (19).

2.2.3 Selective Brain Cooling

During periods of heat stress, it has been observed in some mammals, including humans, the brain can be maintained 1 to 1.5°C below carotid arterial blood temperature (31, 32). This selective brain cooling (SBC) is accomplished by vascular arrangements allowing venous blood cooled by evaporation within the upper respiratory tract and from direct cooling of the surface of the scalp and face to exchange heat through conduction with the warm arterial blood supplying the brain (6).

Some of the mammals that employ SBC use panting as the primary source of heat loss and have an anatomical structure called a carotid *rete*. In artiodactyls[1] and felids[2], the carotid *rete* is large and well developed, whereas in canids[3], it is rudimentary (6, 87).

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[1] Artiodactyla – an order of hooved mammals of the subclass Eutheria (including pigs and peccaries and hippopotami and members of the suborder Ruminantia) have an even number of functional toes.

[2] Felid – any of various lithe-bodied round-headed fissiped mammals many with retractile claws.

[3] Canid – carnivorous and omnivorous mammals of the family canidae and commonly known as canines which includedogs, wolves, foxes, coyotes and jackals.

The carotid *rete* is a plexus of medium-sized arteries supplied by the carotid artery, or branches of it, fully imbedded in the cavernous sinus. The cooled venous blood returning from the nasal cavity, scalp and face proceeds via the angularis oculi veins through the cavernous sinus. Upon entering the cavernous sinus, counter-current heat exchange occurs between warm blood in the internal carotid artery flowing to the brain and the cooled venous blood from the respiratory tract, scalp and face resulting in cooling of the brain (6, 87, 88, 100). The extent of brain cooling is dependent upon the rate of evaporation and the rate of blood flow through the evaporative surfaces of the upper airways. Hence, an increase in $\dot{V}_E$ is an important effector response serving not only to decrease T_c, but also to maintain brain temperature lower than T_c during periods of heat stress.

2.2.4 Selective Brain Cooling in Humans

The idea of SBC occurring in humans is controversial. Arguments against humans utilizing SBC are that humans do not appear to pant and do not have a carotid *rete*. As a result, humans are suggested by some not to have a powerful heat-loss mechanism close to the brain (120). Nybo et al (137) suggested there was no indication of SBC during hyperthermic exercise even though some participants' T_c reached greater than 40°C, but these results are based on indirect evidence since brain temperature was not measured directly.

Other arguments against human SBC is that some of the evidence used in its support is, also, based on indirect evidence including subjective rating of thermal comfort

and indirect measurement of intracranial temperature via tympanic temperature (T_{ty}) (32, 35, 37, 181, 182). The primary argument in opposition to T_{ty} as a measure of intracranial temperature is it is subject to contamination by a low T_{sk} of the head and changes in the arterial blood temperature perfusing the walls of the meatus and the tympanum (25). On the other hand, directly measured changes in temperature within the subdural space of the brain have been found to be highly correlated to changes in T_{ty} (114).

Proponents of humans employing SBC propose a network of emissary veins connecting and draining cooled blood from the facial skin vasculature to the brain during hyperthermia may take the place of a carotid *rete* (34); similar to other mammals without a carotid *rete* where SBC has been confirmed (65). In addition to heat lost via the surface of the head, respiratory heat loss (RHL) has been shown to contribute to SBC in humans (144). Rasch et al (144) measured heat lost via the skin of the head and via the respiratory tract during a mild hyperthermia to determine if the human head could function as a heat sink for SBC. They observed the total cephalic heat loss was greater than the heat produced by the brain and the heat gained via warmed arterial blood and, therefore, could contribute to SBC in humans. Within the total cephalic heat loss, respiratory heat loss played an important role, contributing ~35 to 44% of total heat lost from the head. Therefore, respiratory heat loss appears to possibly be a significant contributor to SBC in humans.

To determine whether respiratory heat loss could significantly influence cranial temperature, White & Cabanac (183) studied the effects of breathing air supersaturated with water, thus inhibiting respiratory evaporative heat loss, on changes in cranial

temperature (measured by T_{ty}) during exercise. They observed an initial separation of T_{ty} and T_{es}, indicative of SBC, started after ~5 min of exercise. Tympanic temperature remained significantly lower than T_{es} until ~3 min after participants were switched from breathing room air with a relative humidity of ~20 % to breathing supersaturated air at 100 % RH, at which point T_{ty} and T_{es} began to converge and the T_{es}-T_{ty} difference became negligible within several minutes. Next, when participants were switched back to breathing dry room air, T_{ty} began to diverge from T_{es} and was significantly lower by the end of the exercise session. These results indicate evaporative heat loss from the upper respiratory tract can influence cranial temperature represented by T_{ty}.

Respiratory heat loss has also been shown to directly affect brain temperature in humans (113). Mariak et al (113) measured the temperature between the midline of the cribiform plate and the frontal lobes of the brain of neurosurgical patients immediately following extubation and subsequently during voluntary hyperventilation with inspiration through the nose and expiration through the mouth. Cribiform plate temperature (T_{cr}) immediately decreased following removal of the endotracheal tube reaching a maximum decline of 0.40 to 0.85°C within 5.3 to 18 min. Additionally, T_{cr} instantly decreased with the onset of hyperventilation and the decrease continued until participants returned to normal breathing. Therefore, respiratory heat loss would appear to be an important contributor to SBC in humans and, accordingly, the increase in ventilation that occurs in humans during hyperthermia (73) may be beneficial to maintaining proper cranial homeostasis.

A final argument supportive of humans using SBC is that during passive hyperthermia, there is an increase in minute ventilation greater than metabolic demand would require and may, therefore, represent a panting reflex in humans (37, 136). This will be discussed below.

The idea of humans utilizing SBC will remain controversial until total brain temperature can be measured directly during a heating protocol or a consensus is reached on what is the best method for measuring human brain temperature indirectly. In addition, the temperature gradients known to occur within the human brain (112, 119) will also need to be taken into account in these further investigations.

2.3 Human Thermoregulation during Exercise

The mechanical efficiency of the human body at rest (147) or during work is only 20 to 25 % with the remaining 75 to 80 % lost as heat (18, 88, 108, 141). At rest, the metabolic rate of humans generates sufficient amounts of heat within the body to achieve a stable T_c above the environmental T_a by modulating the flow of heat to and from the environment (18). Given that humans do not spend all their time at rest another aspect of metabolic heat production is the rate of transformation of chemical energy into mechanical work. At the onset of exercise, there is an increase in metabolic rate, and therefore heat production, in the active skeletal muscles while the heat loss mechanisms are still operating at resting levels (88). This promotes a positive $\dot{S}$ causing T_c to rise. Similar to at rest, the increase in T_c stimulates an increase in cutaneous blood flow and eccrine sweating.

2.3.1 Control of Cutaneous Blood Flow during Exercise

At the initiation of exercise there is a redistribution of cardiac output ($\dot{Q}$) away from inactive tissues of the body including the splanchnic region and renal system, non-exercising skeletal muscles and the cutaneous circulation to the active muscles (21, 94). This redistribution of blood flow is in proportion to the exercise intensity in order to meet the demands of working muscles for oxygen (151). As exercise continues, the heat produced by the ~20 to 25 % efficiency of conversion of stored energy to mechanical work demands removal before it reaches dangerous levels.

Similar to resting conditions, T_c primarily determines the rate at which cutaneous blood flow increases during exercise. As exercise continues, T_c surpasses the threshold for cutaneous vasodilatation resulting in an increased cutaneous blood flow to facilitate $\dot{C}$, $\dot{R}$ and $\dot{K}$ via the skin surface. The rate at which cutaneous blood flow increases is in proportion to the increase of T_c (128). The increased cutaneous blood flow is partially countered by an increased cutaneous vasoconstrictor stimulus due to peripheral baroreceptor mediated response (126). Also, thermolytic responses do not abolish the sympathetic vasoconstriction present at the initiation of exercise but instead, the threshold for the initiation of active vasodilatation is increased to a higher T_c (91, 96, 98). As a result, cutaneous blood flow is lower during moderate exercise than during passive heating at any given T_c (92). When heat dissipation mechanisms are sufficient to bring heat loss into balance with heat production, T_c stabilizes at a higher temperature than at rest. The new level to which T_c settles during exercise is in proportion to the metabolic rate, independent of T_a, and is an alteration in thermoregulation, not an inability to dissipate heat (134).

In a similar fashion to when participants are at rest, T_a plays an important role in the control of cutaneous blood flow during exercise by its influence on T_{sk}. When exercise is performed in a cool environment there is additional inhibition to cutaneous vasodilatation. Evidence indicates when exercise is performed in a low temperature environment the onset of FBF elevation tends to occur at a T_c approximately 0.5°C higher than individuals exercising in hotter environments (24). This is possibly a result of the combination of an increased temperature gradient between T_c and T_{sk} allowing more central heat to be transferred to the skin surface for a given cutaneous blood flow (24) and increased afferent input from cold cutaneous thermoreceptors by the lower T_{sk}.

In brief, the magnitude of cutaneous blood flow during exercise is limited because it is under the influence of the same α-adrenergic vasoconstrictor system responsible for not only thermoregulatory reflexes but also arterial baroreflexes, cardiopulmonary baroreflexes and chemoreflexes within skeletal muscle (153).

2.3.2 Control of Sweating during Exercise

Unlike the control of cutaneous blood flow during exercise, varying skin temperatures during exercise within the "warm" range (33 to 38°C) does not modify the T_c threshold for the onset of sweating, but if T_{sk} is within the "cold" range (29 to 33°C) the T_c threshold is shifted to a higher level and sweating is attenuated (8). Benzinger (8) showed that during steady state rest and exercise when T_{sk} was within the warm range, sweating was initiated at the same T_c regardless of T_{sk}, but when participants exercised in a T_a where T_{sk} was within the cold range, the onset of eccrine sweating showed a progressively higher T_c threshold as T_{sk} decreased from 33°C to 29°. Therefore, $\dot{E}_{sw}$

would be reduced during exercise when T_{sk} is below 33°C but when T_{sk} is above 33°C it woul have no influence. Several other studies have been performed with similar findings (18).

In summary, exercise produces competition between thermoregulatory and non-thermoregulatory systems with the greatest effects on the control of cutaneous blood flow. The increased sympathetic output due to exercise alone and a resting T_{sk} lower than the normothermic level (i.e., < ~33 °C) both serve to increase the T_c threshold for the onset of cutaneous vasodilatation resulting in lower cutaneous blood flow for a given T_c than at rest. Unlike cutaneous blood flow, there is an attenuation of the onset of eccrine sweating to a higher T_c when T_{sk} is below 33°C, but when T_{sk} is above 33°C the T_c threshold for the onset of sweating is not modified from resting conditions.

2.4 Acclimation/-atization of Thermoregulatory Responses

Prolonged exposure to a particular environmental thermal stress (i.e., heat or cold) brings about physiological adaptations to help reduce the strain of living, working and exercising in the new thermal environment (176). When such changes occur within the natural changing environment, the process is referred to as acclimatization. Acclimation brings about similar physiological adaptations, but these adjustments occur in an artificially created and regulated environment such as in a climatic chamber.

2.4.1 Heat Acclimation/-itazation

During the initial days within a hot environment there is a reduced ability to perform physical activity at the same intensity and duration when compared to

performing the same task in a temperate environment (176). Unacclimated/-atized individuals demonstrate elevated T_c and $\overline{T}_{sk}$, increased $\dot{M}$ in proportion to T_c, increased heart rate (HR) and circulatory instability as a result of competition for blood flow between thermoregulatory (e.g., cutaneous vasodilatation) and non-thermoregulatory systems (e.g., baroreceptor mediated cutaneous vasoconstriction) (150). With repeated exposure to a hot environment, the strain on the circulatory system is decreased and there is an increased capacity for heat dissipation.

2.4.1.1 Physiological Adaptations Produced by Repeated Exposure to a Hot Environment

Physiological adaptations to prolonged heat stress over 7 to 14 days include an initial expansion of plasma volume (PV), reduced HR and autonomic nervous system habituation leading to increase cutaneous blood flow, an increased $\dot{E}_{sw}$ and sweat sensitivity and decreased T_c and T_{sk} (138, 153). Cardiovascular changes are the earliest adaptations to occur with repeated exposures to a hot environment. This is followed by decreased T_c thresholds for the onset of cutaneous vasodilatation and eccrine sweating, an increased $\dot{E}_{sw}$ at a given T_c (following most, but not all acclimation protocols) and a subsequent decrease in T_c and T_{sk} (4). A rise in HR to compensate for the extensive vasodilatation of the vascular bed resulting in a large shift of blood to the periphery is a characteristic of the initial exposure to a hot environment (164). Therefore, the most important process that occurs during the initial stage of acclimation/-atization (~2 to 3 days) is PV expansion. This expansion is produced by the influx and retention of protein into the blood accompanied by the movement of water and ions from the interstitial

spaces into the plasma (162). Plasma volume expansion ranges from +3 to +27 % resulting in a subsequent 15 to 25% decrease in HR for the same heat exposure (4).

Another thermoregulatory adaptation is a lower T_c threshold for the onset of increased cutaneous blood flow. Roberts et al (149) showed heat acclimation reduced the T_c threshold for cutaneous vasodilatation, but it did not change the rate at which cutaneous blood flow increased when expressed as a function of T_c (153). One explanation for the change in the cutaneous blood flow:T_c relationship is that heat acclimation/-atization adaptations are accompanied by a progressive decline in sympathetic nervous system activity. As a result, there is less vasoconstrictor outflow to the skin to compete with vasodilatation outflow at a given T_c (153).

The adaptations of the eccrine sweating response following heat acclimation/-atization parallel the cutaneous blood flow adaptations. Sweating begins at a lower T_c and T_{sk} after heat acclimation/-atization (121, 129, 149). Sweat rate is typically described by sweat sensitivity ($\Delta \dot{E}_{sw} \cdot \Delta T_c^{-1}$) and as a result of the shift in the sweating threshold to a lower T_c, there is a greater $\dot{E}_{sw}$ for a given T_c as compared to pre-acclimation/-atization values (164). The adaptations of the sweating and cutaneous blood flow thresholds occur towards the latter half of an acclimation/-atization protocol and reflect longer lasting adaptations to chronic heat stress (4).

An important benefit between increased cutaneous blood flow and increased $\dot{E}_{sw}$ is it results in a greater core to skin thermal gradient. This increases $\dot{C}$, $\dot{R}$ and $\dot{K}$ heat loss

preventing T_{sk} and T_c from rising as high as observed prior to and during the early stages of acclimation/-atization (162). Thus, the observed decrease in T_{sk} and T_c post-acclimation/-atization is a result of the physiological adaptations improving the heat loss mechanisms.

It is important to note that the cardiovascular adaptations are typically observed, with acclimation/-atization to both a hot-dry and hot-humid environment (133). The primary difference between adaptations occurring within a hot-dry or a hot-humid environment is in the eccrine sweating response. When heat acclimation/-atization occurs within a hot-humid environment there is a greater increase in $\dot{E}_{sw}$ via an increase in local sweating from parts of the body where minimal sweating occurred before acclimation/-atization and by an augmented ability to prolong sweating (63, 176). In contrast, acclimation/-atization to a hot-dry environment produces moderate increases in $\dot{E}_{sw}$, with no impact on sweating distribution of body parts (176).

2.4.1.2 Decay of Heat Acclimation/-atization Adaptations

The physiological adaptations described above are not permanent changes but rather decay over time and may disappear after only a few days or weeks out of a hot environment (4). Pandolf (138) reviewed eight pioneering studies and concluded physiological adaptations to a hot-dry environment are better retained than those obtained within a hot-humid environment. Adaptations acquired within a hot-dry environment remain for at least one week and may last up to three weeks, with the major portion lost after one month. In contrast, adaptations to a hot-humid environment may be lost after

only 6 days. Within either environment, the cardiovascular adaptations are the first ones to be lost (4).

Retention of heat acclimation/-atization is quite variable between individuals. A high level of aerobic fitness appears to be associated with greater retention (138). A high initial cardiorespiratory fitness and maintenance of a structured training program are cited as two primary factors in slowing or minimizing the decay of heat acclimation/-atization adaptations (4).

2.4.1.3 Heat Acclimation/-atization Protocol

There are almost as many heat acclimation/-atization protocols as there are studies performed. Whether the heat acclimation/-atization protocol employed utilizes exercise or is performed passively, it takes up to ~14 consecutive days for complete acclimation/-atization to occur with ~75 % of all physiological adaptations occurring within the first seven days (138). For active heat acclimation protocols, employing moderate intensity, short duration and continuous exercise at 40 to 50 % $\dot{V}O_{2max}$ for up to ~90 min in a hot environment on consecutive days appears to be the most effective stimulus (4). For passive heat acclimation protocols, a controlled hyperthermia where T_c is rapidly raised and then maintained at a hyperthermic level (~38.5°C) for up to ~2 hr·day^{-1} provides adequate stimulus to develop heat acclimation adaptations (64). Tables 2.1 and 2.2 outline several of the studies that have been performed, their corresponding heat acclimation/-atization protocols and the physiological variables used to verify successful acclimation/-atization. The time course for the achievement of heat acclimation/-atization is similar for hot-dry and hot-humid environments (138).

Acclimation/-atization appears to be a transient phenomenon requiring repeated heat exposure to produce and maintain physiological adaptations (44). Gill & Sleivert (70) compared the effectiveness of a 10 consecutive-day active heat acclimation protocol to an active intermittent protocol with 10 sessions performed on every other day. They found the intermittent heat exposure protocol was not as effective at producing optimal adaptations. The 10 consecutive day heat acclimation protocol produced a decrease in T_c, T_{sk}, HR, an increased $\dot{E}_{sw}$ and a prolonged exercise time while the intermittent protocol elicited only a reduced T_c, but of a much smaller magnitude. They postulated since adaptations to chronic heat stress decay over time, some of the physiological adaptations are lost between exposures. Therefore, optimal acclimation/-atization protocols utilize repetitive heat exposure sessions on consecutive days.

To summarize, people exposed to a hot environment for ~7 consecutive days, 2 $h \cdot day^{-1}$ acquire significant increases in tolerance to the heat, with full acclimation/-atization occurring within ~14 days. An initial expansion of PV, a reduced HR, a lower T_c threshold for increased cutaneous blood flow and eccrine sweating, an increased sweat sensitivity and decreased T_c and T_{sk} are physiological adaptations that improve heat loss and reduce the strain of living and exercising in a hot environment. Physiological adaptations are similar whether acclimation/-atization is performed in a hot-dry or a hot-humid environment with the exception of a greater sweating response occurring following acclimation/-atization to a hot-humid environment. Following removal from a hot environment, physiological adaptations decay with adaptations acquired within a hot-dry environment being retained longer than those acquired during a hot-humid

environment. Active heat acclimation/-atization protocols utilize short-duration, moderate intensity exercise. Passive heat acclimation protocols typically employ a hotter environment (i.e. 50°C, 20 % RH) and a method to prevent heat loss (i.e., vapour barrier suit) to initially increase T_c rapidly. Once a designated T_c is attained, the quantity of evaporative heat loss is adjusted (i.e., by removal or ventilation of the vapour barrier suit) in order to maintain T_c at the desired hyperthermic level (~38.5°C) for up to 2 $hr \cdot day^{-1}$ for the duration of the acclimation protocol.

2.4.2 Cold Acclimation/-atization

Repeated or prolonged exposure to a cold environment produces a decrease in thermal discomfort when compared to the initial exposure, similar to frequent or extended stays in hot environments. In addition to behavioural modifications, physiological adaptations also occur in humans subjected to a prolonged cold stress. Scholander et al (161) had participants live in the Norwegian mountains above tree line during September to October with only summer clothes and a thin single blanket bag to sleep in at night. During the night, the T_a was ~3 to 5°C. By the end of a 6-week stay, participants were able to sleep well and maintained a warmer $\bar{T}_{sk}$ via a rise in basal metabolic rate when compared to control participants who, with no previous cold exposure, were incapable of sleep due to the thermal discomfort caused by the cold T_a.

Within the research into human cold acclimation/-atization several types of adaptation have been shown to occur. They include metabolic, insulative and hypothermic adaptations (15, 16, 105, 141). A higher metabolic rate leading to greater

heat production and resulting in higher T_{sk} and a normal T_{re} post- acclimation/-atization characterize metabolic cold adaptation as was seen in men exposed to six weeks in the Norwegian mountains (161). Maintaining a lower mean T_{sk} and a normal T_{re} during cold exposure following cold acclimation/-atization characterizes insulative cold adaptation while a decrease in metabolic heat production leading to lower mean T_{sk} and a lower T_{re} within a thermoneutral and cold environment characterize hypothermic cold adaptations (86, 174). The conditions employed to produce and test human cold adaptations where the severity of cold stress, the type of exposure (continuous vs. discontinuous), the variety of exposure durations and the medium employed (air or water) may explain the existence of three alternate forms of cold adaptation (16, 103). Recent research on adaptations to the cold is not the focus of this proposed research and is reviewed by Argyropoulos & Harper (3) and Nedergaard et al (131).

The typical indices of cold acclimation/-atization, seen in all three types of adaptation, are a delay in the time till shivering is initiated and a shift to a lower T_c threshold at which shivering is initiated (51). As a result, T_{sk} and T_c are permitted to decline to a lower level before shivering is initiated when compared to the pre-acclimation levels (51). The delay in shivering and the shift in the shivering T_c threshold are believed to pertain to a decreased importance of peripheral thermoreceptors and an increased importance of central temperature sensitive neurons in stimulation of heat production mechanisms (16, 174). Vybiral et al (174) observed the initial thermogenic response to an acute cold stress in non-acclimatized participants resulted from significant input by the peripheral temperature sensitive neurons as judged by responses to changes in T_{sk}. After ten minutes of exposure, heat production became inversely related to T_{re}

changes. Conversely, cold acclimatized participants showed metabolic heat production was solely stimulated by a decrease in T_{re} indicating central temperature sensitive neurons appear to be the principal stimulus to heat production mechanisms following cold acclimation/-atization. This shift in the role peripheral thermoreceptors and central temperature sensitive neurons play may be a result of habituation to a moderate cold exposure (104).

In summary, with cold acclimation/-atization, humans are capable of adapting to cold environments via metabolic, insulative and/or hypothermic adaptations. Following cold acclimation/-atization, shivering is delayed and initiated at a lower T_c indicating a greater importance of central temperature sensitive neuron input in the stimulation of heat production mechanisms.

2.5 Regulation of Arterial Blood pH by Pulmonary Ventilation

Similar to the human thermoregulation, the regulation of arterial pH ($_{pHa}$) via the control of pulmonary ventilation ($\dot{V}_E$) is an example of a negative feedback loop. It consists of a central respiratory controller with centers located in the pons, medulla and other parts of the brain, a set of chemosensors, mechanoreceptors, lung receptors and various other receptors that provide afferent sensory information to the controller, which in turn sends efferent impulses to the effectors that are the respiratory muscles. The effector response is a change in $\dot{V}_E$ that will decrease afferent sensory inputs to the respiratory control centre and thus, decrease the effector response. In addition, renal responses can also influence pH_a as well as arterial bicarbonate ($[HCO_3^-]_a$). Autonomic control of $\dot{V}_E$ may also be overridden by the motor cortex when voluntary control is

desired (13). Figure 2.2 outlines the control system for the regulation of pH_a by $\dot{V}_E$ in humans.

2.5.1 Chemical Influences on Pulmonary Ventilation

In addition to being used for the regulation of pH_a, oxygen (O_2) delivery and carbon dioxide (CO_2) removal, changes in $\dot{V}_E$ are also used within the regulation of arterial partial pressures of oxygen (P_aO_2) and carbon dioxide (P_aCO_2) and cerebrospinal fluid pH (pH_{CSF}) and P_{CO2} ($P_{CSF}CO_2$) (Figure 2.2). Despite varying amounts of O_2 consumption ($\dot{V}O_2$) and rates of CO_2 production ($\dot{V}CO_2$) adequate $\dot{V}_E$ helps maintains P_aO_2, P_aCO_2, pH_a, pH_{CSF} and $P_{CSF}CO_2$ within very close levels (179). This is a function of increases in P_aCO2 and $P_{CSF}CO_2$ and decreases in P_aO_2, pH_a and pH_{CSF} acting as stimulants to $\dot{V}_E$. As a result, these chemical stimuli are monitored either peripherally via two sets of chemoreceptors in the carotid and aortic bodies or centrally via chemosensitive areas on the ventral surface of the medulla oblongata (Figure 2.2).

2.5.1.1 Peripheral Chemoreceptors

Peripheral chemoreceptors are located within the arterial circulation at the bifurcation of the common carotid arteries and near the arch of the aorta (80, 132).

Between the two groups, the carotid bodies are dominant and are responsible for ~90 % of the total peripheral chemosensitivity in response to hypoxia while the aortic bodies are responsible for the remaining ~10 % (82). Carotid chemoreceptors also respond to changes in P_aCO_2 and pH_a, appearing to be responsible for ~20 % of the

ventilatory response to arterial hypercapnia and acidosis, with the remaining 80 % mediated by the central chemosensitive tissues (69, 179).

2.5.1.2 Central Chemosensitive Areas

The early discovery of the persistence of hyperventilation in response to hypercapnia despite the denervation of the carotid and aortic bodies led to the conclusion the primary site of CO_2 stimulation on $\dot{V}_E$ involves structures other than the peripheral arterial chemoreceptors (123). A non-discrete central respiratory control center in the medulla oblongata was initially thought to be responsible for the changes in $\dot{V}_E$ in response to changes in the acid-base equilibrium (122). This view has been refined to show respiratory control is from three distinguishable areas of chemosensitive neurons organized bi-laterally and located 200 to 400 μm below the ventral medullary surface (11). One zone is located within the rostral area and another zone is located more caudally. Between the two, there is an intermediate zone that appears to play a role in the control of $\dot{V}_E$ in response to changes in T_c (28, 42, 81). Additionally, Mulkey et al (125) showed neurons in the caudal third of the RTN of rats are CO_2-sensitive, responding aggressively to changes in inspired CO_2 in anesthetized animals and to increases in CO_2 in brain slices *in vitro*.

The primary stimulus to central chemosensitive areas appears to be a decrease in the pH_{CSF} bathing the medulla concomitant to an increase in P_aCO_2 (12). In the early stages of central chemoreceptor research it was proposed CO_2 directly stimulates central chemosensitive neurons (52). Now it is thought that CO_2 along with changes in the

pH_{CSF} may both play an excitatory role in control of $\dot{V}_E$ (28, 125). As P_aCO_2 rises, cerebral blood flow increases allowing more CO_2 molecules to move into the extracellular fluid making it more acidic and increasing the stimulation of the central chemosensitive areas resulting in an increased $\dot{V}_E$ (179). The resultant hyperventilation decreases P_aCO_2 allowing the flow of CO_2 out of the brain to increase, thus increasing the pH_{CSF} and decreasing $\dot{V}_E$.

2.5.1.3 Acute Relationship between O_2 and Ventilation

During hypoxia there is an increase in $\dot{V}_E$ under isocapnic conditions when P_aO_2 drops to ~80 mm Hg from normoxic levels, but it is not until P_aO_2 declines to ~60 mm Hg where there is a more substantial increase in $\dot{V}_E$ (81). Further reductions in P_aO_2 produce large non-linear increases until a P_aO_2 of ~25 to 30 mm Hg is reached, upon which there is no increase in $\dot{V}_E$ (81). If hypoxia is continued, a hypoventilation relative to a peak hypoxia-induced hyperventilation typically occurs within 5 min after the onset of hypoxia and may be a result of hypoxic depression of the central nervous system (81). As a result, P_aO_2 plays a minor role in the day-to-day chemical control of $\dot{V}_E$ at sea level, but becomes the more important stimulant at higher altitudes or in pathological conditions where P_aO_2 is decreased.

The hypoxic ventilatory response (HVR), a measure of sensitivity to hypoxia, is measured by several different methods and can be expressed as the change in $\dot{V}_E$ ($L \cdot min^{-1}$) as a function of the change in arterial oxygen saturation (%). A dynamic or progressive HVR test consists of reducing alveolar P_{O2} from normal levels (or higher) to

a minimum of 40 mm Hg over five to ten minutes (12, 175). Alternatively transient hypoxia involves measuring the ventilatory response to a hypoxic stimulus lasting ~20 to 30 breaths after the transition from breathing air to a hypoxic gas mixture. A third method that has been recently recommended utilizes a steady state where inspired P_{O2} is stepped down quickly and maintained at a new level for ~20 min while the end-tidal partial pressure of CO_2 ($P_{ET}CO_2$) is held constant (isocapnia) or allowed to vary naturally (poikilocapnia) (170). This method takes into consideration the ventilatory response to hypoxia in humans is biphasic consisting of an initial rapid increase in $\dot{V}_E$ followed by a subsequent hypoxic ventilatory decline (HVD) occurring between 15 and 30 min (58). As a result, measurements of the acute HVR are made at ~5 min and measures of the HVD are made at ~20 min after inspired P_{CO2} has been stepped down (170).

2.5.1.4 Acute Relationship between CO_2 and Ventilation

The primary influence on the control of $\dot{V}_E$ at rest, under normal environmental conditions is P_aCO_2 and the resultant changes in pH_a (179). With increasing inspired fraction of CO_2 (F_ICO_2), $\dot{V}_E$ increases in direct proportion to the increase in P_aCO_2 (12). It has been shown with unanaesthetized dogs the peripheral chemoreceptors give an initial rapid response occurring within ~6.5 s of a step increase in inspired CO_2 and provide ~37% of the ventilatory response to hypercapnia. The remaining 63% of the steady-state ventilatory response to hypercapnia may be attributed to central chemosensitive areas with a time constant of ~11 s longer than that of the peripheral chemoreceptors (168).

Central chemoreceptor sensitivity to increases in P_aCO_2 and, therefore, decreases in pH_a and pH_{CSF}, is most commonly assessed by a hypercapnic ventilatory response (HCVR) test known as the Read re-breathing technique (145). Originally, this test required the participant to re-breathe from a 4 to 6 L bag containing 5.5 to 8% CO_2 and 30 to 93% O_2, balance nitrogen (N_2), for approximately 5 min. When switched from breathing room air to breathing from the re-breathing bag, the hypercapnic stimulus increases at ~4 mm Hg·min^{-1} rise in P_{CO2} within the re-breathing bag. The rate of increase in $\dot{V}_E$ is associated with the response of the central chemosensitive areas to increasing P_aCO_2 because the hyperoxic condition is assumed to suppress or abolish the peripheral component of the response (60).

Since peripheral arterial chemoreceptors appear to contribute ~37 % of the ventilatory response to hypercapnia, a modified Read re-breathing technique was developed to directly quantify the actual peripheral and central chemoreflex threshold at which P_aCO_2 causes an increase in ventilation over basal levels (40, 57, 124). The modifications include an initial voluntary hyperventilation in room air for up to 5 min in order to lower P_aCO_2 to between 20 to 25 mm Hg. Subsequently, participants are switched to breathing from a re-breathing bag containing a P_{CO2} near mixed venous values (i.e., P_{CO2} of 40 to 42 mm Hg or 5.5 % CO_2 at sea level) while the P_{O2} in the re-breathing bag is maintained at either a given hyperoxic or hypoxic level via the controlled addition of O_2 into the re-breathing bag (57). Once switched to the re-breathing bag, the participant performs three deep breaths with the goal to equilibrate the P_{CO2} in the bag, lungs and arterial blood with the mixed venous blood. A plateau in the $\dot{V}_E$:$P_{ET}CO_2$ plot

over several breaths indicates equilibration. After the initial 3 deep breaths, the participant returns to relaxed breathing until $\dot{V}_E$ exceeds 100 $L \cdot min^{-1}$ or $P_{ET}CO_2$ exceeds 60 mm Hg.

2.5.1.5 Relationship Between Arterial pH and Ventilation

A major influence of acidosis and alkalosis on $\dot{V}_E$ is from changes in the pH_{CSF} surrounding the central chemosensitive areas. In addition, changes in pH_a also play a key role in the control of $\dot{V}_E$. It has been shown through perfusing an isolated carotid body of a cat with a solution with a stable P_{CO2} and P_{O2}, a decrease in pH increased the chemoreceptor carotid sinus nerve impulse activity (89, 90). When pH_a was reduced from 7.45 to 7.25 at a normal P_aCO_2 and P_aO_2, carotid sinus nerve traffic increased to a level common to that seen with a reduction of P_aO_2 from 85 to 40-50 mm Hg. This latter stimulus approximately doubles ventilation at a steady P_aCO_2 (12).

2.5.1.6 Relationship Between Hypercapnia, Hypoxia and Ventilation

Lahiri & Delaney (101) studied the interaction between hypercapnia and hypoxia chemoreceptor activity and the resultant ventilatory response. In anaesthetized cats, increases in P_aCO_2, at different stable levels of P_{aO2}, produced linear increase in $\dot{V}_E$. At more hypoxic levels of P_aO_2 for a given level of hypercapnia, $\dot{V}_E$ showed an increase in amplitude and in sensitivity to the hypercapnic stimulus. In non-humans this multiplicative effect appears to be accounted for by the interaction between hypoxia and hypercapnia at the level of the peripheral chemoreceptors (83, 135). In humans, this relationship is also the result of a peripheral O_2-CO_2 interaction (50). In addition, Dahan

et al (50) have also proposed a role for a central O_2-CO_2 interaction, but did not expanded on how this would occur.

2.5.1.7 Relationship between Core Temperature and Ventilation

It has been known for almost a century that an increase in T_c results in an increased $\dot{V}_E$ in humans (49, 73). Hyperpnea has been shown to occur whether the increased T_c is brought about by being heated in a hot room or submersed in a hot bath (68, 102). In combination with an increased T_c, the increase in $\dot{V}_E$ enhances both $\dot{C}_{res}$ and $\dot{E}_{res}$ leading to greater respiratory heat loss at a raised T_c for a given level of $\dot{V}_E$ (76).

More recently, a T_c threshold has been determined for the onset of hyperthermic induced hypernea. Cabanac and White (37) rendered participants hyperthermic passively via immersion in a warm water bath. Ventilation remained relatively stable at this level until an esophageal temperature (T_{es}) of 38.5°C and a T_{ty} of 38.1°C was reached, at which point $\dot{V}_E$ increased proportionately to the increase in T_c. The increase in $\dot{V}_E$ towards the end of the immersion was caused by an increase in V_T, not f, similar to thermal hyperpnea or second phase panting employed by panting mammals during periods of severe heat stress. It was concluded there exists a T_c threshold for a thermal hyperpnea in hyperthermic humans of ~1°C above normothermic levels. A similar relationship between $\dot{V}_E$ and T_c was evident when $\dot{V}_E$ was normalized for, both, CO_2 production and O_2 consumption during exercise-induced hyperthermia (182).

2.6 Ventilatory Acclimatization

Ventilation responds immediately to acute changes in P_aO_2, P_aCO_2 and pH_a. Chronic exposure to hypoxia, hypercapnia or hypocapnia results in ventilation adapting to a given decrease in P_aO_2 and P_aCO_2 or increase in P_aCO_2. Ventilatory acclimatization describes the time-dependent changes in ventilation resulting from exposure to a changed environment (i.e., hypoxia, hypercapnia and hypocapnia) or pathological conditions over hours, days, weeks and years (54). The following section reviews the physiological changes occurring during ventilatory acclimatization to hypoxia, euoxic hypercapnia and euoxic hypocapnia.

2.6.1 Ventilatory Acclimatization Hypoxia

When humans are subjected to a sufficient degree of hypoxia, there is an immediate increase in $\dot{V}_E$ mediated by the carotid and aortic peripheral chemoreceptors followed by a hypoxic ventilatory decline. Short-term ventilatory acclimatization occurs if hypoxia continues for hours, days or months (54) with $\dot{V}_E$ increasing to a level above that observed during the acute phase with a magnitude dependent on the degree of the hypoxic stimulus. Approximately 2 weeks are required for $\dot{V}_E$ to stabilize at the new level (54). The hyperventilation observed during short-term acclimatization is accompanied by a decrease in P_aCO_2 and a corresponding increase in pH_a and pH_{CSF} (163). In response to this respiratory alkalosis, during short-term acclimatization there is renal compensation in response to the excess concentration of arterial and CSF bicarbonate ($[HCO_3^-]_a$ and $[HCO_3^-]_{CSF}$). Excess HCO_3^- ions are excreted and H^+ ions are conserved by the kidneys, thus helping to decrease pH_a and pH_{CSF}. The degree of decline of pH in arterial blood and CSF is variable with some observations showing a return to

normal levels (163) and others showing incomplete compensation with pH_a and pH_{CSF} remaining alkaline (62). In addition, during short-term acclimatization to hypoxia there is an increased peripheral chemoreceptor drive as measured by a higher HVR (157) with similar findings being observed during various "doses" of intermittent hypoxia exposure (2, 67).

Long-term ventilatory acclimatization is characterized by observations made on indigenous populations of the Andes and the Himalayas. It consists of a minimal or complete lack of an HVR to decreases in P_aO_2 over the physiological range, a higher $\dot{V}_E$ at rest than an un-acclimatized person acutely exposed to the same hypoxic stimulus and a lower $\dot{V}_E$ during exercise or CO_2 breathing (54). For children born near sea level who relocate to altitude, it requires at least 2 years of hypoxic exposure to acquire long-term ventilatory acclimatization and even a longer period of acclimatization for adults (54). For a more in depth review of ventilatory acclimatization to hypoxia and the possible mechanism(s) mediating short and long-term acclimatization, please refer to Dempsey & Forster (54).

2.6.2 Ventilatory Acclimatization to Euoxic Hypercapnia and Euoxic Hypocapnia

When humans are acutely exposed to increases in exogenous CO_2 above normal levels, $\dot{V}_E$ is increased immediately via stimulation of the peripheral chemoreceptors and central chemosensitive areas in order to minimize changes in alveolar carbon dioxide (P_ACO_2), P_aCO_2 and pH_a (54). During chronic exposure to hypercapnia there is an initial rapid increase in $\dot{V}_E$ peaking within 1 hour to 1 week of exposure and a corresponding

repiratory acidosis resulting in an increase in P_aCO_2 and a decline in pH_a and pH_{CSF} (46, 159). This initial increase in $\dot{V}_E$ is followed by a subsequent decline to a level, either above normal (46, 54, 159) or back to normal (143) for the duration of the hypercapnic exposure. The decline in $\dot{V}_E$ occurs within 3 to 10 days of exposure (46, 54) and during prolonged exposure to moderate hypercapnia, pH_a and pH_{CSF} are restored to almost normal levels via renal compensatory excretion of H^+ and retention of HCO_3^- as reviewed by Dempsey (54).

Furthermore, following prolonged exposure to hypercapnia there may be a decreased HCVR. Schaefer et al (159) found that following a 42 day exposure to 1.5% CO_2 in 21% O_2, increases in $\dot{V}_E$ were significantly lower in response to 5% CO_2 (17.91 $L \cdot min^{-1}$ pre-exposure to 14.58 $L \cdot min^{-1}$ post-exposure). This reduction in the HCVR appears to occur within 24 h of chronic exposure to hypercapnia (46). Intermittent, long-term exposure to hypercapnia also appears to decrease the sensitivity of the HCVR. Florio et al (61), looking at the ventilatory response to CO_2 of divers and non-divers, observed the slope of the $\dot{V}_E$:$P_{ET}CO_2$ relationship of non-divers (3.25 $L \cdot min^{-1} \cdot mmHg$) was significantly greater than that of divers (2.16 $L \cdot min^{-1} \cdot mmHg$) and the x-intercept of non-divers (32 mmHg) was significantly lower than divers (35.3 mmHg). Delapille et al (53) observed similar differences in CO_2 sensitivity between divers and non-divers.

Contrary to what is observed during chronic euoxic hypercapnia, prolonged exposure to euoxic hypocapnia is accompanied by a decrease in P_{CO2} and $[HCO_3^-]$ and increase in pH_a and pH_{CSF} similar to that observed during ventilatory acclimatization to

hypoxia. Dempsey et al (55) observed arterial P_aCO_2 was reduced an average of 8.2 mm Hg and 7.9 mm Hg and lumbar CSF [HCO_3^-] was reduced by 1.7 meq·L^{-1} and 2.9 meq·L^{-1} following 26 hours of normoxic hyperventilation. The decrease in P_aCO_2 and $[HCO_3^-]_a$ was accompanied by an increase in pH_a and pH_{CSF} which remained elevated by the end of the 26th hour of normoxic hypocapnia. Neither the decrease in P_{CO2} and [HCO_3^-] nor the increase in pH_a and pH_{CSF} were significantly different from the alterations observed during hypoxic-hypocapnic hyperventilation.

Additionally, prolonged euoxic hypocapnia produced by hyperventilation affects the HCVR. Brown et al (27) first showed, following a 24 hr period of hyperventilation where arterial CO_2 content was decreased by 29% and pH_a was increased by 0.10, the ventilatory response to carbon dioxide was increased via greater sensitivity to inspired carbon dioxide. Ren & Robbins (146) further observed a lowering of the threshold of the HCVR response, as evidenced by a leftward shift of the $\dot{V}_E$:$P_{ET}CO_2$ relationship, dependent upon the magnitude of the prolonged hypocapnic stimulus. The lower threshold of the HCVR observed following prolonged euoxic hypocapnia via hyperventilation appears to be due to the associated alkalosis, whereas the increased sensitivity of the HCVR response appears to be a result of hyperventilating (146).

In summary short-term ventilatory acclimatization occurs when humans are exposed to prolonged hypoxia. Acute hypoxic exposure results in an initial increase in $\dot{V}_E$ followed by a further increase if hypoxia continues over days or months resulting in a respiratory alkalosis that is compensated for by increased renal excretion of HCO_3^-

thereby helping to lower pH_a and pH_{CSF}. Long-term acclimatization to hypoxia requires either being born at altitude or spending at least 2 years of residence at altitude following relocation. Ventilatory acclimatization to hypercapnia involves an initial hyperventilation and a subsequent decline to normal or above normal rate where it remains throughout the hypercapnic exposure. Similar to hypoxic acclimatization adaptations, there is renal compensation in order to return pH_a and pH_{CSF} to normal levels. Chronic exposure to hypercapnia also results in a decreased sensitivity towards a given CO_2 stimulus. Prolonged exposure to a euoxic hypocapnia via hyperventilation results in decreased arterial and CSF P_{CO2} and $[HCO_3^-]$ and an increase in pH_a and pH_{CSF} along with an increased sensitivity to a given CO_2 stimulus.

2.7 Thesis Rationale

The rationale for this thesis has been divided into two parts. Part 1 contains the rationale for 2 studies examining the relationship between $\dot{V}_E$, core temperature and heat acclimation. Part 2 outlines the rationale for the final study exploring the relationship between central chemosensitivity and heat acclimation.

2.7.1 Part 1: Ventilation, core temperature and heat acclimation

As indicated by equation 2.1, two avenues of evaporative heat loss are from the skin and the upper respiratory tract, of which evaporation of sweat from the skin is, quantitatively, the most important heat loss mechanism for humans. Respiratory heat loss accounts for ~10% of total body heat loss within a thermoneutral environment and yet has been shown to contribute up to 44% of total cephalic heat loss during mild hyperthermia (144). As a result, respiratory heat loss has been suggested to contribute to SBC in humans (37).

Ventilation increases proportionately with T_c during both passive and active hyperthermia after surpassing a T_c threshold (37, 155, 182). The change in the pattern of $\dot{V}_E$ observed during passive hyperthermia is ambiguous with reports of either an elevated f and a decreased V_T, similar to first phase panting, (45, 173) or an increased V_T and a decreased f, similar to thermal hyperpnea or second phase panting (37). Unlike passive heating, during active heating via exercise, the increase in $\dot{V}_E$ appears to be predominantly a result of an initial increase in V_T followed by increases in f (115, 155). The mechanism for the observed increase in $\dot{V}_E$ occurring during hyperthermia in humans is not resolved, but both the increase in T_c and the increase in $\dot{V}_E$ occurring during

hyperthermia serves to augment the capacity for convective and evaporative heat loss through the respiratory system (76).

Cabanac & White (37) hypothesized a physiological rational for the increase in $\dot{V}_E$ during hyperthermia is that it may be a thermolytic response employed to increase respiratory heat loss and contribute to SBC in humans. Using a passive heating protocol, an 80% increase in $\dot{V}_E$ was observed along with a 65% increase in HR, but a non-significant increase in $\dot{V}O_2$ when participants were heated to a T_{es} of ~39°C. These results supported their hypothesis that the origin of the increase in $\dot{V}_E$ during hyperthermia was thermal rather than metabolic.

Additionally, White & Cabanac (182) observed a hyperthermic-induced increase in $\dot{V}_E$ using a short-term, high intensity and a long-term, lower intensity exercise protocol in a thermoneutral environment. They observed the T_{ty} threshold for a hyperthermic-induced increase in $\dot{V}_E$ during the shorter more intense exercise was significantly lower when compared to the longer session. It was suggested since T_{sk} and T_c increased at a faster rate during the shorter exercise session, the possibility exists that the T_{ty} thresholds for ventilation may be modified by $\dot{T}_c$ and $\dot{T}_{sk}$, similar to the other human thermolytic responses of vasodilatation and eccrine sweating (178). Therefore, the ventilatory increase observed during hyperthermia in humans appears to respond in a similar fashion to other thermolytic responses.

If the increased $\dot{V}_E$ observed during hyperthermia is a thermolytic response, it is assumed $\dot{V}_E$ will adapt in a similar manner to other heat loss responses following acclimation to a hot environment. That is, it is hypothesized the T_c threshold for a thermally-induced increase in $\dot{V}_E$ will be lower and there will be a greater increase in $\dot{V}_E$ during periods of heat stress following heat acclimation, similar to the adaptations observed with eccrine sweating and cutaneous blood flow. An exhaustive literature review did not uncover any research comparing the T_c threshold for thermal hyperpnea and the slope of the $\dot{V}_E$:T_c relationship prior to and following a typical heat acclimation protocol during passively or actively induced hyperthermia in humans.

2.7.2 Part 2: Central chemosensitivity and heat acclimation

There is a greater $\dot{V}_E$ for a given level of P_aCO_2, at an iso-oxic P_aO_2, in hyperthermic humans when compared to normothermic iso-oxic hypercapnic responses (5, 49, 142, 154, 173). Whether this effect is a result of increasing the responsiveness of central temperature sensitive neurons to normal levels of stimuli by the direct or indirect influence of temperature is unknown (173). What is known is that central chemosensitive areas in the ventral surface of the medulla oblongata and the peripheral chemoreceptors in the carotid body can act like thermosensitive tissues. Increasing the temperature of the chemosensitive areas in the ventral surface of the medulla above normal temperature, while maintaining the chemical environment surrounding these neurons, has been shown to enhance $\dot{V}_E$ in anaesthetized and ventilated cats (42, 43, 109). Similarly, heating the carotid bodies *in vitro* and *in situ* increased the discharge frequency of the carotid sinus nerve and induced hyperventilation in anaesthetized and ventilated cats (14, 59, 66, 117).

The increases in carotid sinus nerve discharge frequency with higher temperatures results in a corresponding augmentation of the thermal coefficient (Q_{10}) and energies of apparent activation (μ) indicating the carotid bodies conform to the criteria to be considered as thermosensitive tissues (66, 189). Therefore, the question arises, if central chemosensitive areas and the peripheral chemoreceptors in the carotid body have thermosensitivity, whether there may be a cross-adaptation of the ventilatory response to hypercapnia during hyperthermia following heat acclimation. An extensive review of literature did not reveal any research performed comparing the human ventilatory response to hypercapnia following a passively induced hyperthermia preceding and subsequent to heat acclimation.

2.8 Hypotheses

1) Acclimation to a hot environment will result in adaptation of ventilation and its components during, both, a passively and actively-induced hyperthermia.

2) Heat acclimation will increase the sensitivity of the central chemoreflex ventilatory response to CO_2 during a passive hyperthermia. In addition, it is hypothesized heat acclimation will also modify the central chemoreflex ventilatory response to CO_2 during normothermia.

3) Arterialized P_{CO2}, bicarbonate concentration ($[HCO_3^-]_a$) and pH_a will NOT be modified following acclimation to a hot environment.

2.9 Testable Questions

1) Following acclimation to a hot environment, will the increase in cutaneous blood flow and the initiation of eccrine sweating occur at a lower core temperature during, both, a passive and active heating protocol? Additionally, will there be a greater gain in cutaneous blood flow and eccrine sweating for a given change in T_c?

2) Following acclimation to a hot environment, will the core temperature threshold for thermally-induced increase in ventilation shift to a lower level and will the gain of the $\dot{V}_E$:T_c relationship be augmented during a passively and actively induced hyperthermia? Will the absolute levels of $\dot{V}_E$, V_T and f_v change during an acute heat stress following heat acclimation?

3) Will heat acclimation modify the ventilatory recruitment threshold and the sensitivity of the central chemoreflex ventilatory response to CO_2 during a normothermic- or hyperthermic-hyperoxic hypercapnic ventilatory response tests measured by a modified Read re-breathing test?

4) Will the pattern of ventilation observed during normothermic- and hyperthermic-hyperoxic hypercapnic ventilatory response tests be modified by acclimation to hot environment?

5) Will the arterialized P_{CO2}, bicarbonate concentration ($[HCO_3^-]_a$) and pH_a be modified following acclimation to a hot environment.

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Table 2.1 Comparison of active heat acclimation protocols employed in the literature and the physiological variables measured to establish heat acclimation/-atization.

Studies	Environment	Duration	Method Employed	Physiological Variables
Buono et al (29)	35°C, 75% RH	7 days	Cycle Ergometer @ 75W and Treadmill @ 1.34m/s at 3% grade. - 4 x 25min sessions with 5 min rest between.	T_r, T_{sk}, HR.
Gill & Slieivert (70)	38°C, 70% RH	10 days	Rowing Ergometer @ 70% $\dot{V}O_{2peak}$ for 30min	T_r, T_{sk}, HR, $\dot{E}_{sw}$, RPE
Gisolfi (71)	DB - 48.9°C WB - 29.7°C RH - 25%	8 days	Treadmill for 100min at 5.6km/h.	T_r, T_{sk}, BP, HR, $\dot{E}_{sw}$
Greenleaf et al (72)	40°C, 42% RH	12 days	Cycle Ergometer @ 45% to 50% $\dot{V}O_{2peak}$ for 120 min	T_r, BP
Horstman & Christensen (84)	DB - 45°C WB - 23°C RH – 15%	11 days	Cycle Ergometer @ 40% $\dot{V}O_{2max}$ for 120min.	T_{re}, HR, T_{sk}, blood samples
Nadel et al (129)	**Hot-Dry:** 45°C, 16 Torr[ι] **Hot-Humid:** 36°C, 35 Torr	10 days	Cycle Ergometer @ 50% $\dot{V}O_{2max}$. - 2 x 30min sessions with 15min rest between.	T_{es}, T_{sk}, $\dot{E}_{sw}$
Pandolf et al (139)	49°C, 20% RH	10 days	Treadmill @ 1.56m/s @ ~45% of $\dot{V}O_{2max}$ - 2 x 50min sessions with 10min rest between.	HR, T_r, T_{es}, T_{sk}, $\dot{E}_{sw}$, RPE, blood analysis
Rowell et al (152)	DB* - 48.4°C WB** - 25.6°C RH - 16%	11-12 days	Treadmill at 3.5mph (5.6km/h) @ 0% grade for 70-75min.	Sweat loss, HR, T_r, T_{sk}
Sawka et al (158)	I: 49°C, 20% RH II: 40°C, 30% RH III: 49°C, 20% RH	10 days (I & II) 6 days (III)	Treadmill @ 1.56m/s or 1.34m/s. - 2 x 50min sessions with 10min rest between.	T_r, T_{sk},
Shvartz et al (166)	DB - 39.4°C WB - 30.3°C RH - 53%	8 days	Bench stepping at 41W for 3hrs or until exhaustion.	HR, T_r, T_{sk}, $\dot{E}_{sw}$
Wyndham et al (186)	DB - 45°C WB - 32°C RH - 41%	10 days	Cycle Ergometer @ ~50% $\dot{V}O_{2max}$ - 4 x 55min sessions with a 5min rest between.	HR, T_r, T_{sk}, $\dot{E}_{sw}$

*Dry Bulb Temperature; **Wet Bulb Temperature; ⁴Relative Humidity; [ιWater vapour pressure.

Table 2.2 Comparison of passive heat acclimation protocols employed in the literature and the physiological variables measured to establish heat acclimation/-atization.

Studies	Environment Employed	Duration (Days)	Method Employed	Physiological Variables
Candas et al (38)	T_{DB} – 48°C T_{WB} – 32.82°C RH - 36%	10	**Resting Heat Exposure (3 hr)** - no control of T_{es}. • *Position:* lying on hammock.	T_{es}, T_{sk}, m_w
Fox et al (63)	**Hot- Wet:** **Phase 1 – Heating:** T_{DB} – 49°C T_{WB} – 26°C RH – 16% **Phase 2 – Control T_c** T_{DB} – 38°C T_{WB} – 26°C RH – 39% **Hot-Dry:** **Phase 1 – Heating:** T_{DB} – 49°C T_{WB} – 26°C RH – 16% **Phase 2 – Control T_c** T_{DB} – 45 to 55°C T_{WB} –23.25 to 31.6°C RH – 15 to 20%	12	**Controlled Hyperthermia (2 hr)** - T_{aural} controlled @ 38.2°C. - *Hot-Wet:* via ventilation of vapour barrier suit. - *Hot-dry:* via moving into different areas of thermal stress within the climatic chamber. **Hot-Wet:** • *Position:* reclined in chair. **Hot-Dry:** • *Position:* reclined in a chair.	T_{aur}, T_{sk}, HR, Sweat loss
Fox et al (64)	**Phase 1 - Heating** T_{DB} – 43°C T_{WB} – 43°C RH – 100% **Phase 2 – Control T_c:** T_{DB} – 38°C T_{WB} – 26°C RH – 39%	12	**Controlled Hyperthermia (0.5, 1 or 2 hr)** - T_{oral} controlled @ either 37.3, 37.9 or 38.5°C via ventilation of vapour barrier suits. • *Position:* reclined in deck chairs.	T_{oral}, HR, Sweat loss
Henane & Bittel (78)	T_{DB} – 45°C T_{WB} – 26.6°C RH – 24%	9	**Controlled Hyperthermia (1.5 hr)** - T_{ty} controlled @ 38.0°C by varying air humidity and velocity. • *Position:* lying on wire mesh bed.	T_r, T_{ty}, T_{sk}, m_{sw}

Studies	Environment Employed	Duration (Days)	Method Employed	Physiological Variables
Henane & Valatax (79)	**Phase 1 – Slow Heating:** T_{DB} – 45°C T_{WB} – 23°C RH – 14% **Phase 2 – Rapid Heating & Control T_c** T_{DB} – 55°C T_{WB} – 40°C RH – 41%	9	**Controlled Hyperthermia (1 hr)** - T_{ty} controlled @ 38.0°C by varying air humidity and velocity. • *Position:* lying on wire mesh bed.	T_r, T_{sk}, m_{sw}
Libert et al (106)	T_{DB} – 48°C T_{WB} – 32°C RH – 33%	10	**Resting Heat Exposure (2.75 hr)** - no control of T_{es}. • *Position:* lying on hammock made out of 7 rubber bands.	T_{es}, T_{sk}, m_w
Shido, O. et al (165)	T_{DB} – 46°C T_{WB} – 25.8°C RH – 20%	9-10	**Resting Heat Exposure (4 hr)** - no control T_{re}. • *Position:* lying down or sitting in a chair.	T_r, T_{sk}, m_{sw}, HR.

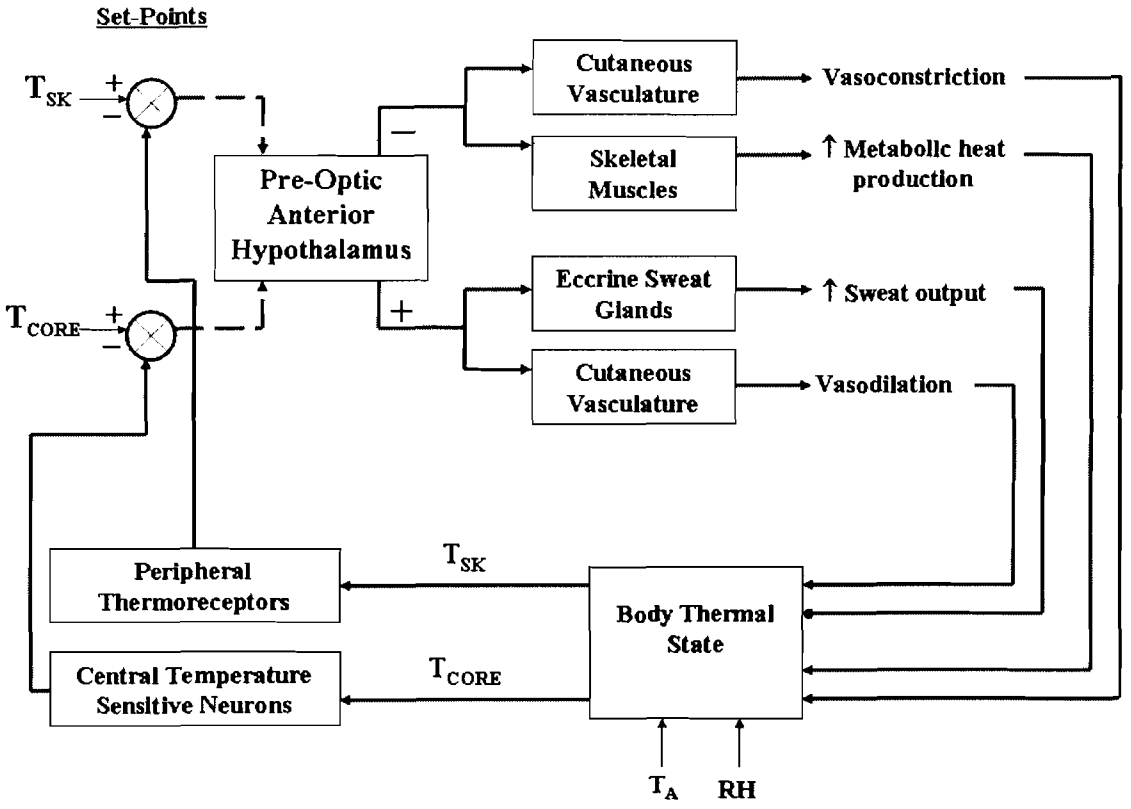

Figure 2.1 Flow diagram of the human autonomic thermoregulatory system when at rest utilizing a neuronally represented set-point model for the regulation of core temperature. The comparator symbol (⊗) represents the theoretical reference set-point to which T_c and T_{sk} afferent signals are compared. The dashed arrows represent the error signal (difference between afferent T_c and T_{sk} signals and the reference set-point). A positive error results in the initiation of heat loss mechanisms and a negative error signal produces a stimulation of heat conservation and heat gain responses. The solid arrows represent the flow of afferent and efferent nervous signals within the negative feedback loop.

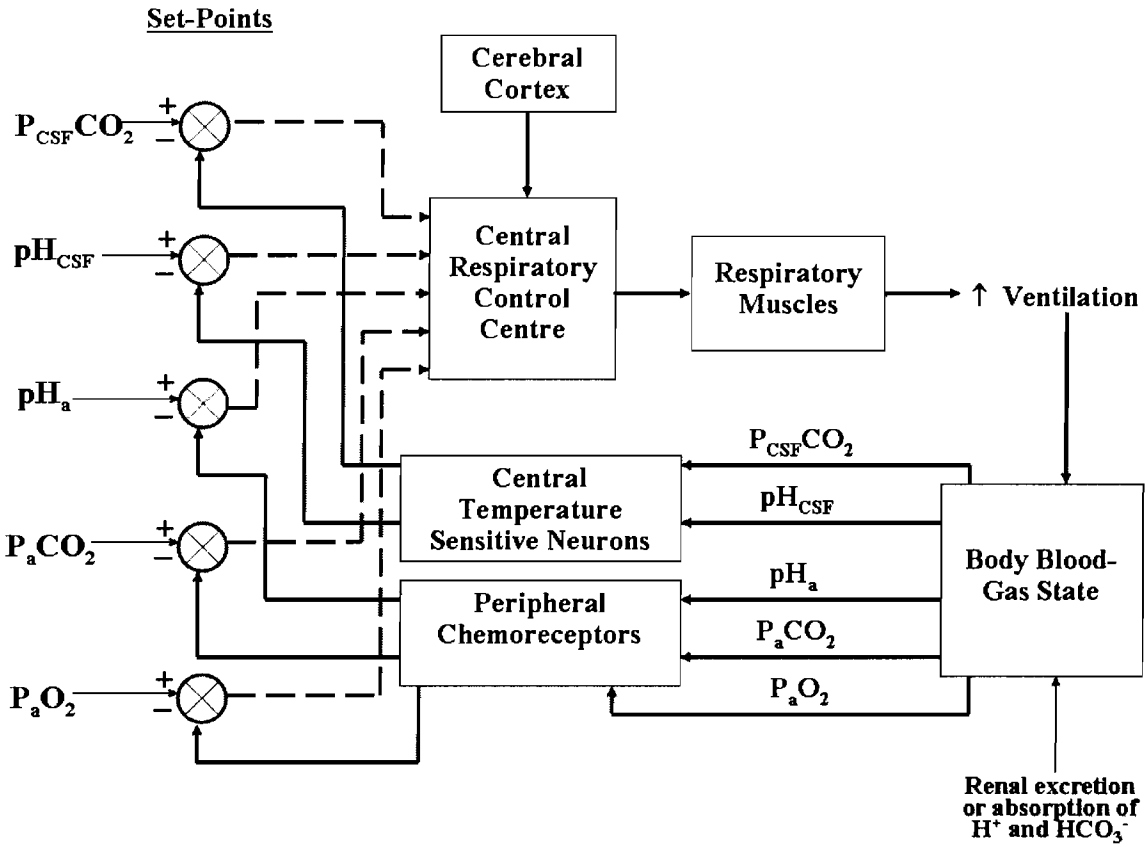

Figure 2.2 Flow diagram outlining the chemical regulation of arterial pH via the control of pulmonary ventilation. The comparator symbol (⊗) represents theoretical references to which $P_{CSF}CO_2$, pH_{CSF}, pH_a, P_aCO_2 and P_aO_2 afferent signals are compared. The dashed line represents the error signal created by the difference between afferent signals and the reference point. The solid arrows represent the flow of afferent and efferent nervous signals within the negative feedback loop. A positive error signal for $P_{CSF}CO_2$ and P_aCO_2 will stimulate an increase in ventilation while a negative error signal will decrease ventilation. Contrarily, a positive error signal for pH_{CSF}, pH_a and P_aO_2 will result in depression of ventilation while a negative error signal will result in an increased ventilation.

Chapter 3 – STUDY 1

Changes to the ventilatory and thermoregulatory responses during a passively-induced hyperthermia after 10 days of passive heat acclimation

Andrew E. Beaudin

Running Head: "Thermal Hyperpnea Following Heat Acclimation"

Keywords: Core temperature, cutaneous vasodilatation, eccrine sweating, pulmonary ventilation, thermoregulation, threshold.

3.1 Abstract

This study examined whether human pulmonary ventilation ($\dot{V}_E$) during a passively-induced hyperthermia would adapt similarly to measures of cutaneous vasodilatation (CBV) and eccrine sweating ($\dot{E}_{sw}$) following a 10-day, 2 h·day^{-1} passive heat acclimation (HA) to 50°C and 20 % RH. Following HA, the esophageal temperature threshold for onsets in CBV, $\dot{E}_{sw}$ and $\dot{V}_E$ were all significantly lowered ($p \leq 0.05$) relative to the un-acclimated state. Unlike, CBV_{TEMPLE} and $\dot{E}_{sw}$, $\dot{V}_E$ during the passive heating protocol was not significantly effected by HA ($p = 0.350$). Heat acclimation significantly increased tidal volume ($p = 0.034$) and showed a trend for a decreased breathing frequency ($p = 0.083$). In conclusion, following passive HA, the hyperthermic-induced increases in $\dot{V}_E$ adapted similarly to both CBV and $\dot{E}_{sw}$ and the pattern of breathing became deeper and slower. These results support the hypothesis human hyperthermic hyperventilation is a thermoregulatory response.

3.2 Introduction

In humans, cutaneous vasodilatation and eccrine sweating are the primary thermolytic responses during heat stress. An additional avenue of heat loss, seldom considered in humans, is from pulmonary ventilation. An increase in core temperature (T_c) has been long recognized to stimulate pulmonary ventilation in resting humans (5, 10, 22, 24, 26, 31, 43). More recently, this temperature influence was demonstrated for exercising humans (51). The mechanism through which hyperthermia stimulates the human respiratory centre is still not resolved.

An increase in T_c and the resultant increase in pulmonary ventilation enhance human respiratory heat loss (26) and provide a substantial portion of total human cephalic heat loss (37). Based on the observations of a distinct T_c threshold in humans during a passively-induced hyperthermia and a subsequent non-metabolic-induced increase in pulmonary ventilation, Cabanac and White (10) proposed that this hyperthermic-induced increase in ventilation was a thermoregulatory heat loss response important in cranial thermoregulation and the development of selective brain cooling[4].

Heat acclimation is the process through which prolonged or repeated, daily exposure to an artificial heat stress produce adaptations in body temperatures and primary human thermoregulatory heat loss mechanisms. Adaptations include decreases in the T_c threshold for the initiation of cutaneous vasodilatation and eccrine sweating, greater thermoregulatory responses at a given T_c and decreased resting core and mean skin

[4] **Selective brain cooling** is defined as "lowering the brain temperature, either locally or as whole, below aortic (arterial blood) [core] temperature." (1).

temperatures (33, 34, 39, 46). Additional, non-thermoregulatory adaptations include an increase in plasma volume and, occasionally, a decrease in heart rate during subsequent exposure to a heat stress (35, 40).

The degree to which physiological adaptations occur during heat acclimation is dependent upon the amount of stress imposed upon the thermoregulatory system (20, 23). An increase in T_c to ~38.5 to 39°C for ~2 $h \cdot day^{-1}$ for 7 to 14 consecutive days is considered to provide an adequate stimulus to produce full heat acclimation (17, 20, 35, 50). The majority of heat acclimation studies employ exercise at 40 to 60 % of one's maximal oxygen consumption within a hot environment to actively raise T_c (2, 50). Unfortunately, active acclimation protocols are often accompanied by an endurance training effect that would alter the relationship between ventilation and O_2 consumption and CO_2 production (29, 41, 48) and, therefore, are not ideal for studying heat acclimation induced changes to hyperthermic-induced increases in ventilation. An alternative, to prevent a training effect, is to utilize repeated passive heat exposure with controlled hyperthermia to provide a sufficient stress upon the thermoregulatory system to produce heat acclimation (20). Therefore, if heat acclimation modifies the human ventilatory response during an acute hyperthermia, it may be more evident following a passive heat acclimation protocol, than subsequent to an active protocol when it may be concealed by the concomitant training effect.

Based on the working hypothesis, the increase in pulmonary ventilation during periods of heat stress is a human thermoregulatory heat loss response, the objectives of this study were to determine if the hyperthermic ventilatory response during a passively-

induced hyperthermia would adapt similarly to cutaneous vasodilatation and eccrine sweating following passive heat acclimation and to determine whether the pattern of the hyperthermic-induced increase in ventilation would be modified following heat accalimation. It was hypothesized, following a heat acclimation protocol employing controlled hyperthermia, an increase in ventilation would be initiated at a lower T_c, ventilation would be higher at a given T_c and the breathing pattern would be modified to increase respiratory heat loss during a passively-induced hyperthermia (30).

3.3 Methods

3.3.1 Participants

A power calculation was performed using an effect size of a 0.30 ± 0.20°C (mean ± SD) decrease in the T_c threshold for the initiation of thermoregulatory heat loss responses based on results from previous passive heat acclimation studies in the literature (19, 28). A sample size of 10 university-aged males was utilized as it would provide an estimated power of 0.99. Table 3.1 contains participant individual characteristics. Participants were non-smokers and asked to avoid consuming caffeine or alcohol, eating and strenuous exercise for a minimum of 4 h prior to each testing session. They were given a 30 min orientation that included an overview of the protocol, the instrumentation and the potential risks. Participants were then given a minimum 24 h reflection period, after which each participant signed and submitted an informed consent. The Office of Research Ethics at Simon Fraser University approved this study.

3.3.2 Instrumentation

Esophageal temperature (T_{es}) was measured using a paediatric sized thermocouple (9 FR, Mallinckdrot Medical Inc., St. Louis, MO, USA) inserted through the nose into the esophagus to a depth equivalent to the level of the eighth and ninth thoracic vertebrae (T8/T9); a position corresponding to the level of the left ventricle (32). For the heat acclimation sessions, rectal temperature (T_{re}) was measured by a thermistor (9 FR, Cincinnati Sub-Zero, Cincinnati, OH, USA) inserted 15 cm past the anal sphincter. Esophageal thermocouples and T_{re} thermistors were calibrated at several different physiological core temperatures (Appendix A) using temperature regulated, stirred water bath (Cenco Instruments, Chicao, IL, USA) monitored by a platinum thermometer (Fisher

Scientific, Nepean, ON, Canada). Skin temperatures (T_{sk}) were measured using copper, constantan thermocouples (Omega Engineering Inc., Stanford, CT, USA) attached to the left temple (T_{temple}), shoulder (T_{sh}), lower back (T_{lb}) and thigh (T_{th}). Temple temperature was expressed on its own and mean T_{sk} ($\overline{T}_{sk}$) was expressed as the un-weighted mean of T_{sh}, T_{lb} and T_{th}.

A laser-Doppler flowmeter 5-in-1 needle probe (MP12-V2, Moor Instruments Ltd, UK) measured cutaneous blood cell velocity of the right temple (CBV_{TEMPLE}). The probe was inserted into a holder, attached to a heating unit (SHO2, Moor Instruments Ltd, UK) allowing for the control of local skin temperature (T_{sk}) at 35°C initially, while allowing continuous LDF measurements. The LDF probe was calibrated using a polystyrene microspheres flux standard solution (moorLAB, MP12-V2, Moor Instruments Ltd, Devon, UK).

Forehead eccrine sweat rate ($\dot{E}_{sw}$) was measured using the ventilated capsule method (7). A capsule (surface area: 5.31 cm^2) was secured to the forehead using a headband and flushed with a dry compressed air source a rate of 1 $L \cdot min^{-1}$. The relative humidity (RH) of the dry air source was verified by a resistance hygrometer (RH201C, Omega Engineering Inc., Stanford, CT, USA) within a sealed capsule through which the air initially passed. The air then passed through the forehead capsule where it was humidified after participants began to sweat and, finally, the humidified air passed through a third sealed container enclosing a capacitance hygrometer (HMT337, Vasaila, Helsinki, Finland) in order to measure the RH of the air after passing over the forehead. The HMT337 capacitance hygrometer was employed because it is capable of measuring

RH in near condensing conditions. Eccrine sweat rate was calculated via the equation used by Bullard (7) with the inclusion of the surface area (SA) of the sweat capsule (m^2):

$$\dot{E}_{sw}\ (mg \cdot m^{-2} \cdot s^{-1}) = [\ \dot{F}_{AIR}\ (L \cdot s^{-1}) \times (\Delta\ RH \div 100) \times \rho_{steam}\ (mg \cdot L^{-1})\ ] \div SA\ (m^2) \qquad (3.1)$$

where $\dot{E}_{sw}$ is the calculated eccrine sweat rate; $\dot{F}_{AIR}$ is the air flow rate through the forehead capsule; Δ RH is the change in RH between the first and second humidity sensor; ρ_{steam} is the density of the saturated steam at the ambient dry bulb temperature (°C); and SA is the surface area of skin covered by the sweat capsule.

Breath-by-breath measurement and recording of ventilation ($\dot{V}_E$) and its components was performed via a metabolic cart (Vmax 229c, Sensormedics, Yorba Linda, CA, USA) with inspired and expired gas samples being drawn at ~600 $mL \cdot min^{-1}$. The metabolic cart uses a paramagnetic sensor to determine oxygen content and non-dispersive infrared spectroscopy to measure carbon dioxide content of the inspired and expired gases. Sensors were calibrated prior to the start of each testing session using three gases of known concentration (air; 26 % O_2 with the balance N_2; and 4 % CO_2, 16 % O_2, balance N_2). A two-way Mass Flow Sensor (Sensormedics, Yorba Linda, CA, USA) was connected to a low resistance mouthpiece through which participants breathed while wearing a nose clip. The flow sensor was calibrated using a 3 L standardized volume syringe (Sensormedics, Yorba Linda, CA, USA) prior to beginning data collection.

Pulse oximetry (Masimo Radical, Irvine, CA, USA) was used to continuously measure heart rate (HR) from the left earlobe

Body temperatures, CBV_{TEMPLE} and RH data were collected breath-by-breath via a data acquisition system (National Instruments, Austin, TX, USA) triggered by an analogue flow signal originating from the metabolic cart. The data acquisition system was controlled by LabVIEW software program (Ver 7.1, National Instruments, Austin, TX, USA) on a personal computer. Rectal temperature was recorded at 30 s intervals during all acclimation sessions using a portable data logger (Mini Logger Series 2000, Mini-Mitter, Bend, OR, USA) controlled by a personal laptop computer.

Arterialized blood sampling was performed having the participant wear a waterproof glove extending up to the middle of the forearm and immersing their hand, up to the wrist, in a water bath maintained at 42°C for a minimum of 10 min (18). Capillary tube blood samples were then drawn by puncturing the tip of one of the heated fingers with a lancet (BD, Franklin Lakes, NJ, USA). Samples were analyzed immediately by a portable blood gas analyzer (ABL77, Radiometer, Copenhagen, Denmark) for haemoglobin ([Hb]) and haematocrit (Hct). Increases in plasma blood volume (PV) from baseline were estimated by the equation employed by Dill & Costill (16) based on the assumption of constant red blood cell mass:

$$\% \Delta PV = 100 [(Hb_{PRE}/Hb_{ACC}) \times ((1\text{-}Hct_{ACC}) / (1\text{-}Hct_{PRE}))] - 100 \quad (3.2)$$

where Hb_{PRE} and Hct_{PRE} are the pre-acclimation baseline values and Hb_{ACC} and Hct_{ACC} are the values measured at the end of the heat acclimation protocol. Haemoglobin was measured in $g \cdot 100\ mL^{-1}$ and Hct, was expressed as a fraction (volume of RBC (μL) ÷ blood sample volume (μL)).

Heat acclimation was performed within a walk-in climatic chamber (L – 5.08 m, W – 3.75 m and H – 2.49; Tenney Engineering Inc., Union, NJ, USA).

3.3.3 Protocol

Each participant underwent one pre- and one post-heat acclimation passive heating protocol. Passive heating consisted of head out immersion in a hot water bath while wearing a bathing suit (10). Following instrumentation, each participant sat in a comfortable chair for 10 min within a thermoneutral environment in order to obtain resting data. The mean pre-acclimation ambient temperature and RH within the room housing the water bath were 22.76 ± 1.43°C and 31.12 % while during post-acclimation tests, the mean conditions were 22.58 ± 1.35°C and 30.27 %. Subsequent to the rest period, each participant was moved into the water bath within ~1 min where they remained immersed up to the shoulders until their T_{es} reached ~39.00°C. Prior to acclimation, the water bath was maintained at 40.42 ± 0.19°C and post-acclimation, the mean water bath temperature was 40.49 ± 0.21°C.

The HA protocol mimicked the procedure used by Fox et al (19). It consisted of a controlled hyperthermia during a passive exposure to an environment controlled at 50°C and 20 % RH for 120 $min \cdot day^{-1}$ for 10 consecutive days. Each participant was dressed in

shorts, T-shirt and running shoes, was instrumented for T_{re} and then put on a vapour barrier suit consisting of a hooded jacket and overall type pants over their shorts and t-shirt. To minimize heat loss, the jacket was sealed tightly at the waist; the pants were sealed at the ankles and a pair of fleece gloves were worn when each participant initially entered the climatic chamber. Once dressed in the vapour barrier suit, each participant was seated outside the climatic chamber for 5 min in order to acquire a resting T_{re} after which they were moved into the climatic chamber. Each participant was seated on a chair when they entered the climatic chamber initially, but were allowed to sit, stand, talk to other participants inside the chamber, study, read or listen to music. Throughout the HA protocol, within each acclimation session, T_{re} was raised within ~60 min of exposure to between 38.50 and 39.00°C. Subsequently, T_{re} was maintained at this level for the remainder of each session by varying the amount of evaporative heat loss permitted by removing portions of the vapour barrier suit or turning on a personal fan.

All 10 acclimation sessions were performed at the same time each day and the pre- and post-acclimation passive heating tests were performed within the same 2 h window to control for the fact human thermoregulatory adaptations occurring with HA have been shown to be fixed to the time of day each participant is exposed to the heat (47).

Capillary tube blood samples were taken on day 1 and day 10 of acclimation prior to instrumentation. The day 1 sample was used as the baseline measurement for [Hb] and Hct within equation 3.2. Water was available *ad libitum* throughout all acclimation sessions. Figure 3.1 shows a schematic representation of the entire protocol.

3.3.4 Statistical Analyses

Pre- and post-acclimation T_{es} thresholds for the initiation of an increase in CBV_{TEMPLE}, eccrine sweating and $\dot{V}_E$ responses during the two passive heating protocols were determined by plotting each variable against T_{es}. Thresholds were determined using a piecewise linear regression method (49) written in LabVIEW software (Ver 7.1, National Instruments, Austin, TX, USA). The program iteratively determines the optimal fit of two linear regressions to the data when they are forced to join at a value at which a datum occurs. Initially, the first linear regression is fitted to the first 3 data points and the second regression is plotted through the remaining data. Subsequently, the first regression is extended by one datum and the second regression is decreased by one. With each growth and decline step, 20 iterations of each regression line are performed to minimize the mean squared errors (MSE) for each. This process continues until the 2nd regression line consists of only the final 3 data points and the first consists of all previous data. The optimal fit of the two regressions was where the sum of the MSE of both regression lines was minimized. The thresholds were taken as the value of the datum where the two regressions lines intersect and the sensitivity of CBV_{TEMPLE} and $\dot{V}_E$ to rises in T_{es} was calculated as the slope of the 2nd linear regression. Individual $\dot{E}_{sw}$ sensitivities to increases in T_{es} were assessed by plotting a mono-exponential function to the individual $\dot{E}_{sw}$ vs T_{es} plots after T_{es} began to rise using commercial graphing software (Sigma Plot 9.0, Systat Software Inc., Point Richmond, CA, USA) and the following equation:

$$\dot{E}_{sw}(T_{es}) = \dot{E}_{sw}(\text{baseline}) + \Delta\dot{E}_{sw}(ss) \times (1 - e^{(-(T_{es} - (\text{delay})/\tau)})} \quad (3.3)$$

where $\dot{E}_{sw}$ (T_{es}) is the $\dot{E}_{sw}$ at any T_{es} above the previous baseline steady-state; $\dot{E}_{sw}$ (baseline) is the steady-state level of $\dot{E}_{sw}$ prior to it beginning to increase; $\Delta\dot{E}_{sw}$(ss) is the estimated maximal steady-state $\dot{E}_{sw}$; "delay" is the increase in T_{es} prior to sweating onset; and tau (τ) is the change in T_{es} when $\dot{E}_{sw}$ (T_{es}) reached 63.2 % of total estimated $\Delta\dot{E}_{sw}$(ss) and taken to represent the sensitivity of the eccrine sweating response to increases in T_{es}. Correlated 1-tailed t-tests were performed to compare the pre- and post-acclimation T_{es} thresholds for the onset of increases in CBV_{TEMPLE}, $\dot{V}_E$ and $\dot{E}_{sw}$ and the sensitivities of all to increases in T_{es}. The alpha level was set at less than or equal to 0.05 for all correlated comparisons.

In addition, a 2-way repeated measures ANOVA with the factors of a change in Absolute T_{es} (Levels: 37.30, 37.70, 38.10, 38.50 and 38.90°C) after T_{es} had begun to rise and achieved within, both, the pre- and post-acclimation passive heating trials and Acclimation State (Levels: pre and post). Dependent variables include thermoregulatory responses, body temperatures, ventilation and its components, as well as metabolic and cardiovascular responses. Thermoregulatory variables consisted of CBV_{TEMPLE} and $\dot{E}_{sw}$; body temperature included $\bar{T}_{sk}$ and T_{temple}; and the ventilatory variables included pulmonary minute ventilation ($\dot{V}_E$), total breath (T_{TOT}), inspiratory, (T_I) and expiratory breath times (T_E), inspiratory flow rate (V_T/T_I), estimated alveolar ($\dot{V}_A$) and dead space ($\dot{V}_D$) ventilation, V_D/V_T, and end-tidal partial pressures of O_2 ($P_{ET}O_2$) and CO_2 ($P_{ET}CO_2$). The metabolic variables included oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and the respiratory exchange ratio (RER), while the cardiovascular measure was for HR. If the main effect of Acclimation State and/or the interaction between the two main factors were significant, dependent t-tests were employed to compare the pre- and

post-acclimation conditions at each T_{es}. A Bonferonni correction factor was employed to maintain the *a priori* alpha (α) level of 0.05 for post-hoc comparisons.

Finally, to determine whether resting conditions were significantly different than that observed at the conclusions of the pre- and post-acclimation passive heating trials, the mean values at un-immersed rest and at a Tes of ~39.00°C were compared. All statistical analyses were performed with SPSS 15.0 (SPSS Inc, Chicago, Illinois, USA).

3.4 Results

Rectal temperature response during heat acclimation protocol

Individual mean T_{re} responses for the 10-day HA protocol are shown in Figure 3.2. Briefly, when participants entered the chamber, T_{re} either decreased slightly or remained stable for ~15 to 20 min, after which it began to rise steadily, reaching the target of 38.50°C in ~60 min.

Adaptations following heat acclimation

Individual T_{es} thresholds and sensitivities for CBV_{TEMPLE}, eccrine sweating and $\dot{V}_E$ during the pre- and post-acclimation passive heating trials are given in Table 3.2 for an n = 7. One participant was removed because his post-acclimation $\dot{V}_E$ sensitivity was greater than 4 SDs above the mean. Two other participants were removed because one showed no increase in $\dot{V}_E$ during both the pre- and post-acclimation trials and another showed an increase in $\dot{V}_E$ during only the post-acclimation trial. Table 3.2 B contain the individual values for these 3 participants. Mean T_{es} thresholds were significantly lower ($p \leq 0.038$) for CBV_{TEMPLE}, $\dot{E}_{sw}$ and $\dot{V}_E$ following HA, but the sensitivity of CBV_{TEMPLE} and $\dot{V}_E$ to increases in T_{es} were not significantly different ($p \geq 0.300$) between the pre- and post-acclimation conditions. In addition, the pre- and post-acclimation mean τ and $\Delta\dot{E}_{sw}(ss)$ were not significantly different ($p \geq 0.915$). Representative breath-by-breath plots for CBV_{TEMPLE} and $\dot{E}_{sw}$ versus T_{es} during the pre- and post-acclimation passive heating trials used to determine the T_{es} thresholds, sensitivities, τ and $\Delta\dot{E}_{sw}(ss)$ are shown in Figure 3.3 and a similar representative plot for $\dot{V}_E$ is given in Figure 3.4.

Table 3.3 contains mean pre- and post-acclimation body temperatures and thermoregulatory measurements at un-immersed rest and at maximal observed values when T_{es} was ~39.00°C during both passive heating trials. The rate at which T_{es} increased during both heating trials is also included. There was a significantly lower ($p \leq 0.048$) post-acclimation resting mean T_{es} and $\bar{T}_{sk}$, but there was only a trend ($p = 0.081$) for resting T_{temple} to change is a similar manner. Plasma volume was significantly ($p = 0.005$) expanded by a mean of 20.44 ± 12.66 % above pre-acclimation baseline levels by the 10th day of the HA protocol.

Table 3.4 shows the mean values of ventilatory, metabolic and cardiovascular responses for 9 participants at un-immersed rest and at the maximal observed values during the pre- and post-acclimation passive heating tests. Participant 1 was excluded because of his excessive ventilatory sensitivity to increases in T_{es}. Mean $\dot{V}_E$ was significantly higher ($p \leq 0.034$) when T_{es} was ~39.00°C during the two passive heating trials, but un-immersed resting and maximum values were not different between the pre- and post-acclimation conditions. The maximum pre-acclimation $\dot{V}_E$ observed was accompanied by significant increase ($p = 0.031$) in V_T and a non-significant change ($p = 0.108$) in f while the post-acclimation maximum $\dot{V}_E$ was accompanied by only a significant increase ($p = 0.005$) in f. Post-acclimation, there were trends for un-immersed resting V_T to be higher ($p = 0.060$) and f to be lower ($p = 0.081$), but neither were significantly different ($p \geq 0.511$) at a T_{es} of ~39.00°C compared to the pre-acclimation condition. In addition, there was a significant rise ($p \leq 0.021$) in $\dot{V}_A$ and $\dot{V}_D$ during, both, the pre- and post-acclimation trials, but these increases were not different ($p \geq 0.316$) between acclimation states. This breathing pattern resulted in $P_{ET}CO_2$ being

significantly lower ($p = 0.011$) and $P_{ET}O_2$ being significantly higher ($p = 0.002$) at the end of the two passive heating tests, but, again, there was no difference ($p \geq 0.331$) between the pre- and post-acclimation conditions. In addition, during the pre-acclimation trials, the maximum $\dot{V}O_2$, $\dot{V}CO_2$ and RER were all significantly higher ($p \leq 0.028$) when T_{es} was ~39.00°C than at un-immersed rest but only maximum mean $\dot{V}CO_2$ and RER were significantly higher ($p \leq 0.021$) in the post-acclimation trials when compared to resting levels. Finally, at un-immersed rest and at a T_{es} of ~39.00°C, the maximum mean HR was not significantly different ($p \geq 0.170$) between the pre- and post-acclimation conditions.

Body temperatures and thermoregulatory responses during passive heating protocols

Pre- and post-acclimation responses for T_{es}, $\overline{T}_{sk}$ and T_{temple} during the passive heating tests, with respect to time, are shown in Figure 3.5. Esophageal temperature was significantly lower at rest ($p = 0.048$) and decreased further after being immersed in the warm water during the post-acclimation trial as compared to the pre-acclimation trials. Subsequently, the post-acclimation T_{es} increased at a significantly faster rate ($p = 0.036$; Table 3.2) surpassing the pre-acclimation T_{es} approximately 7.5 min after participants were immersed. Post-acclimation, $\overline{T}_{sk}$ was also significantly lower ($p = 0.036$) at rest and T_{temple} showed a trend to be lower ($p = 0.081$) at rest, but once immersed in the water bath, $\overline{T}_{sk}$ and T_{temple} were similar between the pre- and post-acclimation trials as T_{es} increased.

Figure 3.6 A shows the mean $\overline{T}_{sk}$ and T_{temple} as a function of Absolute T_{es} during, both, the pre- and post-acclimation passive heating trials for 9 participants. Participant 1

was excluded from all RM ANOVA analyses. Acclimation State did not have a significant effect ($F_{(1,8)} \leq 1.99$; $p \geq 0.196$) on either the $\overline{T}_{sk}$ or T_{temple} response. Contrarily, Acclimation State had a significant main effect on CBV_{TEMPLE} ($F_{(1,8)} = 7.03$; $p = 0.029$) and $\dot{E}_{sw}$ ($F_{(1.8)} = 9.78$; $p = 0.014$) with HA significantly increasing both responses (Figure 3.6 B and C, respectively). Additionally, the interaction between changes in Absolute T_{es} and Acclimation State showed a trend for CBV_{TEMPLE} ($F_{(4,32)} = 2.84$ $p = 0.073$; Figure 3.6 B) and was significant for $\dot{E}_{sw}$. ($F_{(4,32)} = 4.45$; $p = 0.025$; Figure 3.6 C), with both being higher at lower levels of T_{es} during the post-acclimation heating trials then converging and becoming similar to the pre-acclimation trials at higher absolute levels of T_{es} as each response neared its maximum output.

Ventilatory, metabolic and cardiovascular responses during passive heating protocols

Ventilation and its components of V_T and f along with the durations of the respiratory cycle (i.e., T_{TOT}, T_I and T_E) are shown in Figure 3.7. Overall, $\dot{V}_E$ during the passive heating trials was not significantly effected by Acclimation State ($F_{(1,8)} = 0.99$; $p = 0.350$) nor the interaction between Absolute T_{es} and Acclimation State ($F_{(4,32)} = 0.36$; $p = 0.717$). Rather, irrespective of Acclimation State, the main effect of changes in Absolute T_{es} had a significant effect ($F_{(4,32)} = 8.08$; $p = 0.015$) on $\dot{V}_E$, with increases in T_{es} resulting in a non-linear increase in $\dot{V}_E$. The increase in $\dot{V}_E$ was accompanied by a significant effect of Absolute T_{es} on V_T ($F_{(4,32)} = 11.52$; $p = 0.001$) and a non-significant effect on f ($F_{(4,32)} = 0.152$; $p = 0.827$). Even though $\dot{V}_E$ was not significantly affected by Acclimation State, HA had a significant positive effect on V_T ($F_{(1,8)} = 6.53$; $p = 0.034$) and showed a trend to lower f ($F_{(1,8)} = 3.84$; $p = 0.086$). In addition, the main effect of Acclimation State showed a trend for the respiratory cycle timing components of T_{TOT}

($F_{(1,8)} = 3.42$; $p = 0.102$), T_I ($F_{(1,8)} = 0.093$; $p = 0.083$) and T_E ($F_{(1,8)} = 3.31$; $p = 0.107$) to be higher after HA, but none of the timing components were affected by the factor of changes in Absolute T_{es} irrespective of Acclimation State ($F_{(4,32)} \leq 0.55$; $p \geq 0.509$; Figure 3.7 D, E and F).

Figure 3.8 shows the mean $\dot{V}_A$ and $\dot{V}_D$ responses along with the changes in $P_{ET}CO_2$ and $P_{ET}O_2$ at the levels of Absolute T_{es} during the pre- and post-acclimation passive heating tests. The main effect of a change in Absolute T_{es}, irrespective of Acclimation State, was significant for increases in $\dot{V}_A$ ($F_{(4,32)} = 8.16$; $p = 0.014$) and $P_{ET}O_2$ ($F_{(4,32)} = 7.22$; $p = 0.016$) and for decreases in $P_{ET}CO_2$ ($F_{(4,32)} = 9.89$; $p = 0.009$) as T_{es} increased. Absolute T_{es} only showed a trend for an increase in $\dot{V}_D$ ($F_{(4,32)} = 2.84$; $p = 0.107$). The Acclimation State main effect was significant for $P_{ET}O_2$ ($F_{(1,8)} = 7.35$; $p = 0.027$) explained by significantly higher values ($p \leq 0.040$) at esophageal temperatures between 37.3 to 38.1°C and a trend to be higher ($p = 0.094$) when T_{es} was 38.5°C.

Finally, the main effect of Absolute T_{es} was significant for V_T/T_I ($F_{(4,32)} = 5.74$; $p = 0.032$) with V_T/T_I increasing proportionately with increases in T_{es}, but the Acclimation State main effect was not significant ($F_{(1,8)} = 1.49$; $p = 0.257$). In addition, Acclimation State showed a trend ($F_{(1,8)} = 3.42$; $p = 0.102$) for the V_D/V_T ratio to be lower during the post-acclimation passive heating trials.

Figure 3.9 shows that the main effect of changes in Absolute T_{es} was significant for increases ($F_{(4,32)} \geq 5.40$; $p \leq 0.05$) in $\dot{V}O_2$, $\dot{V}CO_2$ and RER, irrespective of Acclimation State. There was a trend ($F_{(1,8)} \leq 4.64$; $0.05 \leq p \leq 0.107$) for all of the

metabolic variables to be higher following HA. Finally, there was also a trend ($F_{(1,8)}$ = 3.83; p = 0.086) for HR to be higher at all levels of Absolute T_{es} during the passive heating test following HA (Figure 3.9 D).

3.5 Discussion

The primary finding of this study was that following acclimation to a hot environment the T_{es} threshold for the hyperthermic-induced increase in $\dot{V}_E$ was significantly lower during a passively-induced hyperthermia. The hyperthermic-induced increase in $\dot{V}_E$ during both the pre- and post-acclimation passive heating trials was a result of an increase in V_T, as f remained relatively unchanged as T_{es} increased (Figure 3.7 A to C). A secondary main finding was that, following HA, there was a significant increase in V_T and there was a trend for f to be lower at all levels of Absolute T_{es}. This modification of the breathing pattern would serve to increase heat loss from the respiratory tract (8, 30). These findings, therefore, support the hypothesis that the increase in $\dot{V}_E$ arising during hyperthermia in humans (5, 10, 22, 24, 26, 31, 43) adapts to repeated bouts of heat stress and is a thermoregulatory heat loss response (10).

The decline in the T_{es} threshold for the hyperthermic-induced increase in $\dot{V}_E$ by 0.21°C was similar to that observed for the traditional human thermoregulatory heat loss responses of cutaneous vasodilatation and eccrine sweating within the present HA study (Table 3.2) and previous studies (19, 20, 28, 52). Therefore, the shift in the T_{es} threshold for the initiation of the observed hyperthermic hyperpnea was considered to be a result of HA.

The observation of an increased V_T while f remained unchanged as T_{es} was raised, irrespective of acclimation state, is similar to what has been previously observed with a passively-induced hyperthermia in humans (5, 10, 22, 26, 43), but contrary to others who have observed an increase in, both, V_T and f (4, 31, 42). As a consequence of

this breathing pattern, there was greater increase in $\dot{V}_A$ (~90 %) than $\dot{V}_D$ (~60 %), resulting in a compromised acid-base balance as $P_{ET}CO_2$ was significantly lower and $P_{ET}O_2$ was significantly higher when T_{es} was ~39.00°C (Table 3.4 and Figure 3.8). This breathing pattern is similar to second phase panting employed by animals, such as the dog and the ox, to enhance respiratory heat loss (RHL) during a prolonged, severe heat stress (25, 38).

Unlike CBV_{TEMPLE} and $\dot{E}_{sw}$ where the post-acclimation values were higher at the same lower levels of T_{es} during hyperthermia, the total $\dot{V}_E$ response was not significantly affected by HA. Rather, the pattern of the hyperthermic ventilatory response during the passive-induced hyperthermia following HA was slower and deeper resulting from the trend for T_{TOT}, T_I and T_E to be higher during the post-acclimation heating trials (Figure 3.7). Consequently, V_T was higher and f tended to be lower during the post-acclimation trials (Figure 3.7). A benefit of this breathing pattern is that it increases the V_T/f ratio, which has been shown to be capable of increasing RHL a small, but significant amount (30). When $\dot{V}_E$ is achieved by a higher V_T and a lower f, as was the case during the post-acclimation trial, convective heat loss has been shown to be increased when breathing either dry gases at room temperature (25 to 26°C and <1 % RH) or humidified air at higher temperatures (30 to 33°C; 100 % RH) (8). Therefore, in addition to the contributions of an increased T_{es} and $\dot{V}_E$ to increasing RHL (26), the earlier increase in $\dot{V}_E$ and the slower, deeper breathing pattern would serve to enhance heat loss from the respiratory tract, potentially promoting a greater degree of selective brain cooling, thus prolonging proper brain functioning, mental awareness, thermoregulatory control and exposure time.

These ventilatory adaptations are difficult to compare to previous results in the literature as this is the first study to compare the relationship between $\dot{V}_E$ and its components with T_c during a passively-induced hyperthermia in humans prior to and following acclimation to a hot environment. Aside from the decrease in the T_{es} threshold for the increase in $\dot{V}_E$, the switch to a slower, deeper breathing pattern appears to be an important adaptation of the hyperthermic ventilatory response following HA. The role of both adaptations appear to be to augment RHL and, possibly, the degree of selective brain cooling observed in humans during hyperthermia (9, 10, 51).

The modifications of the ventilatory response observed during the post-acclimation passive heating trials may only be considered adaptations resulting from HA if participants were successfully acclimated. Participants within the present study were considered to be successfully heat acclimated based on the attainment of several well defined physiological adaptations (17, 35, 50). The principal indication of successful HA was the significant decrease in resting T_{es} by ~0.10°C. The second index was the significant decrease in the T_{es} thresholds for the initiation of cutaneous vasodilatation and eccrine sweating of ~0.20 and 0.30°C, respectively, resulting in both responses being greater at a given T_{es} during the post-acclimation passive heating tests (Figure 3.6). A third confirmation was the significant decrease in resting $\overline{T}_{sk}$, prior to immersion, and the trend for resting mean T_{temple} to be lower post-acclimation (Table 3.3). The final indication participants were successfully heat acclimated was the mean expansion of plasma volume by ~20 %. The decrease in resting T_{es}, resting $\overline{T}_{sk}$ and resting T_{temple} along with the expansion of plasma volume are all within the typical ranges reported within previous HA studies (3, 19, 28, 33, 34, 39, 45, 46). One unexpected result was the

trend for HR to be higher during the post-acclimation passive heating trial (Figure 3.9). Typically, HR decreases during a heat stress subsequent to HA (50). A couple factors appear to have contributed to higher HR during the post-acclimation trials. One, CBV_{TEMPLE} was significantly higher during the post-acclimation heating trials (Figure 3.6) at the lower levels of T_{es}. Assuming this was reflective of the whole body skin blood flow response, an increase in HR would be expected in order to prevent a decrease in systemic blood pressure. Two, there was a trend for $\dot{V}O_2$ and $\dot{V}CO_2$ to be higher during the post-acclimation trials which, again, would require HR to be increased in order to maintain O_2 delivery and CO_2 removal. In addition, the lower HR typically observed following HA may be a result of an aerobic training effect rather than a HA effect as the majority of previous studies employed an active HA protocol and a decreased HR during a subsequent heat stress following a passive, controlled hyperthermic HA protocol does not always occur (20, 21).

Within this study, several limitations must be considered. First, hyperthermia was induced via head-out water immersion. The increased hydrostatic pressure of water immersion has been shown to reduce functional residual capacity, vital capacity and expiratory reserve volume (6, 15, 36). As a result, several studies observing changes in the normothermic breathing pattern during water immersion after $\dot{V}_E$ had returned to resting levels have observed either, a decrease in V_T and an increase in f (11, 14), an increased V_T and no change in f (12) or no change in the breathing pattern (13, 44). Within the present study, it appears when $\dot{V}_E$ returned to resting levels at ~5 min after immersion and it was accompanied by a lower V_T and an increased f within both, the pre- and post-acclimation, passive heating trials (Figure 3.10). Therefore, there is the

possibility the increase in f observed by others with a hyperthermic-induced increase in $\dot{V}_E$ (4, 31, 42) was not observed because f was already increased as a result of the hydrostatic effect of the water immersion. This is not believed to be the case as hyperthermic hyperventilation has also been shown to be the result of increased V_T with either a maintenance or decrease in f when hyperthermia was induced via high room temperatures (5, 24, 43). Hence, the breathing pattern observed during hyperthermia within the present study was believed to be the result of an increase in T_{es} and not because the increased hydrostatic pressure of water immersion.

A second limitation within the study protocol was that participants were heated until a T_{es} of ~39°C was achieved, irrespective of their resting T_{es}. Therefore, the increase in T_{es} from resting conditions to the conclusion of the passive heating protocols varied between individuals and acclimation states. This variance may have contributed to why one participant showed no increase in $\dot{V}_E$ during either the pre- or the post-acclimation heating trials and two other participants only showed one T_{es} threshold for $\dot{V}_E$ during either, the pre- or the post-acclimation trial (Table 3.2). Within the passive heating trials where no T_{es} threshold was observed, there is the possibility that T_{es} was not increased a sufficient amount to induce a hyperthermic hyperventilation within these participants.

Two final limiatation to consider is, one, during the pre-acclimation passive heating trials, there was a significant increase in mean $\dot{V}O_2$ and $\dot{V}CO_2$ by the conclusion of the trials and during the post-acclimation trials, $\dot{V}CO_2$ was significantly increased. The extent to which the increase in $\dot{V}_E$ observed during hyperthermia was a result of

increases in metabolism needs to be established. Two, with the significant expansion of PV observed there is the possibility it may have contributed to the modifications of the post-acclimation hyperthermic ventilatory response observed as vascular distension has been shown to be capable of stimulating $\dot{V}_E$ (27). It does not appear an increased distention of the vasculature contributed to the post-acclimation ventilatory response as resting $\dot{V}_E$ was not different between the pre- and post-acclimation trials, as would be expected if the increase in PV had influenced post-acclimation $\dot{V}_E$.

In conclusion, following heat acclimation the initiation of an increase in $\dot{V}_E$ during a passively-induced hyperthermia in humans was shifted to a significantly lower core temperature, similar to the onset of cutaneous vasodilatation and eccrine sweating. In addition, even though overall $\dot{V}_E$ at each level of T_{es} was not modified by HA, the modification of the breathing pattern of the hyperthermic-induced increase in $\dot{V}_E$ appeared to be in order to enhance respiratory heat loss and thus contributing to increased cranial heat loss. These adaptation are in agreement with the hypothesis that hyperthermic hyperventilation is a thermoregulatory heat loss response in humans.

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Table 3.1 Individual and mean characteristics of the participants.

Participant	Age (y)	Height (m)	Weight (kg)	BMI ($kg \cdot m^{-2}$)
1	29	1.80	82.8	25.6
2	21	1.70	67.2	23.3
3	29	1.75	80.2	26.1
4	23	1.60	68.5	26.8
5	25	1.80	72.6	22.4
6	30	1.86	73.3	21.2
7	22	1.68	59.8	21.2
8	23	1.88	65.9	18.7
9	19	1.85	72.6	21.2
10	19	1.73	72.4	24.2
Mean *(SD)*	**24** *(4.11)*	**1.77** *(0.09)*	**71.5** *(6.7)*	**23.1** *(2.6)*

Table 3.2 A: Pre- and post-acclimation individual and mean (SD) esophageal temperature thresholds (°C) for CBV_{TEMPLE}, $\dot{E}_{sw}$ and $\dot{V}_E$ along with the sensitivity to an increase in T_{es} for CBV_{TEMPLE} (arbitrary units·°C^{-1}) and $\dot{V}_E$ (L·min^{-1}·°C^{-1}). Additionally included are the τ (°C) and estimated maximal steady state $\dot{E}_{sw}$ ($\Delta\dot{E}_{sw}$(ss); mg·s^{-1}·m^{-2}) for 7 participants. **B:** Table of values for the same variable as in A for 3 participants excluded from the calculation of the mean ± SD in A. Participant 1 was excluded because his post-acclimation $\dot{V}_E$ sensitivity was greater than 4 SD above the mean; participant 4 was excluded because he showed no increase in $\dot{V}_E$ during either the pre- or post-acclimation trials; and participant 10 was excluded because he showed an increase in $\dot{V}_E$ during only the post-acclimation trial.

A:

		Pre-Acclimation				Post-Acclimation			
Participant		**CBV_{TEMPLE}**	**$\dot{E}_{sw}$**	**$\Delta\dot{E}_{sw}$(ss)**	**$\dot{V}_E$**	**CBV_{TEMPLE}**	**$\dot{E}_{sw}$**	**$\Delta\dot{E}_{sw}$(ss)**	**$\dot{V}_E$**
2	Threshold:	37.33	37.48	2.07	38.97	37.45	37.39	1.29	38.97
	Sensitivity:	*741.53*	*0.28*		*43.28*	*321.83*	*0.11*		*28.32*
3	Threshold:	37.49	37.66	1.82	38.45	37.21	36.80	1.96	38.41
	Sensitivity:	*522.12*	*0.49*		*9.42*	*179.11*	*0.82*		*22.73*
5	Threshold:	37.39	37.82	1.79	38.06	37.15	37.32	1.82	38.11
	Sensitivity:	*349.72*	*0.20*		*7.94*	*391.75*	*0.37*		*12.72*
6	Threshold:	37.29	37.46	1.89	38.60	37.13	37.18	2.31	37.71
	Sensitivity:	*236.35*	*0.82*		*30.18*	*181.21*	*0.99*		*3.62*
7	Threshold:	37.51	37.83	1.93	38.12	37.12	37.06	1.66	37.85
	Sensitivity:	*458.73*	*0.45*		*7.21*	*257.02*	*0.34*		*9.86*
8	Threshold:	37.24	37.82	1.75	37.82	36.92	37.51	1.79	37.16
	Sensitivity:	*153.37*	*0.31*		*2.52*	*377.41*	*0.40*		*2.21*
9	Threshold:	37.17	37.29	2.08	38.23	37.21	37.42	1.80	38.00
	Sensitivity:	*522.71*	*0.58*		*24.54*	*112.65*	*0.27*		*31.54*
Mean	Threshold:	**37.35**	**37.62**	**1.90**	**38.32**	**37.17***	**37.24***	**1.80**	**38.03***
(SD)		*(0.13)*	*(0.22)*	*(0.13)*	*(0.38)*	*(0.16)*	*(0.25)*	*(0.31)*	*(0.57)*
	Sensitivity:	**426.36**	**0.45**		**17.87**	**260.14**	**0.47**		**15.86**
		(198.05)	*(0.21)*		*(15.06)*	*(107.58)*	*(0.31)*		*(11.76)*

* indicates a significant difference between pre- and post-acclimation conditions with $p \leq 0.05$;

B:

Participant		Pre-Acclimation CBV_{TEMPLE}	Pre-Acclimation $\dot{E}_{sw}$	Pre-Acclimation $\Delta\dot{E}_{sw}$(ss)	Pre-Acclimation $\dot{V}_E$	Post-Acclimation CBV_{TEMPLE}	Post-Acclimation $\dot{E}_{sw}$	Post-Acclimation $\Delta\dot{E}_{sw}$(ss)	Post-Acclimation $\dot{V}_E$
1	Threshold:	37.44	37.38	1.94	37.97	37.16	37.33	1.83	37.74
	Sensitivity:	*325.82*	*0.52*		*31.07*	*684.78*	*0.47*		*55.32*
4	Threshold:	37.42	37.71	1.82	N/A	37.14	37.46	1.81	N/A
	Sensitivity:	*242.50*	*0.39*			*304.50*	*0.40*		
10	Threshold:	37.21	37.39	1.87	N/A	36.89	37.00	1.84	37.53
	Sensitivity:	*536.65*	*0.49*			*354.29*	*0.19*		*1.46*

Table 3.3 Mean (SD) of body temperatures and thermoregulatory responses during un-immersed rest and the maximum values observed during head out immersion passive heating trials (n = 10). Additionally, the rate of T_{es} increase ($\dot{T}_{es}$) was calculated as the difference between the minimum T_{es} observed and the maximum T_{es} achieved, divided by the duration of the T_{es} rise.

	Pre-Acclimation		Post-Acclimation	
	Rest	**@ ~39°C**	**Rest**	**@ ~39°C**
T_{es} (°C)	37.42 *(0.14)*	39.03 *(0.05)*	37.33* *(0.19)*	39.03 *(0.04)*
$\bar{T}_{sk}$ (°C)	31.54 *(0.98)*	39.24 *(0.18)*	30.69* *(1.49)*	39.17 *(0.27)*
T_{TEMPLE} (°C)	33.40 *(1.01)*	36.95 *(0.46)*	33.05$^{¥}$ *(0.94)*	36.68 *(0.54)*
CBV_{TEMPLE} (a.u.)	129.31 *(48.97)*	518.70 *(124.24)*	144.85 *(53.41)*	567.77 *(172.08)*
$\dot{E}_{sw}$ ($mg \cdot m^{-2} \cdot s^{-1}$)	0.09 *(0.03)*	1.96 *(0.16)*	0.10 *(0.02)*	1.95 *(0.15)*
$\dot{T}_{es}$ ($°C \cdot h^{-1}$)	5.36 *(0.74)*		6.10* *(0.51)*	
Plasma Volume Expansion (%)	N/A		20.44† *(12.44)*	

* significant difference between pre- and post-acclimation with $p \leq 0.05$; † significance difference from zero (i.e. baseline levels on acclimation Day 1) with a $p \leq 0.01$; ¥ represents a trend ($0.05 < p \leq 0.10$) for a difference between pre- and post-acclimation tests.

Table 3.4 Mean (SD) of ventilatory and metabolic measurements during un-immersed rest prior and at the end of the passive heating protocol when T_{es} was at its maximum observed (n = 9). Participant 1 was removed because his $\dot{V}_E$ sensitivity was greater than 4 SDs above the mean.

	Pre-Acclimation		**Post-Acclimation**	
	Rest	**@ ~39°C**	**Rest**	**@ ~39°C**
$\dot{V}_E$ ($L \cdot min^{-1}$)	8.85 *(2.11)*	16.14* *(6.17)*	8.91 *(1.83)*	16.59* *(6.19)*
T_I (s)	1.86 *(0.40)*	1.92 *(0.61)*	2.36 *(0.91)*	1.83 *(0.66)*
T_E (s)	2.56 *(0.69)*	1.75* *(0.45)*	3.25 *(1.16)*	1.90* *(0.43)*
T_{TOT} (s)	4.53 *(1.06)*	3.35 *(1.43)*	5.81 *(2.23)*	3.75* *(1.07)*
V_T (L)	0.635 *(0.115)*	0.945* *(0.369)*	0.830¥ *(0.222)*	1.027 *(0.500)*
f ($breaths \cdot min^{-1}$)	14.20 *(3.26)*	17.42 *(4.51)*	11.48¥ *(3.72)*	17.46* *(5.14)*
V_T/T_I ($L \cdot s^{-1}$)	0.36 *(0.08)*	0.56* *(0.21)*	0.38 *(0.12)*	0.58* *(0.22)*
$\dot{V}_A$ ($L \cdot min^{-1}$)	5.65 *(1.45)*	11.35* *(5.61)*	6.12 *(1.37)*	11.62* *(6.16)*
$\dot{V}_D$ ($L \cdot min^{-1}$)	3.19 *(1.06)*	4.79* *(1.42)*	2.79 *(0.97)*	4.96† *(1.40)*
$\dot{V}_D / V_T$	0.46 *(0.09)*	0.39 *(0.11)*	0.39 *(0.09)*	0.39 *(0.14)*
$P_{ET}CO_2$ (mm Hg)	37.42 *(2.54)*	31.68* *(6.58)*	37.80 *(1.48)*	31.65* *(7.06)*
$P_{ET}O_2$ (mm Hg)	99.22 *(4.09)*	112.02* *(10.81)*	100.85 *(2.89)*	113.47* *(9.23)*
$\dot{V}O_2$ ($L \cdot min^{-1}$)	0.214 *(0.06)*	0.274* *(0.082)*	0.250 *(0.067)*	0.280 *(0.074)*
$\dot{V}CO_2$ ($L \cdot min^{-1}$)	0.177 *(0.055)*	0.306* *(0.119)*	0.209 *(0.055)*	0.307* *(0.115)*
RER	0.83 *(0.04)*	1.12* *(0.22)*	0.84 *(0.05)*	1.09† *(0.15)*
HR ($beats \cdot min^{-1}$)	62.26 *(8.22)*	107.88 *(9.52)*	61.31 *(10.22)*	115.86 *(14.30)*

* significant difference between un-immersed rest and when T_{es} was at its maximum observed with a $p \leq 0.05$;
† significant difference between un-immersed rest and when T_{es} was at its maximum observed with a $p \leq 0.001$;
¥ represents a trend for a difference between pre- and post-acclimation with $0.05 < p < 0.10$.

Figure 3.1 Overview of the study protocol using passive heating via head-out immersion in hot water and acclimation performed in a climatic chamber.

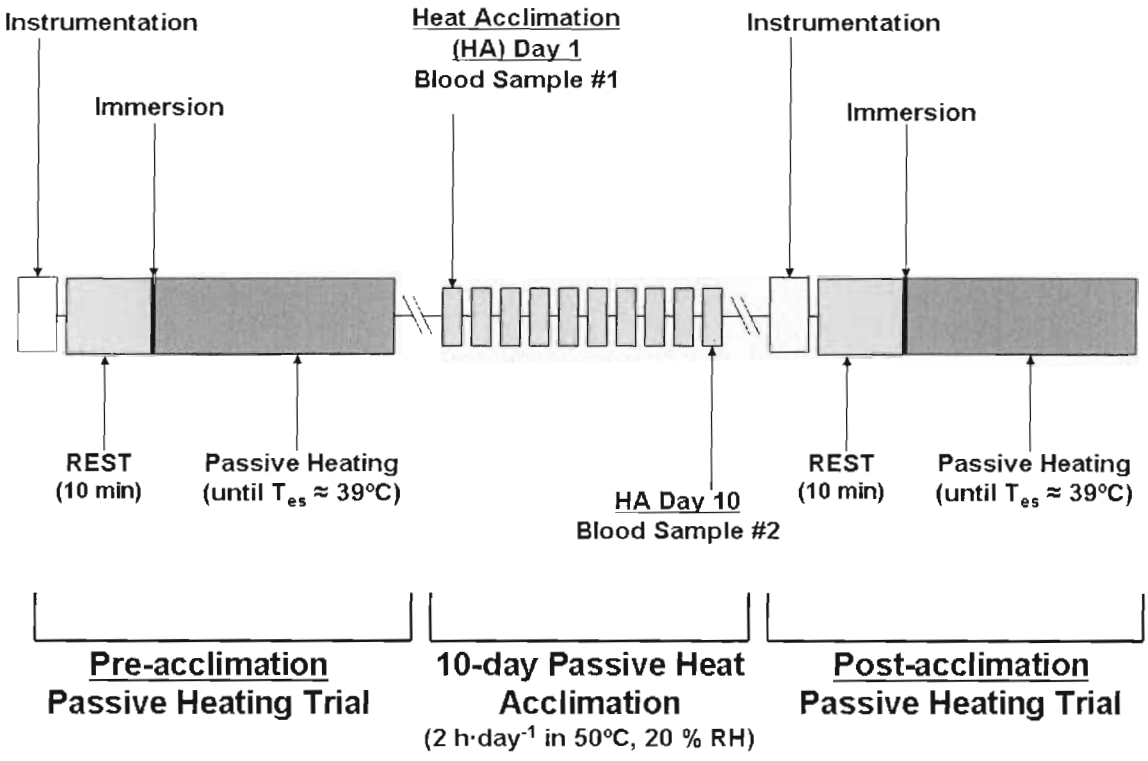


Figure 3.2 Individual mean rectal temperature responses for all 10 heat acclimation sessions. The box shows the range of T_{re} between 38.5 and 39.0°C. Each datum is a 5 min mean and is the mean T_{re} at the same time point averaged over all 10 acclimation days. Error bars represent ± SD.

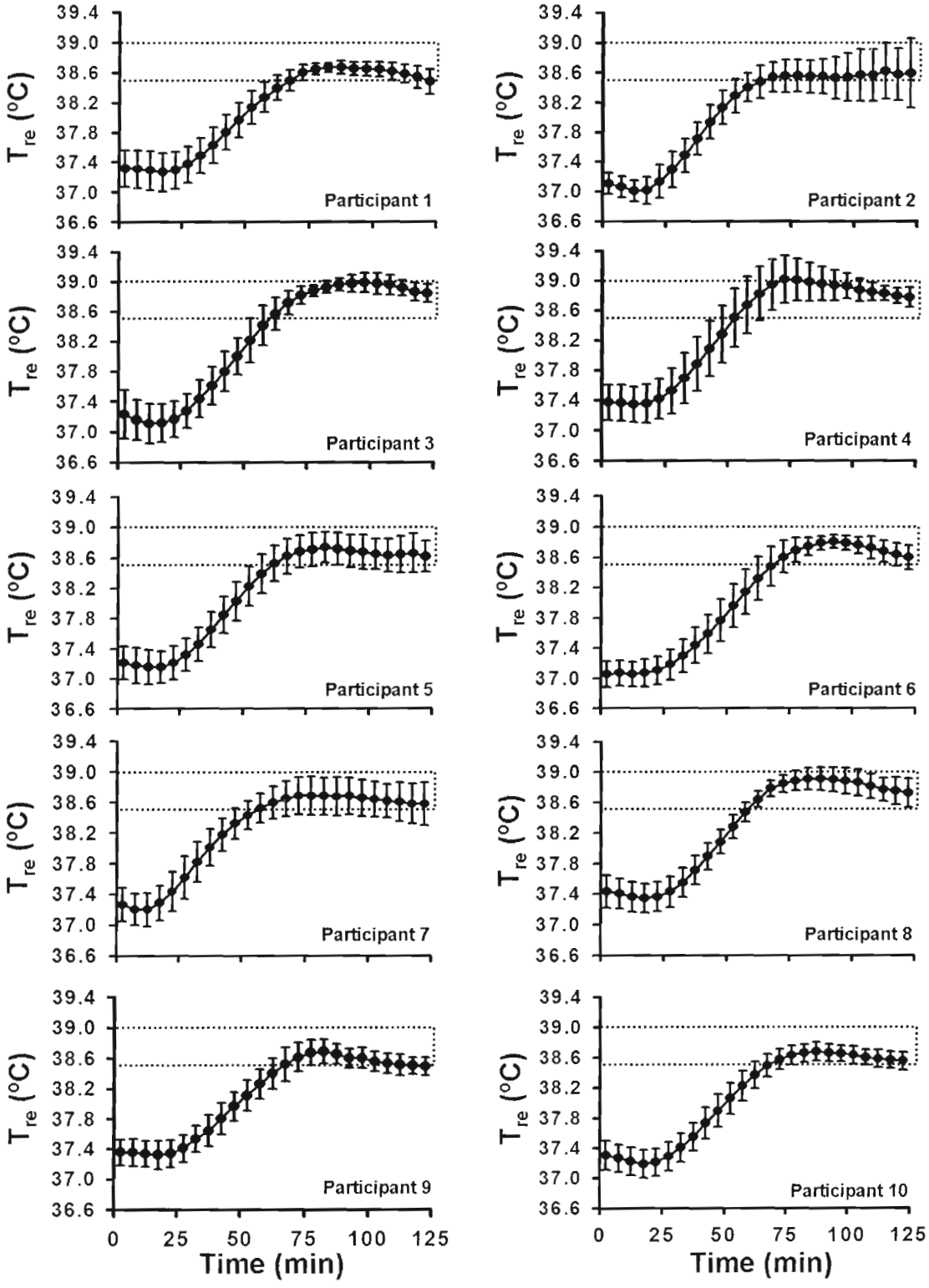


Figure 3.3 Representative response from a single participant for pre- (closed symbols) and post- (open symbols) acclimation passive heating trials. Breath-by-breath values were used to determine individual T_{es} thresholds and sensitivities for each variable. The $\dot{E}_{sw}$ plot **(B)** shows the fitted mono-exponential function (solid line). Arrows indicate pre- (solid) and post- (dashed) acclimation T_{es} thresholds for this participant.

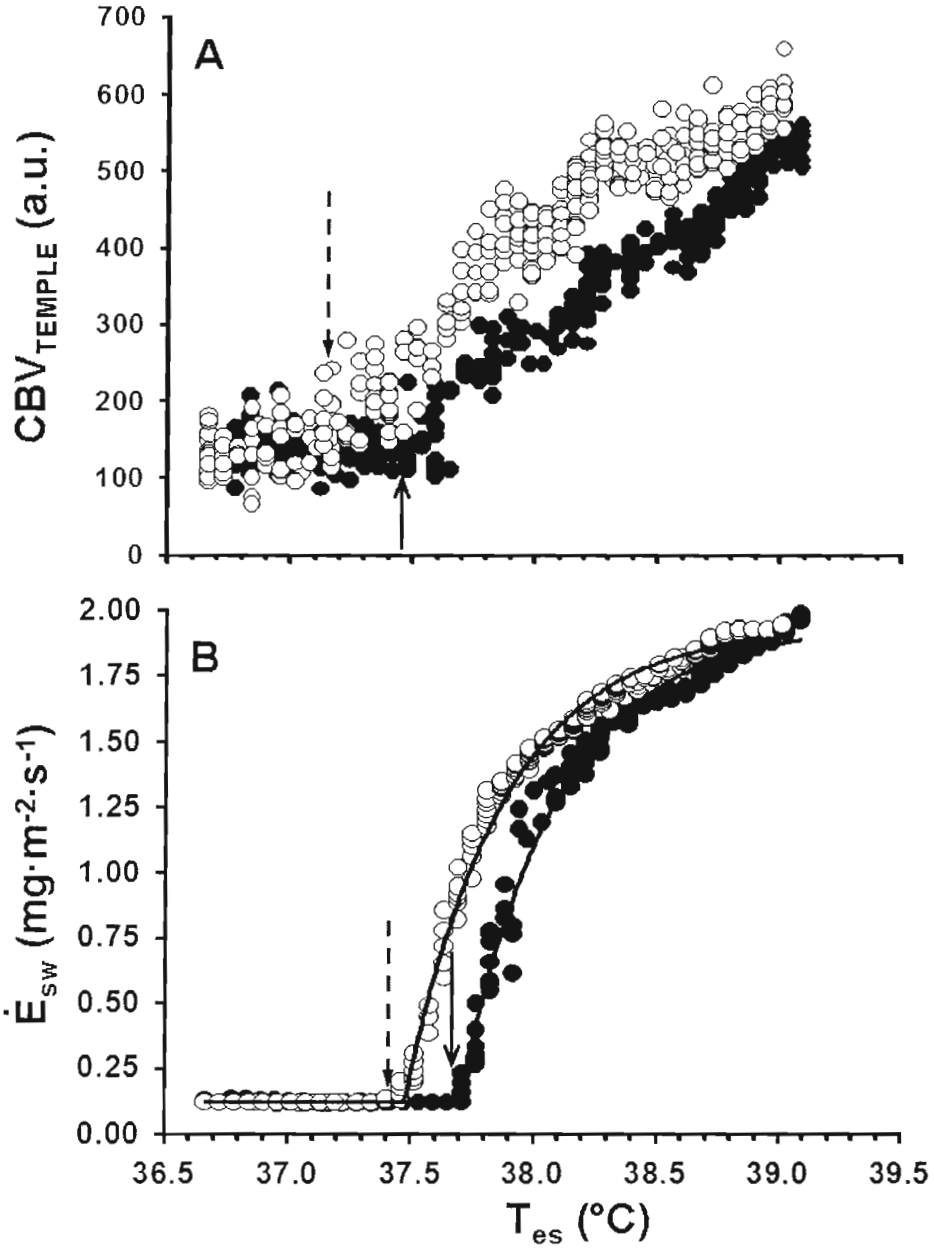


Figure 3.4 Representative plot of ventilation vs. esophageal temperature (T_{es}) from a single participant for pre- (closed symbols) and post- (open symbols) acclimation passive heating trials. Arrows indicate pre- (solid) and post- (dashed) acclimation T_{es} thresholds for this participant.

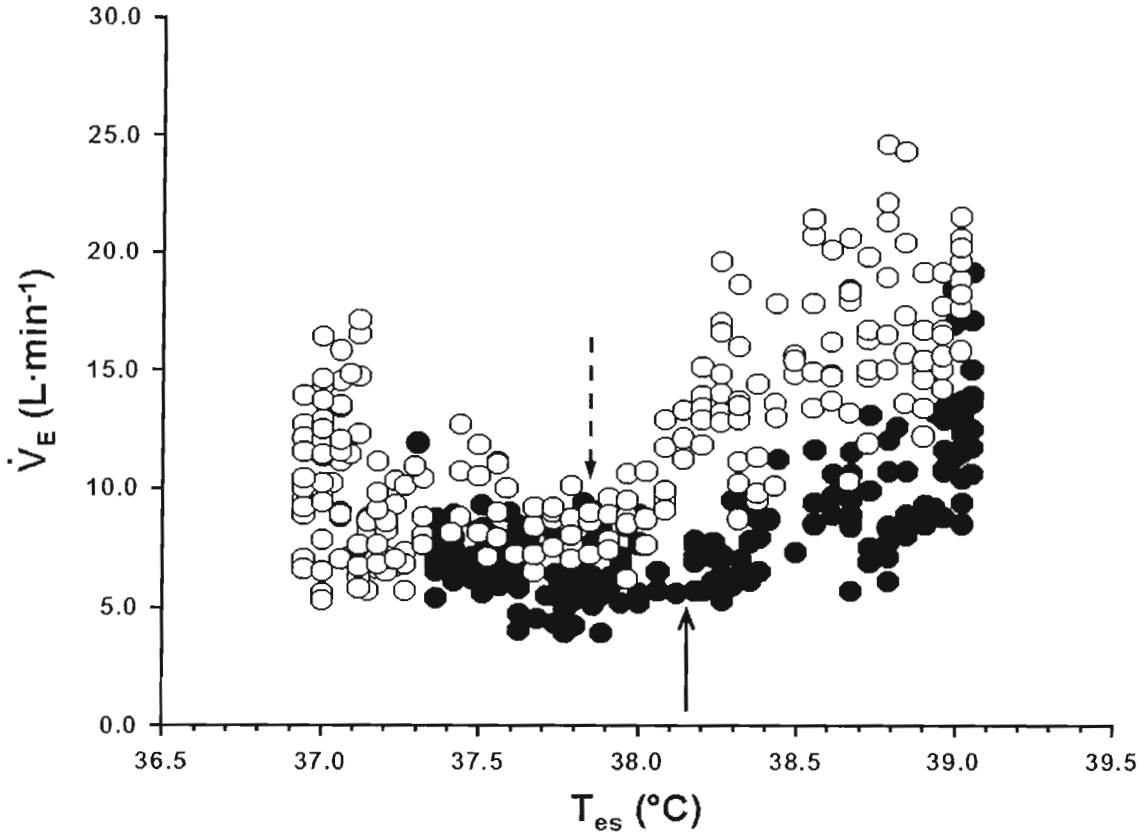


Figure 3.5 A: Mean T_{es} response during the pre- (●) and post- (○) acclimation passive heating protocols; **B:** $\bar{T}_{sk}$ (▲, Δ) during the pre- (closed symbols) and post- (open symbols) acclimation with respect to time; **C:** T_{temple} (■, □) during the pre- (closed symbols) and post- (open symbols) acclimation with respect to time. Each datum is a 10 s mean for 10 participants. Error bars represent ± SD. P-values are shown for the pre- vs. post-acclimation comparison of resting values.

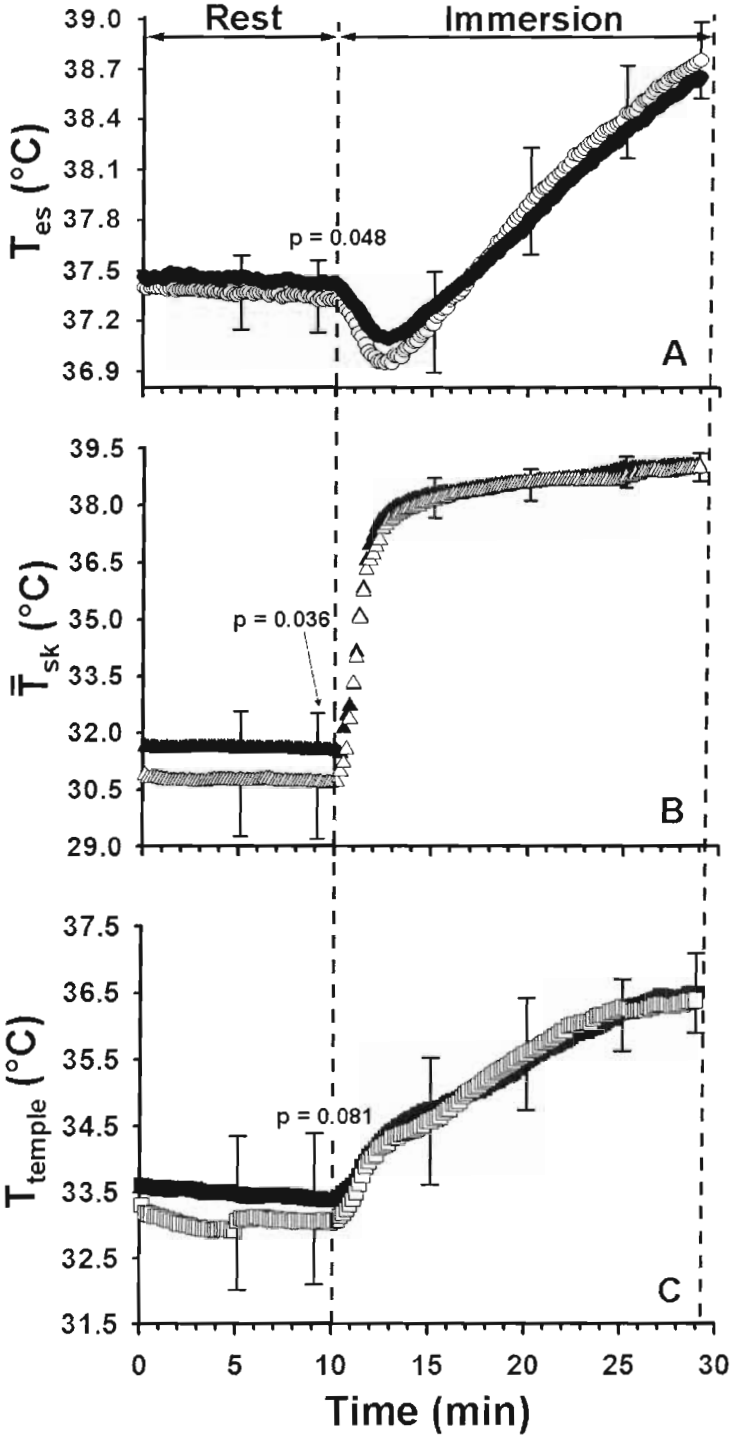


Figure 3.6 Mean T_{sk} (triangles; °C; **A**) and T_{temple} (circles; °C; **A**), CBV_{TEMPLE} (arbitrary units; **B**) and forehead $\dot{E}_{sw}$ ($mg \cdot m^{-2} \cdot s^{-1}$; **C**) at the same absolute T_{es} during the pre- (closed symbols) and the post- acclimation (open symbols) passive heating trials. Error bars represent ±SD and p-values are for comparisons between pre- and post-acclimation responses at the absolute levels of T_{es}. All plots have an n = 9.

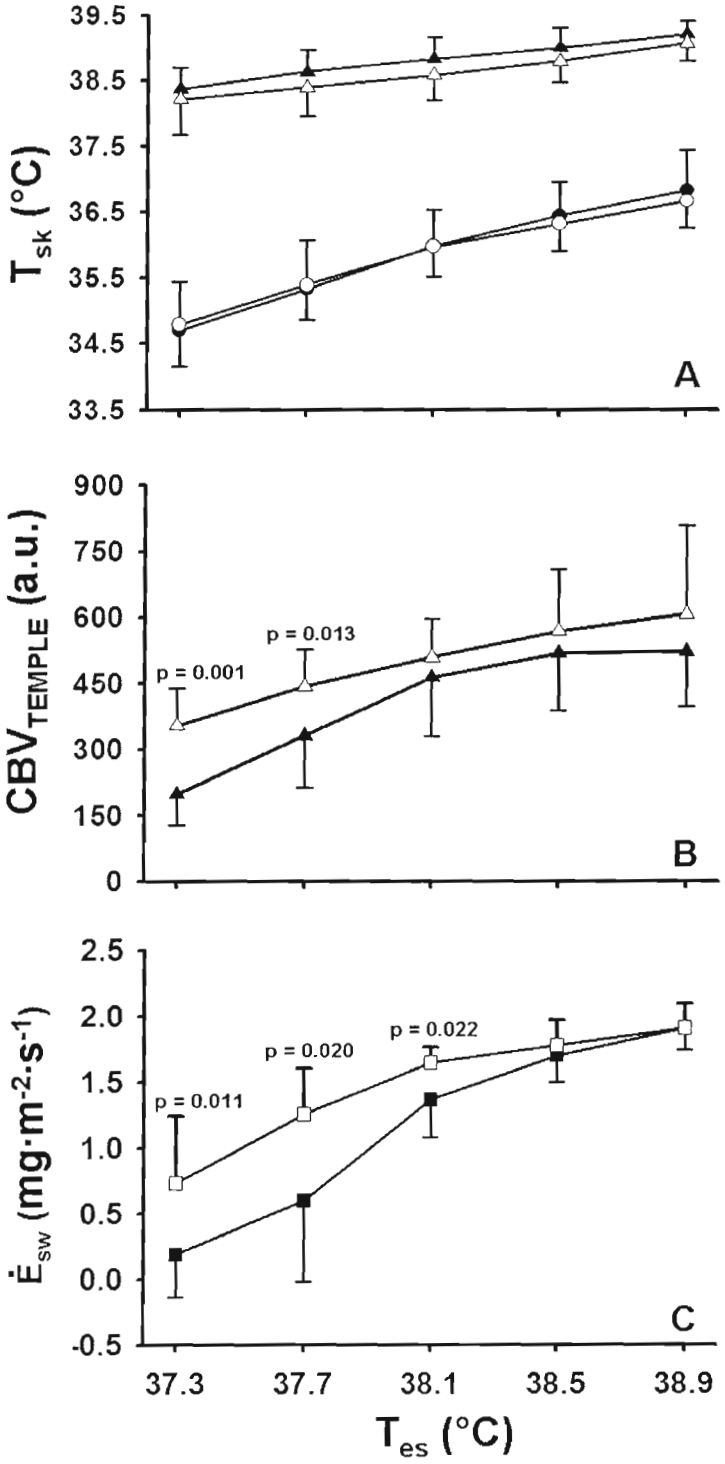


Figure 3.7 Pulmonary ventilation ($\dot{V}_E$), tidal volume (V_T), breathing frequency (f), total breath time (T_{TOT}), inspiratory time (T_I) and expiratory time (T_E) at the different levels of absolute T_{es} during the pre- (closed symbols) and the post- (open symbols) acclimation passive heating protocols. P-values are for comparisons between pre- and post-acclimation conditions. All plots are for n = 9.

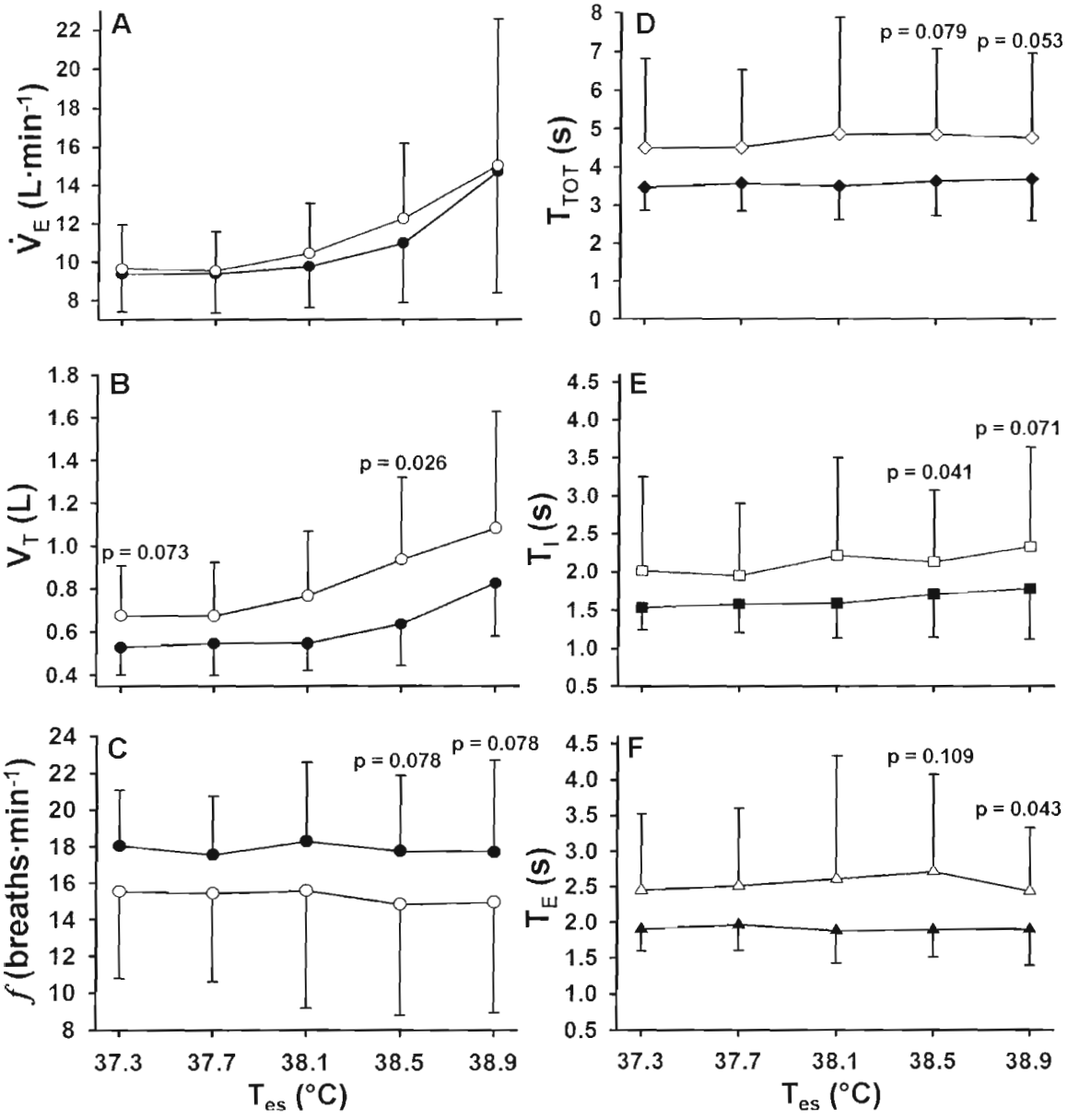


Figure 3.8 Alveolar ventilation ($\dot{V}_A$), dead space ventilation ($\dot{V}_D$) as well as the end-tidal partial pressure of CO_2 ($P_{ET}CO_2$) and O_2 ($P_{ET}O_2$) plotted as a function of absolute T_{es} during the pre – (closed symbols) and the post-acclimation (open symbols) passive heating tests. P-values given are for pre- and post-acclimation comparisons at each absolute T_{es}. All plots for are for an n = 9.

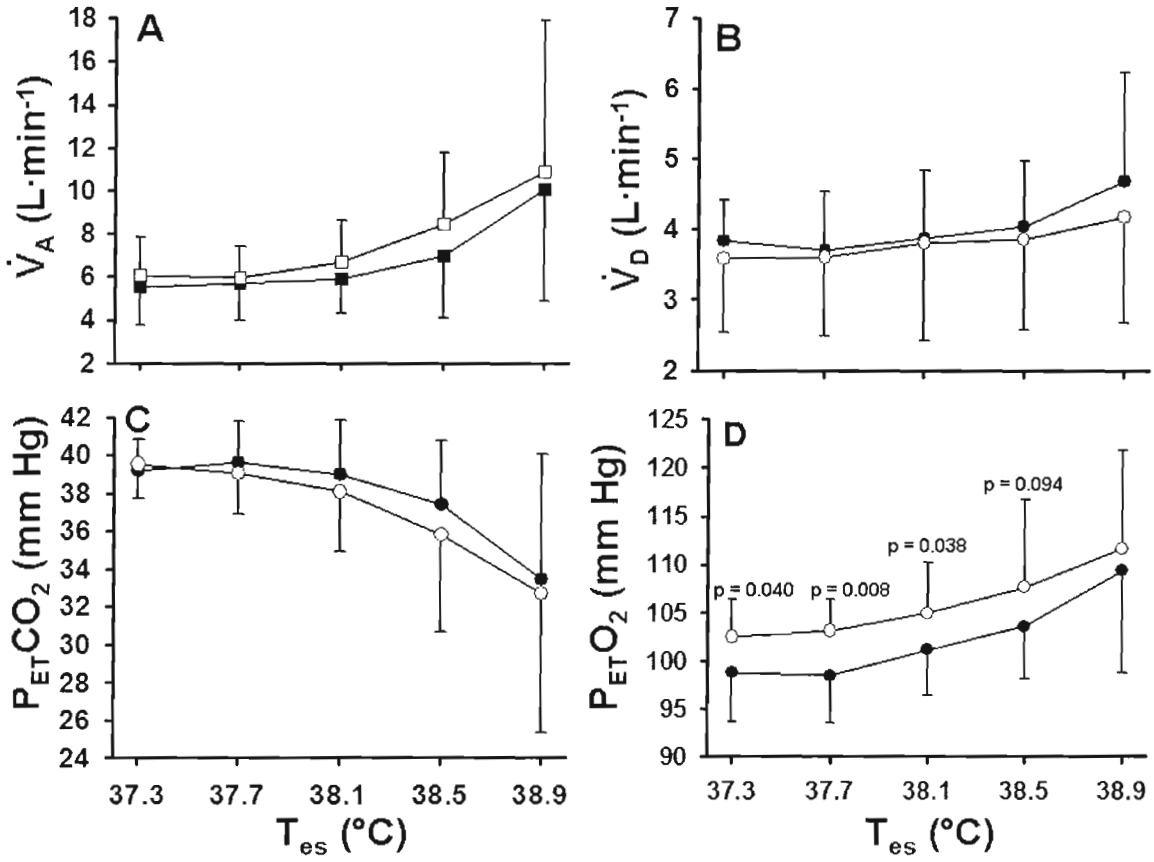


Figure 3.9 Metabolic and cardiovascular measures as a function of T_{es} during the pre- (closed symbols) and post- (open symbols) acclimation passive heating protocols. P-values are given for post hoc comparisons between the pre- and post-acclimation passive heating tests. All plots are for an n = 9.

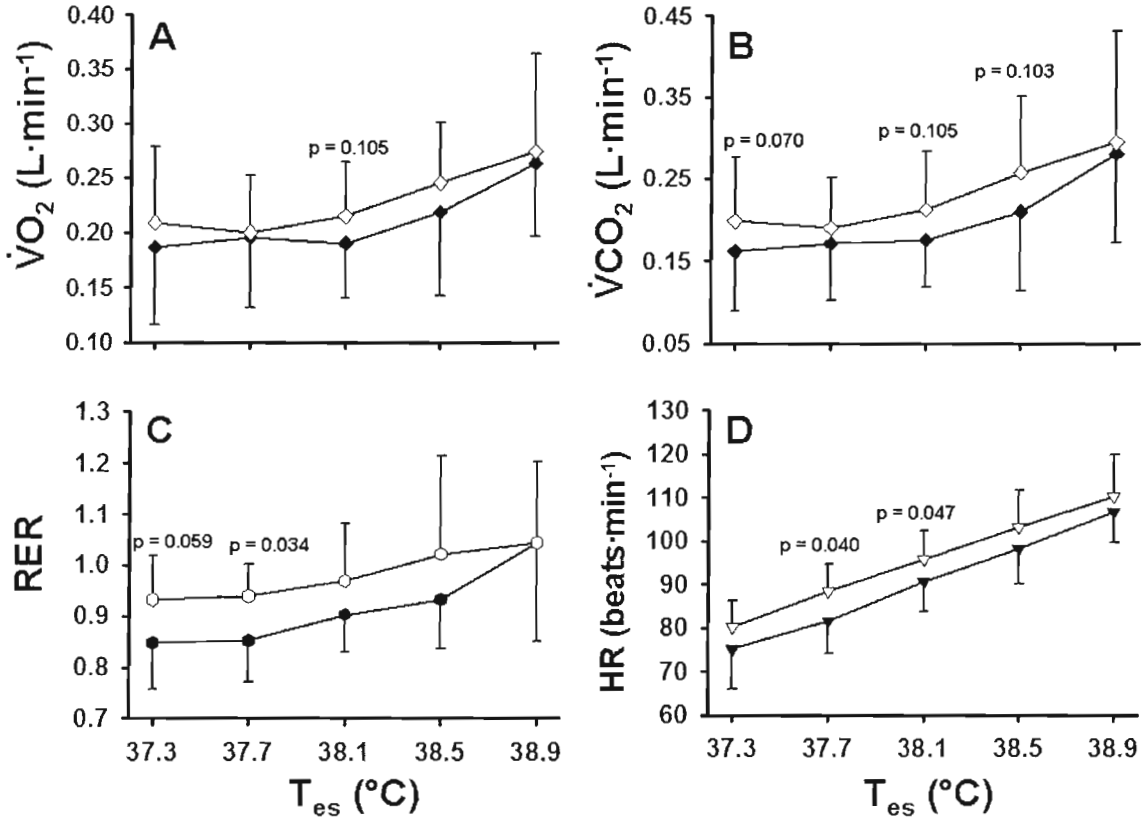
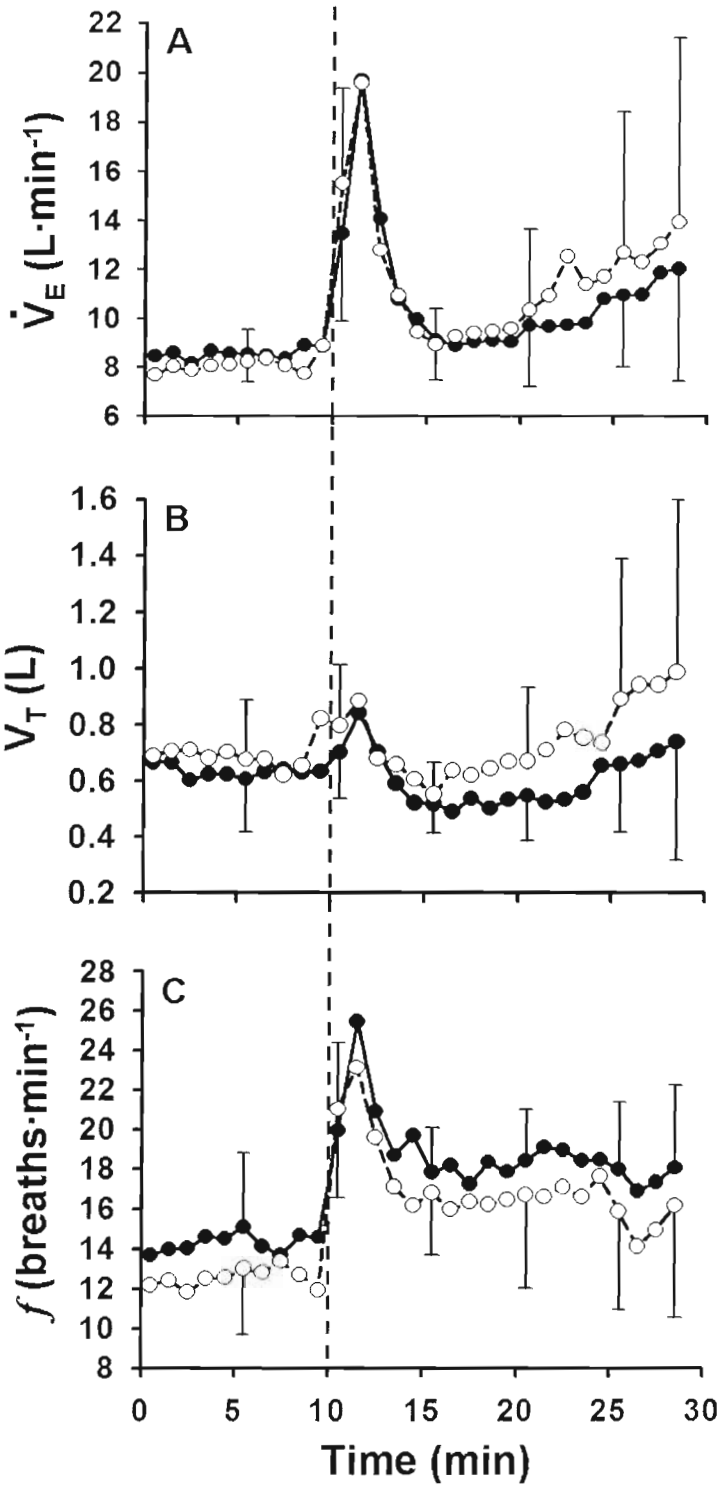


Figure 3.10 Mean $\dot{V}_E$, V_T and f for the pre-and post-acclimation passive heating trials up to the maximum time achieved by all participants to show the change in ventilatory pattern once participants were immersed up to the neck in a 40°C water bath. Dashed line indicates when participants started to move into the tub. Immersion was completed in ~1 min. All plots are for an n = 9.



Chapter 4 – STUDY 2

Ventilatory and thermoregulatory relationships with core temperature during an actively induced hyperthermia after 10 days of passive heat acclimation

Andrew E. Beaudin

Running Head: "Exercise Ventilation, Core temperature and Passive Heat Acclimation."

Keywords: Adaptation, breathing pattern, cutaneous vasodilatation, eccrine sweating, thermal hyperpnea, thermoregulation, threshold.

4.1 Abstract

This study determined whether thermolytic and ventilatory responses during an incremental exercise test from rest to exhaustion adapt similarly following a passive heat acclimation (HA). Ten participants performed 2 exercise tests separated by 10-days of exposure to 50°C and 20 % RH, 2 h·day^{-1} within a climatic chamber. Following HA, the esophageal temperature (T_{es}) thresholds for the onset of increases in cutaneous blood velocity (CBV) and forehead eccrine sweat rate ($\dot{E}_{sw}$) were significantly decreased ($p \leq 0.017$) relative to the pre-acclimation conditions. Similar significant decreases ($p \leq 0.034$) were observed for the T_{es} thresholds for the ventilatory equivalents for O_2 and CO_2. Additionally, following HA there was a significant increase in exercise ventilation ($p \leq 0.017$) across all levels of T_{es} observed. In conclusion, exercise ventilation adapted similarly to the thermolytic responses following HA, providing support for the hypothesis that human hyperthermic-induced increase in ventilation is a thermoregulatory heat loss response.

4.2 Introduction

Human pulmonary ventilation increases linearly with oxygen consumption up to ~70 to 85 % of an individual's maximal attainable work rate. At higher exercise intensities $\dot{V}_E$ increases more rapidly than metabolic rate (8, 14). One physiological rationalization for the disproportionate increase in ventilation at high intensity power outputs is that the central respiratory centre in the medulla oblongata receives additional stimulation from metabolic acidosis and excess carbon dioxide production arising from the buffering of lactic acid by plasma bicarbonate (52). This hypothesis, though, is not fully accepted (8, 14, 23, 38, 48) as other potential modulators of exercise ventilation such as plasma potassium and norepinephrine have been identified (31) and, recently, it has been shown that the buffering of lactic acid is not the sole mechanism for the hyperventilation occurring during high intensity exercise (39). An additional stimuli hypothesized to increase ventilation during high intensity exercise is an increase in body core temperature (T_c) (56, 57).

An increase in T_c of ~1°C stimulates an increase in human ventilation during a passively-induced hyperthermia (10, 19, 24, 44). At low to moderate exercise intensities, it has been suggested exercise ventilation is linearly related to increases in T_c (25) as pulmonary ventilation has been shown to be elevated with a superimposed hyperthermia during prolonged, low (11) or moderate (25) intensity exercise. At high exercise intensities there is a distinct T_c threshold for the disproportionate increase in ventilation during incremental exercise tests from rest to exhaustion (58). The mechanism(s) through which an increased T_c increases ventilation are, also, still under debate (57). One proposed mechanism is that human hyperthermic hyperventilation is a thermoregulatory

heat loss response (10, 58) whereby additional ventilatory drive arrives from the pre-optic anterior hypothalamus during hyperthermia and contributes to the development of selective brain cooling.

Repetitive, daily heat stress, sufficient to significantly raise T_c, for ~2 $h \cdot day^{-1}$ for 7 to 14 consecutive days produces adaptations that serve to augment the body's ability to dissipate heat during periods of heat stress (3, 5, 17, 21, 27, 35, 36, 54). Many heat acclimation studies utilize exercise at ~40 to 60 % of one's maximal oxygen consumption within a hot environment to raise T_c (1, 54). Consequently, following an active heat acclimation protocol the relationship between O_2 consumption and CO_2 production with ventilation may be altered as participants can become endurance trained (30, 43, 47). Hence, when exploring the relationship between ventilation and core temperature before and after heat acclimation one must eliminated such exercise training influences on the ventilation:T_c relationship. One way to eliminate the influences of such a training effect is to induce heat acclimation passively utilizing a controlled hyperthermia (18). We reasoned if the relationship between ventilation and core temperature is altered following a passive heat acclimation protocol, it would not be masked as a consequence of an endurance training effect.

In this study, it was hypothesized if the hyperthermic-induced increase in human pulmonary ventilation is a thermoregulatory heat loss response, then the relationship between pulmonary ventilation and its components and T_c during an actively-induced hyperthermia (42) would adapt in a similar manner to cutaneous vasodilatation and eccrine sweating after an individual has been passively acclimated to a hot environment.

4.3 Methods

4.3.1 Paricipants

The same ten healthy, university aged males who volunteered for Study 1 also participated in this study as the two studies were run concurrently. The power calculation for the present study was the same as that performed in the previous study. The mean age, height, weight and BMI of the participants were 24.0 ± 4.1 y (mean ± SD), 1.77 ± 0.09 m, 71.5 ± 6.7 kg and 23.1 $kg \cdot m^{-2}$. Participants were non-smokers and asked to refrain from eating, consuming caffeine or alcohol and performing any strenuous exercise a minimum of 4 h prior to all testing sessions. On the first visit to the lab, participants were given a 30 min orientation where they were informed of the protocol, potential risks associated with the study and the instrumentation being utilized. Following a minimum 24 h reflection period, participants signed and submitted an informed consent prior to the first test day. The Office of Research Ethics at Simon Fraser University approved this study.

4.3.2 Instrumentation

Ventilation ($\dot{V}_E$) and its components were measured and recorded in the same manner as previously outlined in Chapter 3.

Measurement of cutaneous blood cell velocity of the right temple (CBV_{TEMPLE}) has also been described earlier in Chapter 3.

Esophageal temperature (T_{es}), rectal temperature (T_{re}) and skin temperature (T_{sk}) measurements were exactly the same as in Chapter 3.

Similarly, forehead eccrine sweat rate ($\dot{E}_{sw}$) was measured using the same set-up and calculation from Chapter 3.

Chapter 3 outlines the protocol employed to draw and analyze the arterialized capillary tube blood samples and the calculation of plasma volume expansion.

Data collection was performed using the same system as in Chapter 3.

The same walk-in climatic chamber was employed for the HA as in Chapter 3.

4.3.3 Protocol

Each participant performed an active heating protocol on an electrically braked cycle ergometer (Jaegar ER900, Erich Jaeger GmBH & Co Wuerzburg, Germany) before and after a 10-day passive heat acclimation protocol. The acclimation protocol has been previously outlined in Chapter 3.

The active heating protocol consisted of an incremental exercise test to exhaustion and followed that used by White & Cabanac (58). Participants dressed in shorts and t-shirt and were instrumented while sitting on the cycle ergometer. Subsequently, there was a 10 min rest period while sitting on the cycle ergometer. Exercise began with a 5 min warm-up consisting of 2 min of pedalling at 40 revolutions per minute (rpm) and a power of 20 watts (W) followed by 3 min at a cadence of 70 rpm and 40 W. Subsequently, the participant was instructed to maintain 70 rpm while the power was increased 40 W every 2 min. The test was concluded when the participant could no

longer maintain 70 rpm, had reached their age predicted maximal HR, a plateau in oxygen consumption was observed or the participant desired to terminate the test. Pre-acclimation tests were performed on the second visit to the lab and post-acclimation tests were performed a mean of 1.80 ± 0.42 days after the conclusion of the acclimation protocol. Mean pre-acclimation ambient conditions were 24.59 ± 1.17°C and 27.13 ± 7.53 % RH (wet-bulb (WB) = 13.55°C) while the post-acclimation conditions were 23.66 ± 0.89°C and 28.24 ± 5.00 % RH (WB = 13.12°C). Figure 4.1 shows a schematic of the entire protocol.

4.3.4 Statistical Analyses

Pre- and post-acclimation core temperature T_{es} thresholds for the increase in CBV_{TEMPLE}, the initiation of eccrine sweating and the increase in the ventilatory equivalents for O_2 ($\dot{V}_E/\dot{V}O_2$) and CO_2 ($\dot{V}_E/\dot{V}CO_2$) were determined by plotting each variable against T_{es}. Breathing frequency *(f)* and tidal volume (V_T) were also plotted against T_{es} in order to determine the T_{es} level at which V_T plateaued and *f* began to increase (42). Thresholds were determined using a piecewise linear regression function (50) written in LabVIEW software (Ver. 7.1, National Instruments, Austin, TX, USA). Additionally, the T_{es} at which V_T plateaued and *f* began to increase were also determined using the same piecewise linear regression program. The rate at which T_{es} increased ($\dot{T}_{es}$) during the active heating protocols was calculated as the difference between the minimum T_{es} observed prior to T_{es} beginning to increase and the maximum T_{es} achieved near the conclusion of the active heating test, divided by the duration of the increasing T_{es}.

The assessment of the sensitivity of CBV_{TEMPLE} and $\dot{E}_{sw}$ to increases in T_{es} has been previously described in Chapter 3. Sensitivities of $\dot{V}_E/\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$, V_T and f to increases in T_{es} were estimated as the slope of a linear regression fitted to the suprathreshold data. Correlated one-tailed t-tests were employed to compare pre- and post-acclimation T_{es} thresholds and sensitivities with $\alpha \leq 0.05$.

Ventilation and its parameters, along with $\bar{T}_{sk}$, CBV_{TEMPLE} and $\dot{E}_{sw}$ were analyzed using two 2-way repeated measures ANOVA (n = 8) using factors of a change in Absolute T_{es} (Levels: 37.40, 37.60, 37.80, 38.00 and 38.20°C) and Acclimation State (Levels: pre and post). Two participants who had the smallest increase in T_{es} during both the pre- and post-acclimation incremental exercise tests from rest to exhaustion were removed in order to expand the range of core temperatures available for the analysis. If there was a significant main effect of Acclimation State and/or interaction between Absolute T_{es} and Acclimation State, post hoc comparisons at each level of T_{es} were performed using correlated t-tests. Statistical analysis was performed with SPSS 15.0 (SPSS Inc, Chicago, Illinois, USA) and a Bonferonni correction factor was employed to maintain the *a priori* alpha (α) level of 0.05.

4.4 Results

Table 4.1 shows the individual and mean pre- and post-acclimation resting T_{es}, maximum T_{es} achieved and $\dot{T}_{es}$. The mean resting T_{es} and maximum T_{es} achieved were significantly lower ($p \leq 0.030$) during the post-acclimation trials. Additionally, the $\dot{T}_{es}$ was not significantly different ($p = 0.311$) between the pre- and post-acclimation trials.

Individual pre- and post-acclimation T_{es} thresholds for the increase in CBV_{TEMPLE} and the initiation of $\dot{E}_{sw}$ along with the sensitivity of CBV_{TEMPLE} to increases in T_{es}, $\dot{E}_{sw}$ sensitivity (τ) and estimated maximal steady-state output ($\Delta\dot{E}_{sw}(ss)$) are shown in Table 4.2. The mean post-acclimation T_{es} threshold for both CBV_{TEMPLE} and $\dot{E}_{sw}$ were significantly lower ($p \leq 0.030$) than those observed prior to acclimation. The sensitivity of CBV_{TEMPLE} was not significantly different ($p = 0.452$) during the post-acclimation trials when compared to the pre-acclimation trials. Similarly, the mean post-acclimation τ and $\Delta\dot{E}_{sw}(ss)$ were not significantly different ($p \geq 0.139$) from the pre-acclimation response. Figure 4.2 is a representative $\dot{E}_{sw}$ vs. T_{es} plot used to ascertain the T_{es} threshold and fitted with the mono-exponential function.

Plasma volume ($n = 7$) was significantly increased ($p = 0.005$) by a mean of 20.44 ± 12.66 % above baseline levels by the 10^{th} day of HA.

Figure 4.3 shows representative pre- and post-acclimation breath-by-breath plots for $\dot{V}_E/\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$, V_T and f vs. T_{es} used to determine T_{es} thresholds and sensitivities. Heat acclimation resulted in a significant decrease ($p \leq 0.034$) in the mean T_{es} thresholds for $\dot{V}_E/\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$, V_T and f (Table 4.3). The mean sensitivities of $\dot{V}_E/\dot{V}O_2$ and

$\dot{V}_E/\dot{V}CO_2$ to increases in T_{es} were lower following HA, but the difference did not reach significance ($p \geq 0.139$; Table 4.3). Similarly, the mean sensitivity of V_T to increases in T_{es} was lower following HA, but also failed to reach significance ($p = 0.129$) and there was a trend ($p = 0.088$) for the sensitivity of the f:T_{es} relationship to be lower during the post-acclimation heating protocol.

Figure 4.4 shows the mean T_{es} and $\overline{T}_{sk}$ responses during the pre- and post-acclimation active heating trials up to the maximum time achieved by all participants. Following HA, mean T_{es} was significantly lower at rest (Table 4.1) and during the incremental exercise test from rest to exhaustion remained lower than the corresponding mean T_{es} observed during the pre-acclimation heating protocol (Figure 4.4 A). Although $\overline{T}_{sk}$ was lower throughout the entire post-acclimation trial, it was not significantly different than that observed during the pre-acclimation trial (Figure 4.4 B). Additionally, when $\overline{T}_{sk}$ was analyzed according to levels of Absolute T_{es} and Acclimation State, the acclimation main effect, irrespective of changes in Absolute T_{es}, was not significant ($F_{(1,7)} = 0.05$; $p = 0.827$). Therefore, at the same mean T_{es} during the pre- and post-acclimation trials, $\overline{T}_{sk}$ was not significantly different.

Figure 4.5 shows the relationship between CBV_{TEMPLE} and $\dot{E}_{sw}$ with the absolute levels of T_{es} during the pre- and post-acclimation active heating trials. Acclimation State did not have a significant effect on CBV_{TEMPLE} ($F_{(1,7)} = 0.42$; $p = 0.844$), but it did have a significant effect on $\dot{E}_{sw}$ ($F_{(1,7)} = 10.41$; $p = 0.015$). Following acclimation, $\dot{E}_{sw}$ was significantly higher ($p \leq 0.040$) at a T_{es} of 37.4, 37.6 and 37.8°C and even though the

difference did not reach significance, there was a trend ($p = 0.097$) for $\dot{E}_{sw}$ to be higher at a T_{es} of 38.0°C.

Acclimation significantly increased $\dot{V}_E$ ($F_{(1,7)} = 70.95$; $p < 0.001$) at all levels of T_{es} observed during the post-acclimation active heating trials compared to pre-acclimation values (Figure 4.6 A). In addition, there was a significant interaction between changes in Absolute T_{es} and Acclimation State for V_T ($F_{(4,28)} = 3.11$; $p = 0.024$) and a significant main effect of Acclimation State on f ($F_{(1,7)} = 72.80$; $p < 0.001$). Initially, V_T was significantly higher ($p = 0.003$) at a T_{es} of 37.4°C and remained higher, although not significant ($p \geq 0.122$) when the T_{es} was 37.6 and 37.8°C. At a T_{es} of 38.0 and 38.2°C, V_T became similar to that observed during the pre-acclimation trials (Figure 4.6 B). Oppositely, f was not significantly different at the lower levels of T_{es}, but was significantly higher ($p \leq 0.005$) at the two highest levels of T_{es} during the post-acclimation trials (Figure 4.6 C). Furthermore, the interaction between changes in Absolute T_{es} and Acclimation State had a significant effect ($F_{(4,28)} = 12.08$; $p = 0.003$) on $P_{ET}CO_2$ (Figure 4.7 A). Post-acclimation $P_{ET}CO_2$ was significantly higher ($p \leq 0.013$) at 37.40 and 37.60°C, but was not significantly different ($p = 0.279$) at a T_{es} of 37.80°C. At a T_{es} of 38.00 and 38.20°C there was a trend ($p \geq 0.066$) for $P_{ET}CO_2$ to be lower following HA. Additionally, the Acclimation State main effect was significant for $P_{ET}O_2$ ($F_{(1,7)} = 20.42$; $p = 0.003$; Figure 4.7 B) as $P_{ET}O_2$ was significantly higher ($p \leq 0.026$) at all levels of T_{es} except for at 37.80°C where there was a trend for it to be higher ($p = 0.054$). Figure 4.7 C shows that RER was also significantly higher ($p \leq 0.018$) at all levels of T_{es} except at 38.2°C.

Figure 4.8 A shows the time course of $\dot{V}O_2$ during the pre- and post-acclimation active heating trials for one representative participant. The $\dot{V}O_2$ response was almost identical between within both trials. Similarly, Figure 4.8 B shows that the relationship between $\dot{V}_E$ and $\dot{V}O_2$ was, also, very similar between the pre- and the post-acclimation active heating protocols for the same representative participant.

4.5 Discussion

This study provides additional support for the hypothesis that human hyperthermic hyperventilation is a thermoregulatory heat loss response as the $\dot{V}_E$:T_{es} relationship during an active heating protocol adapted in similar manner as the CBV_{TEMPLE} and $\dot{E}_{sw}$ when expressed as a function of T_{es} following HA. The magnitude of the decrease in the T_{es} thresholds for increases in $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ and the decrease in the T_{es} at which V_T plateaued and f began to increase were similar to those observed for increases in CBV_{TEMPLE} and the initiation of eccrine sweating within the present study and previous HA studies (4, 9, 17, 26, 46).

The most recommended and employed method of HA is to exercise at 40 to 60 % $\dot{V}O_{2max}$ for up to 2 $h \cdot day^{-1}$ within a hot environment (1, 5, 54). The benefit of this method is it produces greater thermal strain on the thermoregulatory system by the resultant increase in T_c and, therefore, is believed to produce a greater degree of HA (3, 54). In this study, a passive HA protocol employing controlled hyperthermia (17, 18, 26, 27) was utilized in order to induce a sufficient increase in T_{es} to stimulate the acclimation process and to remove the potential of introducing an endurance training effect frequently accompanying active HA (3, 28, 30, 43, 47). Following HA, the post-acclimation mean $\dot{V}O_2$ was minimally lower (~0.064 $L \cdot min^{-1}$) when averaged over the maximum duration of the active heating protocol achieved by all participants. This decrease was likely the result of a lower Q_{10} as a result of the lower T_{es} maintained throughout the post-acclimation trials (2). In addition, the relationships between $\dot{V}_E$, $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ with $\dot{V}O_2$ were unaltered following HA (Figure 4.8 B and C) and, therefore, the passive HA appeared to have successfully prevented inducing a training effect.

The control for a training effect was important because, even though not agreed upon (8), $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ are believed to reflect the anaerobic threshold when expressed as a function of exercise duration (7, 51) and endurance training can shift the anaerobic threshold to a higher metabolic rate (33). Hence, when $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ were plotted against T_{es}, the observed shift in the $\dot{V}_E$:T_{es} relationship may have been obscured or minimized by a training effect shifting $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ in the opposite direction, if they truly reflect the anaerobic threshold. The two possible solutions were: 1) to use highly trained endurance athletes; or 2) utilize a passive HA protocol. The latter was chosen because endurance training in a temperate environment has been shown to induce some degree of HA (35, 41) and therefore, the significant degree of HA achieved via the passive HA protocol may not have been possible with highly trained endurance athletes using an active HA protocol.

After surpassing the T_{es} thresholds, mean $\dot{E}_{sw}$ and $\dot{V}_E$ were both higher at a given T_{es} during the post-acclimation active heating trial (Figure 4.5 and 4.6, respectively). Thus, $\dot{V}_E$ began to rise above metabolic rate at a lower T_c and was higher at a given T_{es}. Even though exercise chemosensitivity was not measured directly in this study, the higher post-acclimation $\dot{V}_E$ at the given levels of T_{es} may have been the result of an increased sensitivity to CO_2 following HA as chemosensitivity has been shown to increase during exercise (53). This would be similar to what we observed during the passive heating protocol in Chapter 3. At a T_{es} of 37.40 and 37.60°C, $\dot{V}_E$ was 11.30 and 6.57 $L \cdot min^{-1}$ higher during the post-acclimation active heating protocol. It is unlikely the higher mean $P_{ET}CO_2$ by 2.16 and 1.37 mm Hg at 37.40 and 37.60°C, respectively, during the post-acclimation trials would provide sufficient stimuli to the respiratory centre to

produce such large increase in $\dot{V}_E$ (15). Ventilation was also significantly higher at the remaining levels of T_{es} observed (37.80, 38.00 and 38.20°C) even though post-acclimation $P_{ET}CO_2$ was either not significantly different or even tended to be lower than the pre-acclimation levels. Further support for an augmented chemosensitivity to CO_2 following acclimation was that $P_{ET}O_2$ was significantly higher during the post-acclimation trials at all levels of T_{es} except 37.80°C, where there was only a trend, and this would presumably have provided a small depressant affect on $\dot{V}_E$ via suppression of the carotid bodies (20), which was not observed.

As a result of the greater $\dot{V}_E$ at all levels of T_{es}, respiratory heat loss (RHL) would have been greater during the post-acclimation trials as compared to pre-acclimation levels. Utilizing the equation from Varene & Kays (49) with a conversion factor to convert kJ to watts (W) and, for simplicity, the assumptions that the temperature of expired air was ~32°C and 100 % saturated with water vapour (i.e., 100 % RH) (13, 34) the mean RHL during the post acclimation trials over all levels of absolute T_{es} observed was ~10.73 W greater than what was achieved during the pre-acclimation trials. Cabanac & White (10), utilizing a passive heating protocol, observed an increase in $\dot{V}_E$ of ~9 $L \cdot min^{-1}$ above resting levels which, utilizing the same equation, would have increased RHL by ~13.16 W and this was observed to be adequate for tympanic temperature (employed as an index of brain temperature) to be ~0.3°C lower than T_{es} (i.e., trunk temperature). Therefore, the mean increase in RHL of ~10.73 W observed during the post-acclimation trials in the present study would appear to be sufficient to produce a greater degree of selective brain cooling during the post-acclimation trials.

The lower T_{es} threshold for an increase in $\dot{V}_E$ following HA is similar to what was observed in Chapter 3 where a passively-induced hyperpnea was also initiated at a lower T_{es} following HA. The magnitude of the T_{es} threshold decrease of ~0.30°C within the present study was comparable to the ~0.20°C decrease for the hyperthermic-induced increase in $\dot{V}_E$ observed in Chapter 3, Study 1. Within the passive heating protocol, the observation that $\dot{V}_E$ was unchanged during the post-acclimation trials as compared to the pre-acclimation trials even though $P_{ET}CO_2$ was lower or at the same absolute levels of T_{es} was theorized to be the result of an increased sensitivity of the peripheral and central chemosensitive tissues to CO_2. The significance of the ventilatory adaptations observed following HA in the present study is that, similar to what was observed within Study 1, the $\dot{V}_E$:T_{es} relationship adapted in the same manner as the thermoregulatory heat loss measures of cutaneous blood flow and eccrine sweating. Hence, these results support the proposal that exercise ventilation in humans adapts like it is a thermoregulatory heat loss response following HA. Moreover, the enhanced $\dot{V}_E$ at a given T_{es} appears to be, possibly, the result of an increased sensitivity to CO_2, but this still needs to be determined quantitatively with assessment of exercise chemosensitivity before and after HA.

The results of this study are difficult to compare to other results in the literature because, aside from study 1, to the authors' knowledge, there have been no previous studies to directly explore the relationship between $\dot{V}_E$ and T_{es} prior to and following acclimation to the heat. Previous studies that report $\dot{V}_E$ data during an exercise heat-stress tests following HA have either, one, only reported $\dot{V}_E$ data from the post-acclimation trial (40, 43, 45) or, two, examined $\dot{V}_E$ during sub-maximal, steady state exercise within a hot environment and only compared the pre- and post acclimation $\dot{V}_E$

and T_{es} responses as a function of exercise duration (1, 29, 30). None of these studies directly examined changes in pulmonary ventilation as a function of T_{es}.

The above modifications of the $\dot{V}_E$:T_{es} were considered to be adaptations resulting from HA as participants were considered to be acclimated by the presence of several well known thermoregulatory adaptations during the post-acclimation trials (5, 16, 17, 26, 30, 54). The first indication was the 0.30°C decrease in resting T_{es} from the pre- to the post-acclimation trials (Table 4.1) and the second indication was the significant decrease in the T_{es} thresholds for the increase in CBV_{TEMPLE} and the onset of $\dot{E}_{sw}$ by 0.22 and 0.25°C, respectively (Table 4.2). The magnitude of these decreases were similar to previous reports of successful HA studies (4, 9, 17, 18, 26, 37, 46). Third, the higher $\dot{E}_{sw}$ for a given T_{es} following HA is also typically observed with successful HA protocols (3, 5, 54).

Two additional adaptations occasionally used as criteria for successful HA are an increased sensitivity of the $\dot{E}_{sw}$:T_c relationship and a higher maximal sweat production (54). Neither of these adaptations occurred within the present study. Rather, the pre- and post-acclimation mean τ and estimated maximal sweat production ($\Delta\dot{E}_{sw}(ss)$) were not significantly different (Table 4.2) between the pre- and post-acclimation trials. These observations were consistent with the literature as an increase in $\dot{E}_{sw}$ sensitivity is not consistently reported with HA (5, 22, 27, 41) and changes in the eccrine sweating response are some of the last adaptations to occur (6). Patterson et al (37) showed a change in $\dot{E}_{sw}$ sensitivity may take more than 10 days of HA to occur and when sweat sensitivity tests are performed within an ambient temperature similar to the ambient

temperature employed in the present study, an increased $\dot{E}_{sw}$ sensitivity may not be observed following 10 days of HA (35). Finally, the appearance of an increased maximal $\dot{E}_{sw}$ is dependent upon the thermal environment participants were acclimated to and hot-dry conditions such as 50°C and 20 % RH produce only minor increases in sweat output (5, 6, 12, 54).

Two final indications of successful HA were the ~20 % mean expansion in PV and the 0.22°C lower mean maximal T_{es} by the end of the post-acclimation active heating trials (Table 4.1). Plasma volume typically increases by ~3 to 27 % (5, 32, 46, 54) and T_c is ~0.20 to 0.40°C lower at the conclusion of post-acclimation heat stress tests (9, 37, 54). Based on these thermoregulatory and haematological adaptations, participants were considered to be successfully heat acclimated and the changes in the $\dot{V}_E$:T_{es} relationship observed were considered as adaptations to a hot environment.

The rationale for utilizing $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ in determining the T_{es} threshold for hyperthermic hyperventilation during an incremental exercise test to exhaustion has been explained in an earlier study (58). Briefly, since $\dot{V}_E$ can be causally linked to $\dot{V}CO_2$, the ratio of $\dot{V}_E/\dot{V}CO_2$ is utilized to normalize $\dot{V}_E$ to $\dot{V}CO_2$ and any increase in this ratio during incremental exercise tests to exhaustion reflects a greater increase in $\dot{V}_E$ than in $\dot{V}CO_2$ (55). A similar argument may be made for $\dot{V}_E/\dot{V}O_2$.

In conclusion, following heat acclimation, exercise ventilation began to increase at a lower T_{es} and $\dot{V}_E$ was greater at a given T_{es} during an actively induced hyperthermia. The greater post-acclimation $\dot{V}_E$ at a given absolute T_{es} was a result of a higher V_T at

lower levels of T_{es} and then by a greater f at higher levels of T_{es}. These adaptations were similar to those observed with traditionally accepted human thermolytic responses of cutaneous vasodilatation and eccrine sweating. Therefore, these appear to be in agreement with the hypothesis that human hyperthermic hyperventilation is a thermoregulatory heat loss response.

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Table 4.1 Individual and mean (SD) pre- and post-acclimation values for resting T_{es} (°C), maximum observed T_{es} (T_{es} Max; °C) along with rates of T_{es} increase ($\dot{T}_{es}$; °C·h^{-1}) calculated as the difference between the minimum T_{es} and maximum T_{es} observed divided by the duration of T_{es} rise for all participants during an incremental exercise test from rest to exhaustion.

	Pre-Acclimation			Post-Acclimation		
Participant	**Resting T_{es} (°C)**	**T_{es} Max (°C)**	**$\dot{T}_{es}$ (°C·h^{-1})**	**Resting T_{es} (°C)**	**T_{es} Max (°C)**	**$\dot{T}_{es}$ (°C·h^{-1})**
1	37.70	38.47	4.85	37.49	38.64	6.40
2	37.97	38.74	5.29	37.36	38.42	5.30
3	37.33	38.43	6.71	37.12	38.20	5.33
4	37.26	38.33	8.50	37.29	38.26	7.64
5	37.70	38.97	6.43	37.34	38.60	5.40
6	37.64	39.04	8.21	37.23	38.49	6.94
7	37.80	38.48	4.95	37.33	38.04	5.13
8	37.71	38.52	5.37	37.23	37.99	4.56
9	37.40	38.68	5.59	37.20	38.61	5.48
10	37.54	38.60	4.53	37.51	38.80	5.10
Mean	**37.61** *(0.22)*	**38.63** *(0.23)*	**6.04** *(1.39)*	**37.31**† *(0.12)*	**38.41*** *(0.27)*	**5.73** *(0.96)*

* indicates a significant difference between pre- and post-acclimation with a $p \leq 0.05$; † significant pre- vs. post-acclimation difference with $p \leq 0.001$.

Table 4.2 Individual and mean (SD) pre- and post-acclimation T_{es} thresholds (°C) for an increase in CBV_{TEMPLE} and the initiation of eccrine sweating ($\dot{E}_{sw}$) during an incremental exercise test from rest to exhaustion along with the sensitivity of CBV_{TEMPLE} (arbitrary units·°C^{-1}), tau (τ; °C) and the estimated maximum steady state $\dot{E}_{sw}$ ($\Delta\dot{E}_{sw}$(ss); mg·s^{-1}·m^{-2}).

Participant		Pre-Acclimation				Post-acclimation			
		CBV_{TEMPLE}	$\dot{E}_{sw}$	τ	$\Delta\dot{E}_{sw}$(ss)	CBV_{TEMPLE}	$\dot{E}_{sw}$	τ	$\Delta\dot{E}_{sw}$(ss)
1	Threshold:	37.50	37.56	0.54	2.07	37.61	37.32	0.38	1.62
	Sensitivity:	*797.48*				*561.84*			
2	Threshold:	37.98	37.92	0.29	2.20	37.30	37.30	0.44	2.07
	Sensitivity:	*897.38*				*422.09*			
3	Threshold:	37.20	37.47	2.24	3.56	37.09	37.21	1.41	3.07
	Sensitivity:	*753.93*				*92.41*			
4	Threshold:	36.93	36.75	0.28	1.20	37.03	37.09	0.21	1.51
	Sensitivity:	*303.42*				*307.21*			
5	Threshold:	38.25	37.96	0.51	2.01	37.86	37.65	0.30	2.01
	Sensitivity:	*848.68*				*1472.9*			
6[£]	Threshold:	37.50	37.67	0.87	1.91	37.22	37.16	N/A	N/A
	Sensitivity:	*664.17*				*217.76*			
7	Threshold:	37.97	37.91	0.13	1.56	37.37	37.32	0.12	1.41
	Sensitivity:	*526.97*				*634.27*			
8	Threshold:	37.79	37.55	0.35	1.63	37.56	37.50	0.13	1.36
	Sensitivity:	*3544.20*				*1154.98*			
9	Threshold:	37.51	37.45	0.27	1.96	37.50	37.17	0.54	2.09
	Sensitivity:	*469.34*				*1076.22*			
10	Threshold:	37.68	37.59	0.36	1.98	37.59	37.53	0.42	1.75
	Sensitivity:	*393.24*				*553.09*			
Mean *(SD)*	**Threshold:**	**37.64** *(0.41)*	**37.57** *(0.37)*	**0.55** *(0.65)*	**2.02** *(0.66)*	**37.43*** *(0.26)*	**37.34*** *(0.18)*	**0.44** *(0.39)*	**1.88** *(0.53)*
Mean *(SD)*	**Sensitivity:**	**948.29** *(996.41)*				**730.56** *(493.23)*			

* indicates a significant pre/post-acclimation difference with $p \leq 0.05$; [£] participant was excluded from the calculation of the mean (SD) for all variables.

Table 4.3 Individual and mean (SD) values for the T_{es} thresholds (°C) and sensitivities of the ventilatory equivalents for $\dot{V}O_2$ and $\dot{V}CO_2$ (units·°C^{-1}), tidal volume (V_T; L·°C^{-1}) and breathing frequency f (breaths·min^{-1}·°C^{-1}) to increases in T_{es} during the pre- and post-acclimation incremental exercise tests from rest to exhaustion.

		Pre-Acclimation				Post-acclimation			
Participants		$\dot{V}_E/\dot{V}O_2$	$\dot{V}_E/\dot{V}CO_2$	V_T	f	$\dot{V}_E/\dot{V}O_2$	$\dot{V}_E/\dot{V}CO_2$	V_T	f
1	Threshold:	38.11	38.11	37.94	38.17	37.99	37.99	37.55	38.05
	Sensitivity:	*39.11*	*26.82*	*1.06*	*71.73*	*19.98*	*14.25*	*0.66*	*38.07*
2	Threshold:	38.30	38.36	38.18	38.36	37.95	38.09	37.51	38.00
	Sensitivity:	*25.39*	*14.85*	*0.48*	*40.04*	*22.08*	*16.48*	*0.27*	*30.27*
3	Threshold:	37.88	37.88	37.71	37.82	37.63	37.68	37.63	37.63
	Sensitivity:	*17.39*	*10.74*	*0.26*	*35.26*	*20.46*	*11.78*	*-0.17*	*32.88*
4	Threshold:	37.84	37.84	37.02	36.93	37.53	37.65	37.53	37.03
	Sensitivity:	*14.64*	*12.11*	*-0.13*	*22.64*	*14.89*	*11.64*	*0.10*	*26.49*
5	Threshold:	38.64	38.64	38.08	38.64	38.27	38.21	37.86	38.21
	Sensitivity:	*37.93*	*26.09*	*0.28*	*64.72*	*79.99*	*37.33*	*0.48*	*109.22*
6	Threshold:	38.46	38.52	38.58	38.41	37.96	38.07	38.25	38.02
	Sensitivity:	*20.14*	*12.98*	*0.44*	*23.97*	*19.52*	*13.35*	*0.85*	*27.72*
7	Threshold:	38.30	38.30	38.12	38.30	37.73	37.90	37.52	37.73
	Sensitivity:	*68.42*	*56.20*	*-0.46*	*145.39*	*41.12*	*38.37*	*0.05*	*82.00*
8	Threshold:	38.00	38.00	38.00	38.00	37.67	37.85	37.56	37.62
	Sensitivity:	*34.20*	*20.18*	*-0.58*	*53.81*	*13.88*	*9.73*	*1.06*	*269.96*
9	Threshold:	38.30	38.36	38.01	38.36	37.79	37.73	37.67	37.73
	Sensitivity:	*41.93*	*26.17*	*0.97*	*53.94*	*19.15*	*11.27*	*1.61*	*18.25*
10	Threshold:	38.03	38.09	37.57	37.92	37.71	38.09	37.76	38.03
	Sensitivity:	*21.18*	*11.16*	*0.89*	*41.26*	*11.48*	*6.52*	*0.68*	*29.14*
Mean *(SD)*	**Threshold:**	**38.19** *(0.26)*	**38.21** *(0.27)*	**37.92** *(0.42)*	**38.09** *(0.48)*	**37.82**† *(0.22)*	**37.93**† *(0.19)*	**37.68*** *(0.23)*	**37.81*** *(0.34)*
Mean *(SD)*	**Sensitivity:**	**32.03** *(16.10)*	**21.73** *(13.76)*	**0.32** *(0.57)*	**55.28** *(35.53)*	**26.26** *(20.54)*	**17.07** *(11.27)*	**0.56** *(0.53)*	**41.80** *(29.53)*

* indicates significant difference between post- vs. pre-acclimation with $p \leq 0.05$; † indicates significant difference between post- vs. pre-acclimation with $p \leq 0.001$

Figure 4.1 Overview of the entire study protocol. An incremental exercise test form rest to exhaustion was performed prior to and following 10 days of passive heat acclimation employing controlled hyperthermia performed within a climatic chamber..

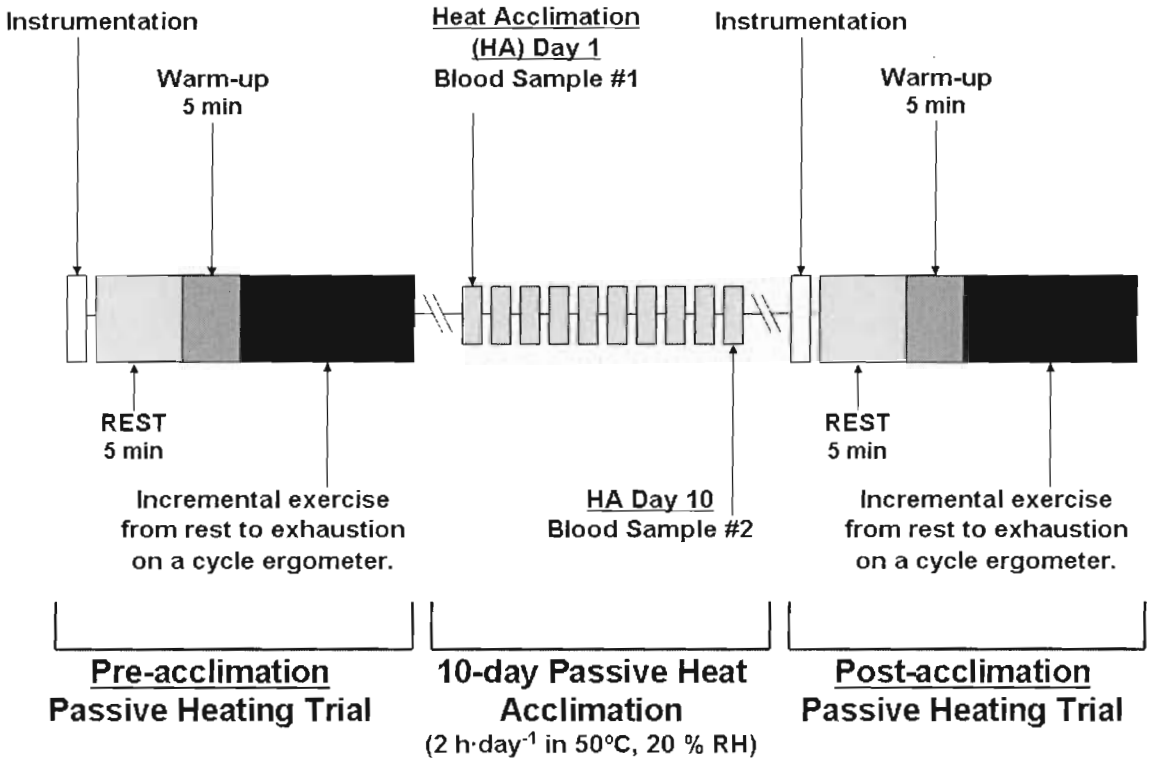


Figure 4.2 Representative (n = 1) pre- (●; solid arrow) and post-acclimation (○; dashed arrow) breath-by-breath $\dot{E}_{sw}$ vs. T_{es} plots during an incremental exercise test from rest to exhaustion used to determine T_{es} thresholds for the initiation of eccrine sweating, tau (τ) and the estimated maximal steady-state $\dot{E}_{sw}$ ($\Delta\dot{E}_{sw}(ss)$) for each participant via a mono-exponential function fitted to the data (solid line) Arrows indicate the T_{es} thresholds determined by piecewise linear regression (50).

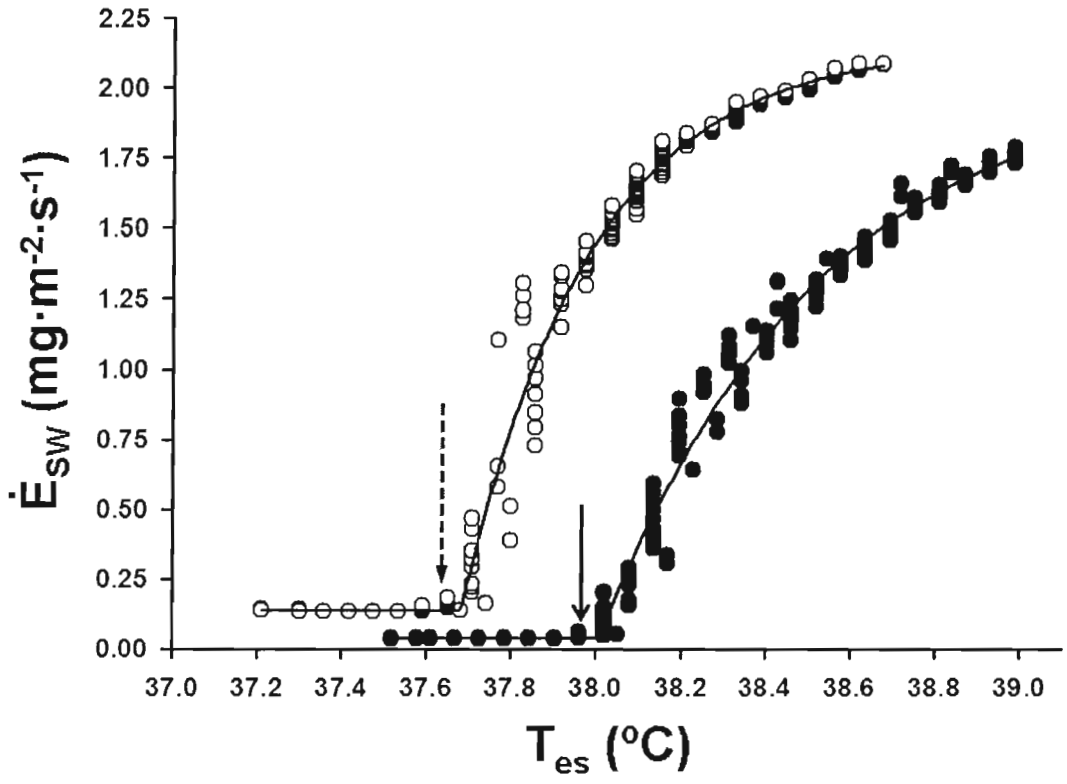


Figure 4.3 Representative plots (n = 1) of the relationships between $\dot{V}_E/\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$, V_T and f with T_{es} during the pre- (●; solid arrow) and post-acclimation (○; dashed arrow) incremental exercise test from rest to exhaustion. Arrows show where the T_{es} thresholds for these four variables were determined to occur using piecewise linear regression (50).

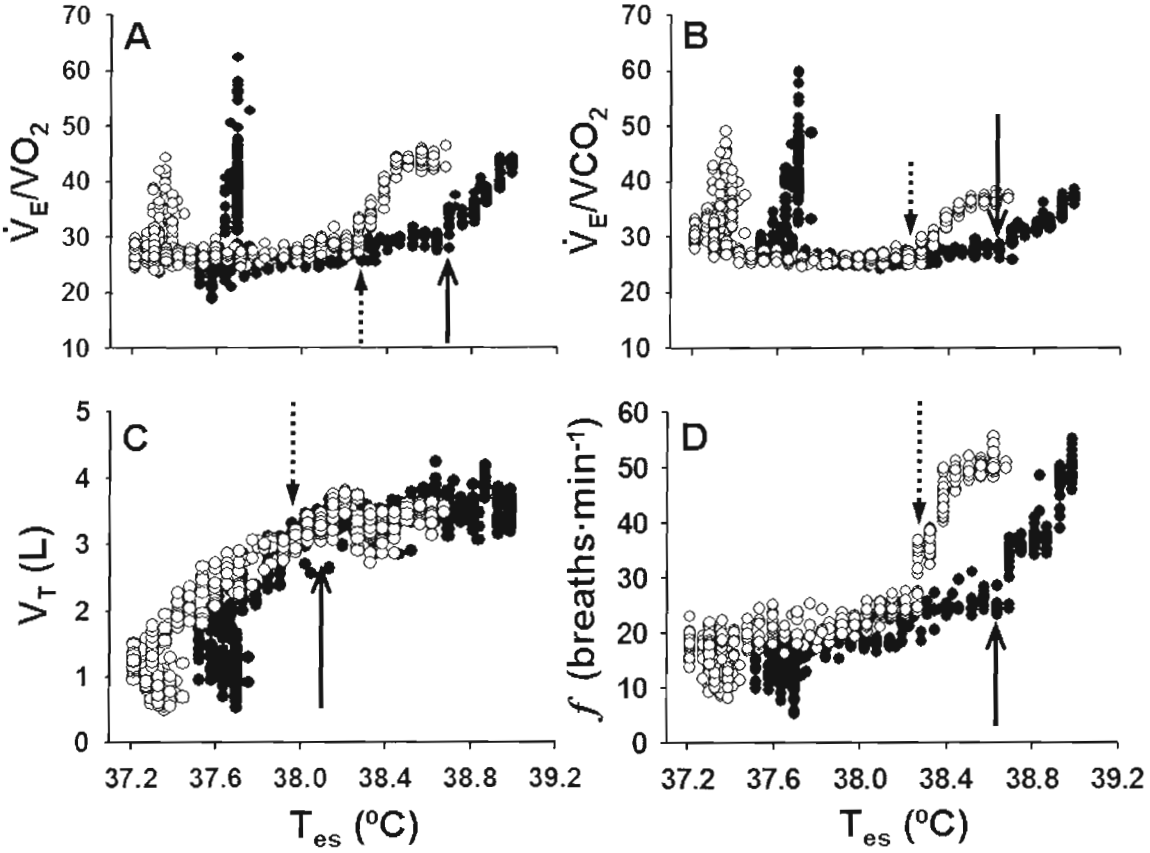


Figure 4.4 Mean T_{es} **(A)** and $\overline{T}_{sk}$ **(B)** responses during the pre- (●, ■) and post-acclimation (○, □) incremental exercise tests from rest to exhaustion up to the maximum time all participants achieved for both trials (n = 10). Each datum is a 10 s mean and the error bars represent ±SD and have been included at 5, 9, 15, 20 and 23 min point. P-values are for comparison between the pre- and post-acclimation trials.

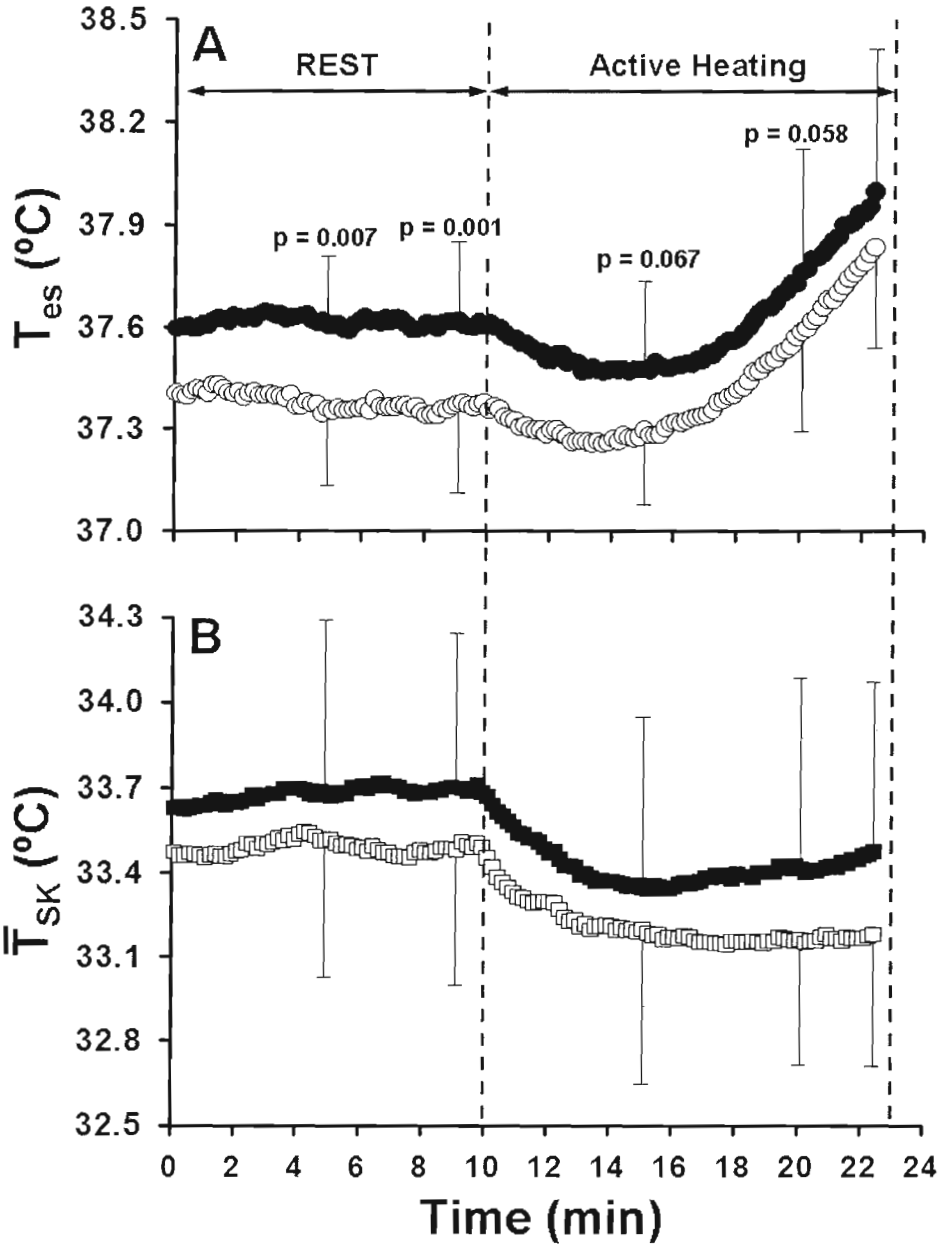


Figure 4.5 Mean CBV_{TEMPLE} and $\dot{E}_{sw}$ (n = 8) at the same absolute mean T_{es} achieved within the pre- (●) and post-acclimation (○) incremental exercise tests from rest to exhaustion after T_{es} had begun to increase. Error bars represent the ±SD and significant p-values are for comparisons between the pre- and post-acclimation trials.

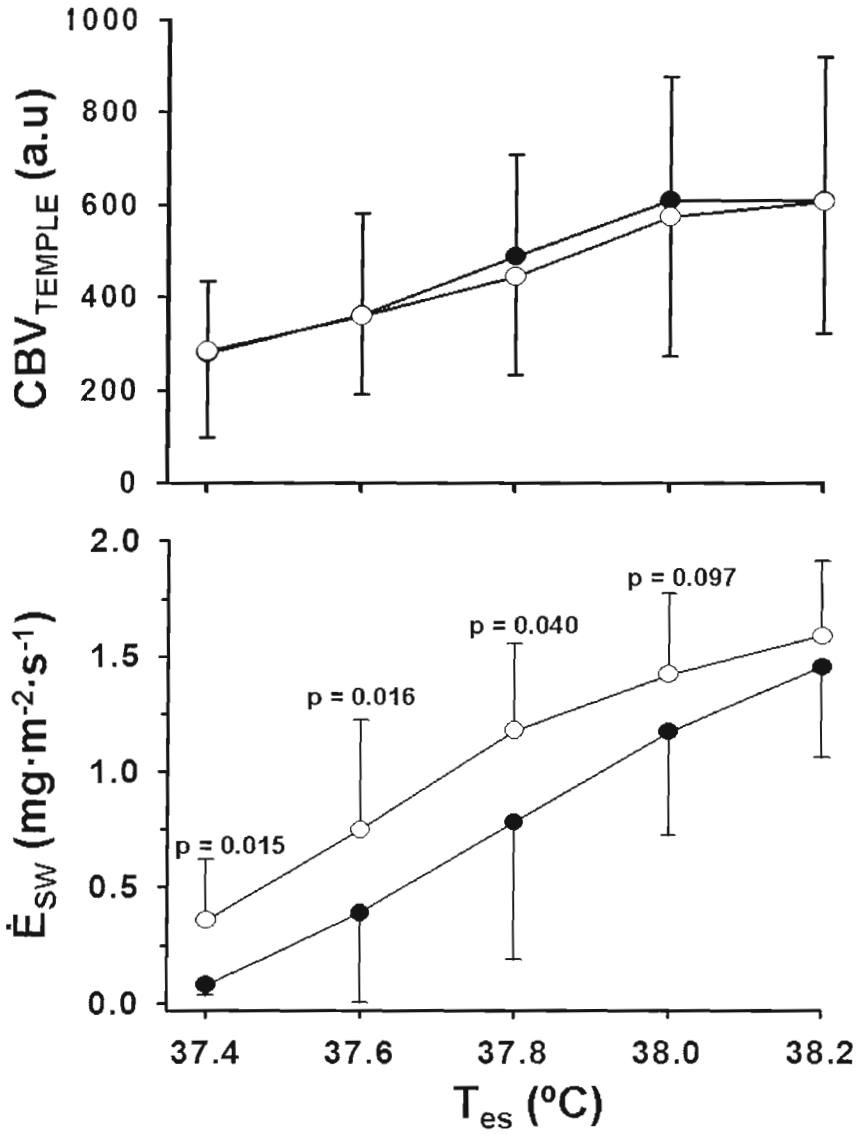


Figure 4.6 Mean pulmonary ventilation ($\dot{V}_E$; A), tidal volume (V_T ; B) and breathing frequency (f ; C) at a mean absolute T_{es} achieved during, both, the pre- (●, ■, ▲) and post-acclimation (○, □, Δ) incremental exercise tests from rest to exhaustion (n = 8). Error bars represent the ±SD and the p-values are given for significant comparisons between the pre- and post-acclimation trials.

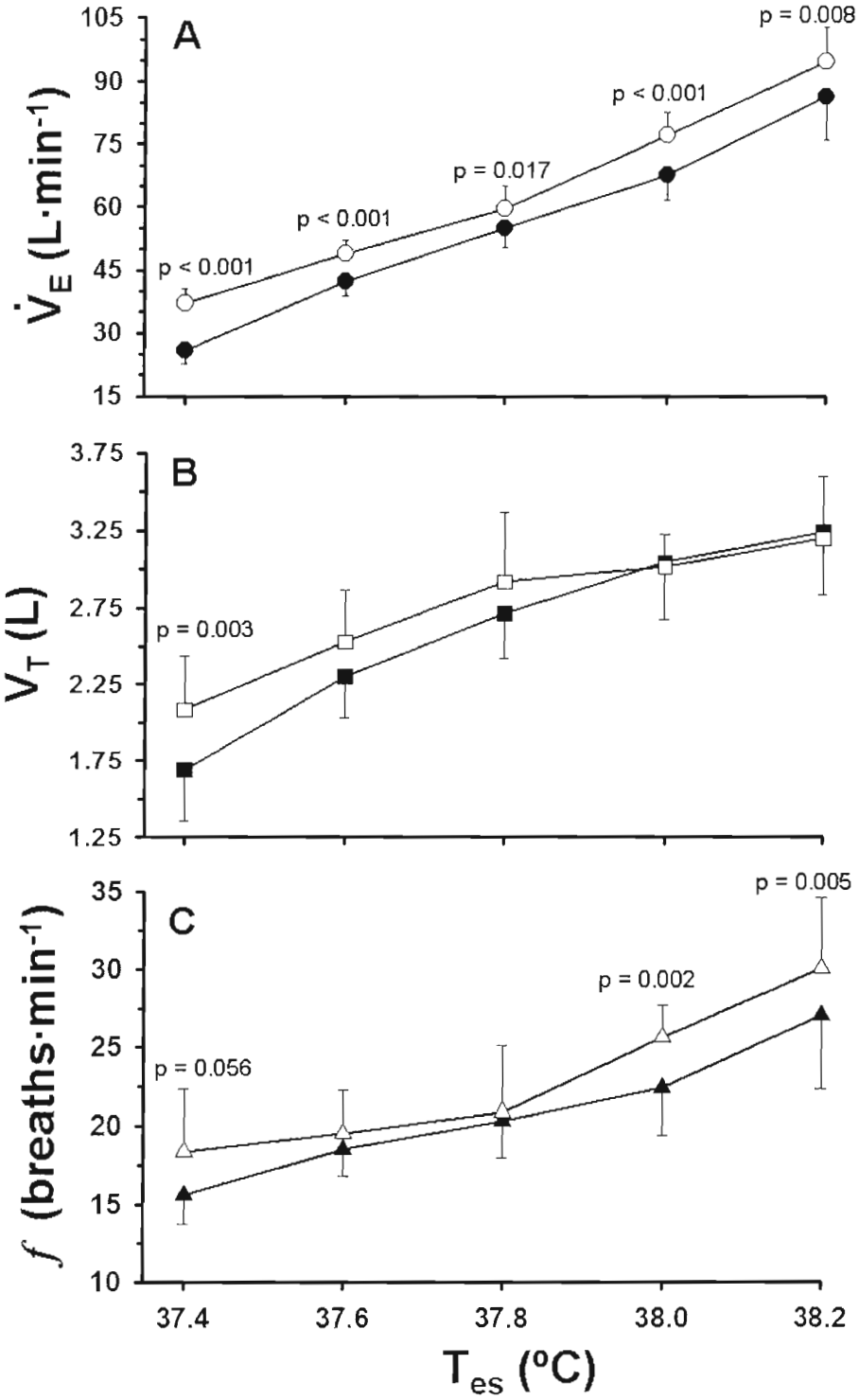


Figure 4.7 Mean end-tidal partial pressure of CO_2 ($P_{ET}CO_2$; **A**), end-tidal partial pressure of O_2 ($P_{ET}O_2$; **B**) and the respiratory exchange ratio (RER; **C**) responses at the same absolute mean T_{es} achieved during the pre- and post-acclimation incremental exercise tests from rest to exhaustion (n = 8). Error bars represent ±SD and p-values are shown when there was either a significant difference or a trend between the pre- and post-acclimation trials.

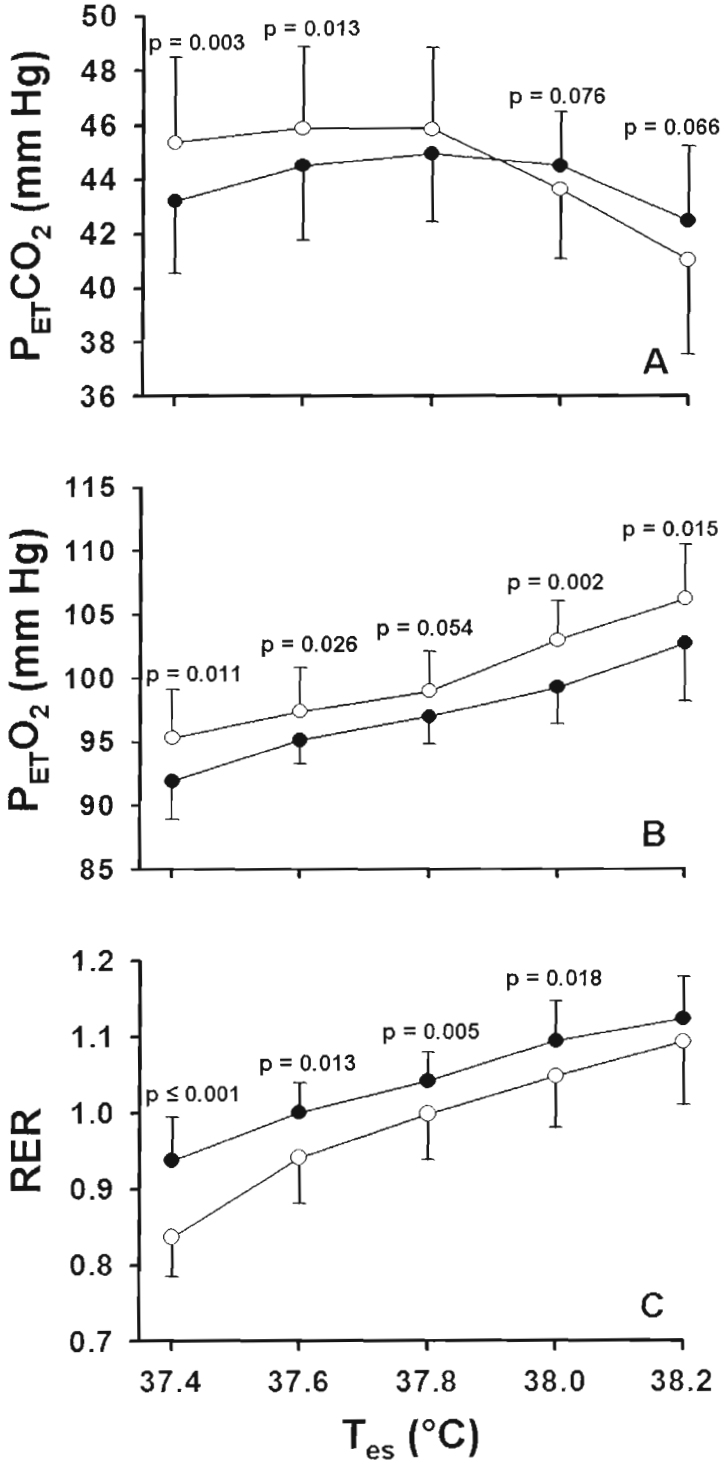
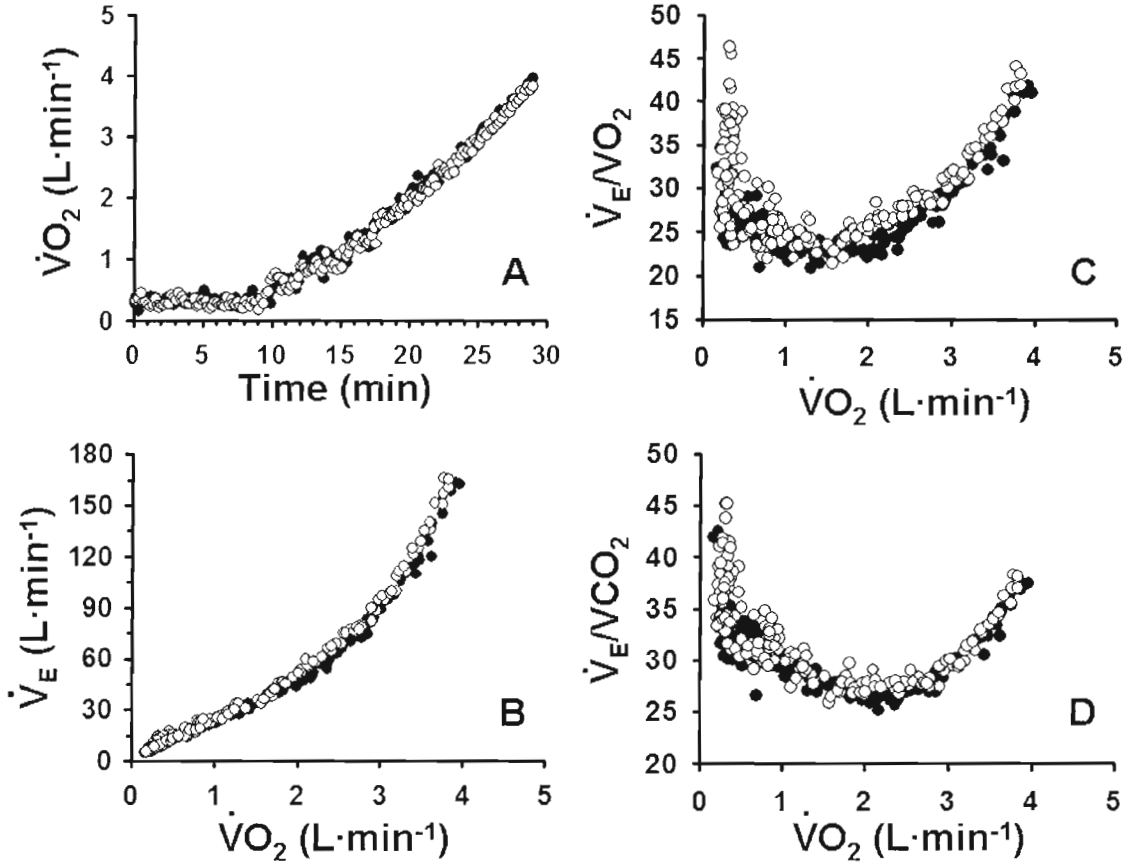


Figure 4.8 Time course of $\dot{V}O_2$ (**A**) and the relationships between $\dot{V}_E$ (**B**), $\dot{V}_E/\dot{V}O_2$ (**C**) and $\dot{V}_E/\dot{V}CO_2$ (**D**) with $\dot{V}O_2$ during the pre- (●) and post-acclimation (○) incremental exercise tests from rest to exhaustion for one representative participant to show the passive heat acclimation protocol was successful in not producing a training effect. Each datum is a 10 s mean.



Chapter 5 – STUDY 3

Central chemoreflex ventilatory response to carbon dioxide at normo- and hyperthermic core temperatures following passive acclimation to a hot environment

Andrew E. Beaudin

Running Head: "Ventilatory Response to CO_2 Following Heat Acclimation"

Keywords: Hypercapnia, hyperoxia, pulmonary ventilation, Read re-breathing, sensitivity, thermoregulation, ventilatory recruitment threshold.

5.1 Abstract

This study examined the normo- and hyperthermic-hyperoxic central chemoreflex ventilatory response to CO_2 before and after passive heat acclimation (HA). HA consisted of exposure to 50°C and 20 % RH for 10 consecutive days, 2 $h \cdot day^{-1}$. The normo- and hyperthermic ventilatory recruitment thresholds (VRT) and hyperoxic central chemosensitivity to CO_2, assessed by a linear regression fit to data supra-VRT, were not altered by HA ($p \geq 0.188$). Hyperthermia increased the pre- ($p \leq 0.010$), but not post-acclimation ($p = 0.166$) central chemosensitivity assessed by regression analysis of supra-VRT data. Analyzing ventilation across the entire observed range of $P_{ET}CO_2$ showed a positive interaction between T_{es} and $P_{ET}CO_2$ levels ($p = 0.027$) explained by higher ventilation for at higher levels of $P_{ET}CO_2$ during, both, pre- and post-acclimation hyperthermic trials. HA did not modify the resting, normothermic arterialized [HCO_3^-], pH_a, P_{O2} or P_{CO2} measures prior to starting either the nHHCVR or the hHHCVR trials. In conclusion, the ventilatory responses to hyperoxic CO_2 re-breathing were not altered by HA and irrespective of acclimation state, $\dot{V}_E$ response was higher at all levels of $P_{ET}CO_2$ during a passively-induced hyperthermia with the difference in $\dot{V}_E$ between the normo- and hyperthermic trials being larger at higher levels of $P_{ET}CO_2$.

5.2 Introduction

An increase in body core temperature stimulates an increase in resting human pulmonary ventilation (6, 18, 20, 21, 33, 42) and this is believed to be the result of an increased sensitivity of the peripheral chemosensitive areas to O_2 and CO_2 and the central chemosensitive tissue to CO_2 (41). A passively-induced hyperthermia has been shown to increase the ventilatory response to, both, hypoxia (11, 29) and hypercapnia (2, 10, 36). Similarly, during (39) and following (32) an exercise-induced hyperthermia there is an augmentation of the central chemoreflex ventilatory response to CO_2. Whether the increased sensitivity of chemosensitive tissues is the direct result of 1) an increased local temperature of the carotid and aortic bodies and the chemosensitive areas of the VMS; 2) an increased thermoregulatory drive directly to the central respiratory control centre to increase respiratory heat loss; or 3) a combination of the two, hyperthermic-hyperventilation is believed to be a human thermoregulatory response contributing to cranial temperature regulation (6, 30, 42). It has been shown both the central and peripheral chemosensitive tissues are thermosensitive (5). In anaesthetized and ventilated cats, with maintenance of their local chemical environment, changes in the local temperature of intermediate area of the VMS gives proportional increases in phrenic nerve firing frequencies (8, 9). As well, changes in temperature of the carotid bodies (17, 28) while the local environment is maintained at euoxic and eucapnic levels produces proportional increases and decreases of firing frequencies in the carotid sinus nerves. Therefore, there is a possibility these temperature responses may be modified when humans are acclimated to a hot environment.

The primary stimulus for successful heat acclimation is an increase in core temperature (T_c) for ~2 $h \cdot day^{-1}$ for 7 to 14 consecutive days (1, 19, 40). An elevation of T_c produces an increase in ventilation (6, Chapter 3) and as such, the induction of hyperthermia over multiple days during the heat acclimation protocol is reasoned to to produce a hyperthermic-hyperventilation on all acclimation days. Chronic hyperventilation, irrespective of the cause, has been shown to decrease the ventilatory recruitment threshold[5] (VRT) and increase the sensitivity to a CO_2 stimulus (4, 31). Hence, the purpose of this study was to determine whether, a passively-induced heat acclimation would modify the hyperoxic central chemoreflex ventilatory response to CO_2 either at a normothermic and/or hyperthermic core temperature. Since central chemosensitive areas and peripheral chemoreceptors have thermosensitive properties and hyperthermic hyperventilation would occur throughout the acclimation protocol, it was hypothesized heat acclimation would decrease the VRT and increase the sensitivity of the hyperoxic central chemoreflex ventilatory response to CO_2.

[5] Ventilatory recruitment threshold (VRT) is the end-tidal partial pressure of CO_2 under which there is no ventilatory stimulation, but upon surpassing there is a proportional increase in ventilation with further increases in CO_2 (14).

5.3 Method

5.3.1 Participants

The present study was also performed concurrently with Study 1 and 2. Therefore, the same 10 participants from the two previous studies were used. Based upon an effect size of a 5.0 ± 3.2 mm Hg decrease in the end-tidal partial pressure of CO_2 threshold and a 0.87 ± 0.4 $L \cdot min^{-1} \cdot mmHg^{-1}$ increase in the sensitivity of the hyperoxic central chemoreflex ventilatory response to CO_2 from a normothermic to a hyperthermic core temperature (2, 32) the employed sample size provided a power ≥ 0.87. Following data collection and analysis, one participant showed an extreme sensitivity to CO_2 during the hyperthermic post-acclimation hyperoxic central chemoreflex ventilatory response to CO_2 that surpassed 4 standard deviations above the mean and was excluded from all ventilation data analysis. All participants were non-smokers and asked to avoid consuming caffeine or alcohol, eating and strenuous exercise for a minimum of 4 h prior to each testing session. Participants were given a 30 min orientation that included an overview of the instrumentation, the protocol and the potential risks. Each participant was given a minimum 24 h reflection period, after which he signed and submitted an informed consent. The Office of Research Ethics at Simon Fraser University approved this study.

5.3.2 Instrumentation

Pulmonary ventilation ($\dot{V}_E$) was measured and calibrated via the same method as described in Chapter 3, except a breathing valve controlled by two inflatable balloons was attached to the mass flow sensor which allowed rapid transfer from breathing room air to breathing from a 5-L re-breathing bag (Anesthesia Association Inc., San Marcos,

CA, USA) containing 5.5% CO_2, 33% O_2 and balance N_2. Pure medical grade O_2 (Praxair, Mississauga, ONT, Canada) was manually titrated into the re-breathing via a port in the breathing valve.

The body core (esophageal and rectal) and skin (left temple, shoulder, lower back and thigh) temperatures were measured, calibrated and expressed as outlined in Chapter 3.

Heart rate (HR) and arterial haemoglobin oxygen saturation (S_aO_2) were measured from the left earlobe, similar to Chapter 3.

Esophageal (T_{es}) and rectal temperature (T_{re}), T_{sk} (lower back, shoulder, thigh and temple), HR and S_aO_2 data were collected using the same data acquisition systems outlined in Chapter 3.

Arterialized blood sampling was also performed as described in Chapter 3. All measurements were corrected to either the normothermic or hyperthermic core temperature of the participants when each blood sample was drawn. The percentage of plasma blood volume (PV) expansion from baseline was estimated using the same equation explained in Chapter 3:

$$\% \Delta PV = 100\ [(Hb_{PRE}/Hb_{ACC}) \times ((1\text{-}Hct_{ACC}) / (1\text{-}Hct_{PRE}))] - 100 \qquad (5.1)$$

Heat acclimation was performed within the same walk-in climatic chamber employed in the passive and active heating studies.

5.3.3 Protocol

Each participant performed 3 modified hyperoxic-hypercapnic modified Read re-breathing tests (7). The first re-breathing test was a familiarization trial performed while sitting in a comfortable chair in thermoneutral air environment. The other two trials consisted of a normothermic (nHHCVR) and a hyperthermic hyperoxic-hypercapnic ventilatory response test (hHHCVR) while immersed up to the shoulders in a water bath. The heat acclimation (HA) protocol was the same as described in Chapter 3.

The familiarization hyperoxic CO_2 re-breathing trial was performed a minimum of one day prior to performing the nHHCVR and hHHCVR which were performed on the same pre- and post-acclimation test day with a minimum of 45 min between each test. The pre-acclimation trials were performed 3.4 ± 3.4 days (mean ± SD) prior to the start of the HA protocol and the post-acclimation trials were performed 1.2 ± 0.4 days following the 10^{th} day of acclimation. The normothermic hyperoxic CO_2 re-breathing trial always preceded the hyperthermic trial to prevent any residual effects of the previous hyperthermic state. Following instrumentation, each participant sat in a comfortable chair for 10 min within a thermoneutral environment in order to obtain resting data. The mean ambient temperature and RH were 22.76 ± 1.43°C and 31.12 % for the pre-acclimation tests and 22.58 ± 1.35°C and 30.27 % for post-acclimation tests. Subsequent to the rest period, each participant was moved into the water bath within ~1 min. For the nHHCVR trials, the mean pre-acclimation water bath temperature (T_{H_2O}) was 35.61 ±

0.32°C and the post-acclimation temperature was 36.06 ± 0.40°C. The hyperthermic trials were performed when T_{es} had reached ~39.00°C after the conclusion of the passive heating protocol outlined in Chapter 3. After attaining a T_{es} of ~39.00°C, the T_{H_2O} was lowered and manually adjusted in order to clamp T_{es} between 38.50 and 39.00°C. Pre-acclimation, in order to clamp T_{es} at the hyperthermic level, mean T_{H_2O} was 38.75 ± 0.23°C and during the post-acclimation trials, the mean T_{H_2O} was 38.71 ± 0.19°C.

Once T_{es} had stabilized at either the normo- or hyperthermic level for a minimum of 10 min, participants were asked to voluntarily hyperventilate for 5 min using steady deep breathes in order to decrease $P_{ET}CO_2$ to between 20 to 25 mm Hg. At the end of the 5 min of hyperventilation, participants were switched from breathing room air to breathing from the re-breathing bag containing 5.5 % CO_2, 33 % O_2, balance N_2 at the end of an expiration. Once switched to the re-breathing bag, the participant took three initial deep breaths to help equilibrate the P_{CO2} in the bag, lungs and arterial blood with mixed venous blood. Subsequently, the participant returned to normal, relaxed breathing and was instructed to breathe normally for the remainder of the test. The test was terminated when $P_{ET}CO_2$ exceeded 60 mm Hg or $\dot{V}_E$ surpassed 100 $L \cdot min^{-1}$. The P_{O2} within the re-breathing bag was maintained greater than 150 mm Hg by manually titrating in 100 % medical grade O_2 into the re-breathing bag. The 5 L re-breathing bag was hidden from sight during all hyperoxic-hypercapnic ventilatory response tests by a opaque curtain so as to not influence the participant's rate and depth of $\dot{V}_E$ via visual feedback.

Capillary tube arterialized blood samples were drawn pre- and post-acclimation prior to instrumentation for the nHHCVR and hHHCVR, during the hHHCVR when T_{es} had stabilized at the hyperthermic level and prior to instrumentation on days 1, 2, 4, 6, 8 and 10 of the acclimation protocol. The blood samples drawn on day 1 of the HA protocol were used as the baseline measurement for haemoglobin concentration [Hb] and haematocrit (Hct) within Equation 5.1. Figure 5.1 shows an overview of the protocol.

All hHHCVR trials were performed within the same two hour window at which participants were acclimated each day, while the nHHCVR were carried out during the 2 h prior to the hHHCVR trial. This was done as the adaptations that arise from a heat acclimation protocol have been shown to be specific to the time of day the acclimation was performed (35).

5.3.4 Statistical Analyses

The individual VRT for the hyperoxic central chemoreflex ventilatory response to CO_2 were determined by plotting breath-by-breath data for $\dot{V}_E$ versus $P_{ET}CO_2$ after participants had been switched to the re-breathing bag, had taken 3 deep breaths and had returned to relaxed breathing. The VRT was determined using the piecewise linear regression function (37) outlined in Chapter 3. Correlated 1-tailed t-tests were performed to compare the VRT and sensitivities between the two acclimation conditions (pre vs. post) and core temperature conditions as well as the within difference between the normo- and hyperthermic pre- and post-acclimation conditions. The alpha level was set at less than or equal to 0.05 for all correlated comparisons.

Additional analysis consisted of a 5 × 2 × 2 repeated measures ANOVA performed on $\dot{V}_E$ and its components. The factors included levels of $P_{ET}CO_2$ (Levels: immersed rest (iREST) and 40, 45, 50 and 55 mm Hg). The two other factors were Core Temperature (Levels: normo- and hyperthermic) and Acclimation State (Levels: pre and post). Dependent variables consisted of $\dot{V}_E$, tidal volume (V_T), breathing frequency (f), total breath (T_{TOT}), inspiratory (T_I) and expiratory times (T_E). Changes in arterialized blood variables of bicarbonate concentration in plasma ($[HCO_3^-]_p$), pH, P_{CO2} and P_{O2} over the acclimation protocols were analyzed using a one-way repeated measures ANOVA with the factor of Acclimation Day (Day 1, 2, 4, 6, 8 and 10). If there was a significant interaction between $P_{ET}CO_2$ with either acclimation state or core temperature, or both, the differences between the pre- and post-acclimation conditions and the normo- and hyperthermic trials were compared used 2-tailed paired t-tests. Alpha level was maintained at 0.05 for all comparisons by employing a Bonferonni correction.

5.4 Results

Mean rectal temperature responses for each participant were previously shown in Chapter 3, Figure 3.2. The mean T_{es} maintained during the nHHCVR trials was 37.27 ± 0.12°C pre-acclimation and 37.12 ± 0.16°C post-acclimation ($p \leq 0.030$). For the pre-acclimation hHHCVR trials, T_{es} was increased a mean of 1.48 ± 0.18°C above the un-immersed resting conditions and clamped at 38.90 ± 0.09°C. Within the post-acclimation trials, T_{es} was increased a mean of 1.54 ± 0.23°C and stabilized at 38.87 ± 0.07°C.

Pre vs. post-acclimation between comparisons

Figure 5.2 shows a representative pre- and post-acclimation plot of $\dot{V}_E$ vs. $P_{ET}CO_2$ used to determine the thresholds and supra-VRT sensitivities of the hyperoxic central chemoreflex ventilatory response to CO_2. Table 5.1 gives the individual VRT thresholds and the supra-VRT sensitivities for the pre- and post-acclimation nHHCVR and hHHCVR trials. The mean VRT for the hyperoxic central chemoreflex ventilatory response to CO_2 during the pre-acclimation nHHCVR and hHHCVR trials were not significantly different from the post-acclimation nHHCVR ($p = 0.555$) and hHHCVR ($p = 0.901$) VRT nor were the supra-VRT sensitivities significantly different for the nHHCVR ($p = 0.375$) and hHHCVR ($p = 0.476$).

The mean $\dot{V}_E$ during the nHHCVR trial, as well as during the hHHCVR trial was not significantly different at all levels of $P_{ET}CO_2$ following HA ($F_{(4,32)} = 0.09$; $p = 0.938$; Figure 5.3 A). With respect to T_{TOT} and its divisions of T_I and T_E, Acclimation State also had no significant effect at different levels of $P_{ET}CO_2$ ($F_{(4,32)} \leq 1.77$; $p \geq 0.220$; Figure 5.3 D, E and F).

Figure 5.4 shows the mean values for $[HCO_3^-]_p$, pH, P_{CO2} and P_{O2} and Hct and [Hb] from arterialized blood samples drawn periodically over the 10-day HA period. There were no significant changes in arterialized blood $[HCO_3^-]_p$, pH, P_{CO2} or P_{O2} ($F_{(5,35)} \leq 1.20$;$p \geq 0.336$) across all levels of Acclimation Day as the HA protocol progressed. However, there was a significant decrease ($F_{(5,30)} \geq 6.75$; $p \leq 0.014$) in Hct and [Hb] by day 6 ($p \leq 0.027$) indicative of an expansion of plasma volume. Using Equation 5.1, plasma volume expanded a mean of 20.44 ± 12.66 % above baseline levels by day 10 of the HA protocol (Figure 5.4 D). Table 5.2 contains the mean values for $[HCO_3^-]_p$, pH, P_{CO2} and P_{O2} prior to instrumentation (Normothermic – Un-immersed) for the nHHCVR and hHHCVR trials and when T_{es} was clamped at the hyperthermic level while immersed in the tub (Hyperthermic – Immersed). There was no significant difference between the pre- and post-acclimation conditions for the 3 times blood samples were drawn.

Pre- and post-acclimation within comparison

Within the pre- and post-acclimation conditions the nHHCVR and hHHCVR VRT were not significantly different ($p \geq 0.627$; Table 5.1). Within the pre-acclimation trials, hyperthermia resulted in a significantly greater ($p = 0.010$) chemosensitivity than that observed during the nHHCVR. Even though the mean sensitivity was higher during the post-acclimation hHHCVR, it was not significantly different ($p = 0.332$) than that observed during the post-acclimation nHHCVR.

Core Temperature had a significant effect on $\dot{V}_E$ ($F_{(1,8)} = 13.19$; $p = 0.007$) with the mean $\dot{V}_E$ being greater during the hHHCVR trials compared to the nHHCVR trials (Figure 5.3 A). Additionally, the interaction between levels of $P_{ET}CO_2$ and Core

Temperature was significant ($F_{(4,32)} = 3.17$; $p = 0.027$) for $\dot{V}_E$. Irrespective of acclimation state, $\dot{V}_E$ was significantly higher at all levels of $P_{ET}CO_2$ during the hHHCVR trials compared to the nHHCVR trials and the difference in $\dot{V}_E$ between the normo- and hyperthermic trials became larger as $P_{ET}CO_2$ increased. There was no significant interaction between increases in $P_{ET}CO_2$ and Acclimation State for either V_T ($F_{(4,32)} = 1.22$; $p = 0.322$) or f ($F_{(4,32)} = 0.62$; $p = 0.601$) with both being similar during the nHHCVR and hHHCVR pre- and post-acclimation trials at the different levels of $P_{ET}CO_2$ (Figure 5.3 B and C). The interaction between increases in $P_{ET}CO_2$ and Core Temperature for V_T showed a trend ($F_{(4,32)} = 2.49$; $p = 0.092$) for V_T to be higher during the hHHCVR trials as $P_{ET}CO_2$ increased, but there was no significant interaction between the increases in $P_{ET}CO_2$ and Core Temperature for f ($F_{(4,32)} = 0.624$; $p = 0.601$).

Irrespective of both Acclimation State and Core Temperature, increases in $P_{ET}CO_2$ had a significant effect on T_{TOT} ($F_{(4,32)} = 8.00$; $p = 0.001$), T_I ($F_{(4,32)} = 3.42$; $p = 0.047$) and T_E ($F_{(4,32)} = 14.06$; $p = 0.001$) (Figure 5.3). Total breath time and T_E initially increased from iREST conditions and then decreased as $P_{ET}CO_2$ increased while T_I initially decreased from iREST and then increased as $P_{ET}CO_2$ increased (Figure 5.3 D, E and F). Core Temperature did not influence the T_{TOT} ($F_{(4,32)} = 0.97$; $p = 0.415$), T_I ($F_{(4,32)} = 1.24$; $p = 0.315$) or the T_E ($F_{(4,32)} = 2.10$; $p = 0.129$) responses across different levels of $P_{ET}CO_2$ increased.

For the arterialized blood variables, there was a trend ($0.069 \leq p < 0.098$) for pH to be more alkaline during both, the pre- and post-acclimation hHHCVR when T_{es} was clamped at the hyperthermic level compared to Normothermic – Un-immersed samples

drawn prior to starting the hyperthermic trials. The P_{CO2} also showed a trend ($p = 0.081$) to be lower when T_{es} was clamped at the hyperthermic level, but only during the pre-acclimation trials and P_{O2} was significantly higher ($p \leq 0.016$) at the clamped hyperthermic T_{es}. The pre- and post-acclimation mean $[HCO_3^-]_p$ measured during the hHHCVR trials when T_{es} was clamped at the hyperthermic level (i.e., Hyperthermic – Immersed) was not different ($p = 0.264$) from the Normothermic – Un-immersed level measured prior to the start of the hHHCVR trials.

5.5 Discussion

There were two principal findings in the present study. The first was that neither the VRT nor the supra-VRT chemosensitivity of the hyperoxic central chemoreflex ventilatory response to CO_2, at both normo- and hyperthermic core temperatures, were modified by a 10-day passive heat acclimation. The second main finding was that when the entire range of $P_{ET}CO_2$ from iREST to 55 mm Hg were employed within an ANOVA (Figure 5.3), Acclimation State, again, had no significant effect on pulmonary ventilation. Similar to the VRT and supra-VRT chemosensitivity, the breathing pattern during the hyperoxic central chemoreflex ventilatory response to CO_2 tests was not modified by HA (Figure 5.3). At all levels of $P_{ET}CO_2$ observed, there were no differences between the pre- and post-acclimation trials for $\dot{V}_E$, V_T, f, T_I, T_E or T_{TOT}.

The mean pre- and post-acclimation nHHCVR and hHHCVR VRT of ~47 mm Hg within the present study are similar to the mean nHHCVR and hHHCVR VRT of ~48 mm Hg observed by Baker et al (2), ~45.3 mm Hg observed by Duffin et al (15) and ~49 mm Hg observed by Jensen et al (24) who all employed a similar hyperoxic-hypercapnic modified Read re-breathing protocol. The supra-VRT chemosensitivity range for the nHHCVR trials of 1.11 to 7.73 $L \cdot min^{-1} \cdot mm\ Hg^{-1}$, even though higher than the normothermic range of ~1.50 to 2.72 $L \cdot min^{-1} \cdot mm\ Hg^{-1}$ observed by Baker et al (2) and the 1.0 to 5.95 $L \cdot min^{-1} \cdot mm\ Hg^{-1}$ range observed by Hirshman et al (22), are similar to those reported in more recent studies where a mean of ~4.5 $L \cdot min^{-1} \cdot mm\ Hg^{-1}$ was observed (24, 25). The range of the hHHCVR supra-VRT chemosensitivity within the present study of 2.06 to 7.46 $L \cdot min^{-1} \cdot mm\ Hg^{-1}$ is larger than that of 2.43 to 3.27 $L \cdot min^{-1} \cdot mm\ Hg^{-1}$ observed by Baker et al (2) who employed a similar protocol, but these

differences are most likely the result of participants within the present study being more sensitive to CO_2 at a normothermic T_c as well as a greater individual variability (22).

An exhaustive review of the literature did not reveal any previous studies that explored the effect of HA on the central or peripheral chemosensitive tissues to a hypercapnic stimulus in either a human or animal model. The only study uncovered exploring changes in human chemosensitivity following acclimation to a thermal environment were performed by Krivoshchekov & Divert (26, 27) who explored the effect of acclimation to a cold environment on chemosensitivity. Contrary to the present finding there was an increase in the hypoxic and hypercapnic ventilatory responses following 10 days of exposure to 13°C for 2 $h \cdot day^{-1}$. It is difficult to compare the present results to those of Krivoshchekov & Divert (26, 27) as acclimation to a cold environment produces very different physiological adaptations than those occurring with acclimation to a hot environment (12). Additionally, unlike heat acclimation where thermoregulatory adaptations are generally consistent between individuals, cold acclimation can take a few different forms (i.e., metabolic, insulative or hypothermic) and may vary between individuals depending on the cold acclimation protocol employed (3). Metabolic cold acclimation is associated with a higher metabolic rate leading to greater heat production and results in a higher T_{sk} and a normal T_{re} post- acclimation (34), while insulative cold acclimation consists of maintaining a lower mean T_{sk} and a normal T_{re} during cold exposure. Finally, a decrease in metabolic heat production leading to lower mean T_{sk} and a lower T_{re} within a thermoneutral and cold environment characterize hypothermic cold acclimation (23, 38). Therefore, there is the possibility that each form of cold acclimation may produce a different modification of either, the hypoxic and/or

hypercapnic ventilatory response, as observed by Krivoshchekov & Divert (27). These areas still need further study.

The implications of the VRT of the hyperoxic central chemoreflex ventilatory response to CO_2 and the sensitivity to a given CO_2 stimulus during hyperthermia not being altered by the passive HA protocol is that the maintenance of $\dot{V}_E$ at the same level even though $P_{ET}CO_2$ was decreased observed in Chapter 3 and the significantly higher $\dot{V}_E$ observed in Chapter 4 now appear not to be the result of an increased sensitivity of the central chemosensitive areas to CO_2, as it was first theorized. Instead, the post-acclimation changes in $\dot{V}_E$ observed in the two previous studies may be more likely the result of increased direct stimulation of the central respiratory centre via afferent signals from cutaneous and/or pre-optic anterior hypothalamic temperature sensitive neurons following HA. These findings, therefore, provide further support for the hypothesis the increase in $\dot{V}_E$ during hyperthermia in humans may be an independent thermoregulatory heat loss response (6, 42, 43).

Aside from HA not modifying the VRT or the chemosensitivity of the hyperoxic central chemoreflex ventilatory response to CO_2, the supra-VRT chemosensitivity during the pre-, but not the post-acclimation hHHCVR was observed to be significantly greater than that during the nHHCVR. The non-significant change in the post-acclimation chemosensitivity between the normo- and hyperthermic trials occurred even though the mean hyperthermic T_{es} at which participants were stabilized and the increase in T_{es} from resting conditions were the same between the pre- and post-acclimation trials. These assessments of chemosensitivity were limited to the range of $P_{ET}CO_2$ above the pre-

determined VRT (i.e., from ~46 to 55 mm Hg; Table 5.1). However, there was a positive interaction between $P_{ET}CO_2$ and Core Temperature within the pre- and post-acclimation trials. These results demonstrate the enhancing effect of Core Temperature on CO_2 central chemosensitivity over a larger physiological range of $P_{ET}CO_2$ than employed in calculation of the supra-VRT chemosensitivity was maintained across different acclimation states.

Limitations of the present study include the possibility there was some apprehension and anxiety due to the prior hyperventilation and/or unfamiliarity with breathing from a mouthpiece may have altered the VRT and sensitivities observed (24). These were not considered to have influenced the ventilatory responses observed as all participants had performed a minimum of one familiarization modified Read re-breathing test prior to the pre-acclimation trials and all had prior experience breathing from a mouthpiece.

It is also possible that the passive heat acclimation protocol may not have provided sufficient thermal and/or ventilatory strain to produce an adaptation of the hyperoxic central chemoreflex ventilatory response to CO_2. We cannot comment on whether the 2 $h \cdot day^{-1}$ increase in T_{es} was an adequate degree of thermal stimulation to chronically alter the response of the central chemosensitive areas to an increase in temperature as, to the best of our knowledge, this has never been explored. On the other hand, chronic euoxic- hyperventilation for 6 to 24 h has been shown to lower the VRT and increase the sensitivity to CO_2 (4, 31). This reported decrease in the VRT and increased sensitivity (4, 31) was most likely the product of the decreased arterial [HCO_3^-]

and an increased arterial pH accompanying the chronic euoxic-hyperventilation (13, 16). Prior to and following the HA protocol, it was confirmed in Chapters 3 and 4 that $\dot{V}_E$ was increased during passively- and actively-induced hyperthermia. As such, during the 2 h acclimation sessions when T_{re} was increased and held constant between 38.50 and 39.00°C, it should have produced a hyperthermic-hyperventilation on each of the 10 days of HA and the repetitive hyperthermic-hyperventilation may have provided sufficient stimulus to produce similar changes in arterial [HCO_3^-] and pH during resting conditions as seen with chronic euoxic-hyperventilation. This does not appear to be the case as resting arterialized $[HCO_3^-]_p$, pH, P_{CO2} and P_{O2} were not significantly different following HA (Figure 5.4). As a result, if central chemosensitive areas can adapt to chronic heat exposure sufficient to raise T_c, then it may require more than 2 h·day^{-1} over 10 consecutive days of passive heat acclimation.

In conclusion, this study showed that the normo- and hyperthermic VRT and sensitivity to CO_2 along with the breathing pattern of the central chemoreflex ventilatory response to CO_2 were not altered by a 10 day passive heat acclimation protocol utilizing controlled hyperthermia. This indicates the post-acclimation ventilatory responses observed during the passive and active heating protocols following HA were not the result of an increased sensitivity to CO_2. Rather, the changes observed were more likely the result of greater stimulation of the respiratory center via cutaneous and/or pre-optic anterior hypothalamic temperature sensitive neurons. This, in turn provides further support to the hypothesis that hyperthermic-hyperventilation in humans is a thermoregulatory heat loss response.

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Table 5.1 Individual and mean (SD) $P_{ET}CO_2$ ventilatory recruitment threshold (VRT; mm Hg) and supra-VRT chemosensitivity ($L \cdot min^{-1} \cdot mm\ Hg^{-1}$) of the pre- and post-acclimation hyperoxic central chemoreflex ventilatory response to CO_2 at a normo- and hyperthermic T_{es} performed during a head out immersion.

	Pre-acclimation				**Post-acclimation**			
	Normothermic		***Hyperthermic***		***Normothermic***		***Hyperthermic***	
Participant	VRT	Sensitivity	VRT	Sensitivity	VRT	Sensitivity	VRT	Sensitivity
1[£]	40.30	4.82	34.00	3.74	36.70	4.36	42.50	13.07
2	46.50	1.93	47.80	2.06	49.60	1.49	49.60	1.13
3	48.10	2.74	46.10	3.48	46.90	1.86	45.00	2.71
4	46.70	3.91	46.10	4.33	44.00	3.86	47.30	5.98
5	43.20	4.66	43.00	5.49	46.90	6.60	43.80	6.05
6	47.60	2.38	41.60	2.71	46.70	3.71	45.80	3.06
7	48.80	1.11	53.10	2.30	48.80	1.66	51.50	2.43
8	46.70	1.63	50.90	3.26	47.10	1.69	49.30	4.35
9	44.00	7.73	47.30	7.34	46.00	6.76	43.60	7.46
10	47.40	3.50	48.10	3.84	46.90	4.91	49.00	3.51
Mean *(SD)*	46.56 *(1.84)*	3.29 *(2.02)*	47.11 *(3.55)*	3.87* *(1.68)*	46.99 *(1.59)*	3.62 *(2.11)*	47.21 *(2.81)*	4.08 *(2.05)*

* indicates a significant difference between the pre-acclimation normo- and hyperthermic conditions with a $p < 0.05$;
[£] participant was excluded from data analysis because his sensitivity during the post-acclimation hHHCVR was greater than 4 SDs above the mean

Table 5.2 Plasma bicarbonate concentration ($[HCO_3^-]_p$), pH, P_{CO2} and P_{O2} from arterialized blood samples (n = 6) taken prior to instrumentation (Normorthermic – Un-immersed) for, both, the normo- and hyperthermic hyperoxic- hypercapnic ventilatory response tests and during the hHHCVR tests when T_{es} was clamped at the hyperthermic level (Hyperthermic - Immersed) prior to starting the modified Read re-breathing protocol.

	Pre-acclimation			**Post-acclimation**		
	nHHCVR	***hHHCVR***		***nHHCVR***	***hHHCVR***	
Variable	Normothermic – Un-immersed	Normothermic – Un-immersed	Hyperthermic - Immersed	Normothermic – Un-immersed	Normothermic – Un-immersed	Hyperthermic - Immersed
$[HCO_3^-]_p$ ($mmol \cdot L^{-1}$)	25.48 *(2.02)*	25.57 *(2.44)*	24.03 *(2.39)*	25.68 *(1.45)*	25.40 *(1.14)*	25.17 *(1.50)*
pH	7.39 *(0.03)*	7.36 *(0.02)*	7.42[¥] *(0.06)*	7.38 *(0.03)*	7.37 *(0.02)*	7.41[¥] *(0.05)*
P_{CO2} (mm Hg)	44.83 *(3.76)*	46.33 *(5.54)*	38.50[¥] *(7.56)*	45.50 *(3.27)*	45.83 *(3.06)*	41.83 *(6.88)*
P_{O2} (mm Hg)	84.17 *(9.35)*	75.17[¥] *(7.25)*	85.17* *(4.83)*	82.67 *(8.04)*	74.50[□] *(5.96)*	86.67* *(4.93)*

* indicates a significant difference between the Nomorthermic – Un-immersed and the Hyperthermic - Immersed conditions within the hHHCVR trials with a p-value ≤ 0.05; [□] indicates a significant difference in the Normothermic – Un-immersed values between the post-acclimation nHHCVR and the hHHCVR with a p-value ≤ 0.05; [¥] indicates a trend for a difference between Normothermic - Unimmersed and the Hyperthermic – Immersed values during the hHHCVR trials with a $0.05 < p \leq 0.10$.

Figure 5.1 Overview of the pre-acclimation hyperoxic-hypercapnic ventilatory response tests. The normothermic trial (nHHCVR) always preceded the hyperthermic trial (hHHCVR). Pre-acclimation trials were followed by a 10 day passive heat acclimation to 50°C and 20 % RH for 2 h·day^{-1} after which the above protocol was repeated. The only difference between the nHHCVR and hHHCVR was that during the hHHCVR trials, a blood sample was drawn when T_{es} had stabilized at the hyperthermic level (e.g., BS #3). uREST and iREST represent un-immersed and immersed resting conditioning.

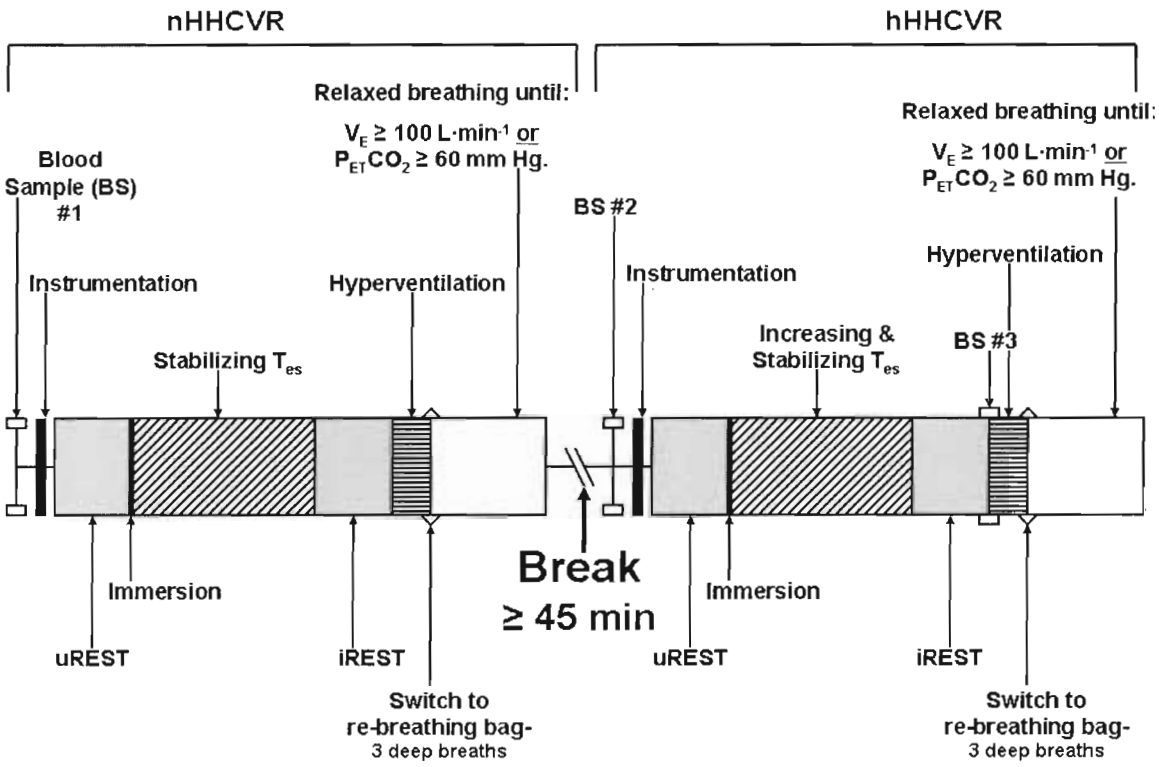


Figure 5.2 Breath-by-breath $\dot{V}_E$ vs. $P_{ET}CO_2$ plot of the pre- and post-acclimation hyperthermic hyperoxic-hypercapnic modified Read re-breathing tests (7) for one participant. The participant had returned to a relaxed breathing subsequent to taking 3 deep breaths in order to equalize P_{CO2} in the bag, lungs and arterial blood with venous blood after being switched to breathing from the re-breathing bag containing 5.5 % CO_2, 33 % O_2, balance N_2. Plot is representative of those fitted with the piecewise linear regression function (37) to determine the $P_{ET}CO_2$ threshold and supra-VRT chemosensitivity of the hyperoxic central chemoreflex ventilatory response to CO_2. Arrows indicate $P_{ET}CO_2$ of VRT. Fitted regression lines have been excluded for clarity.

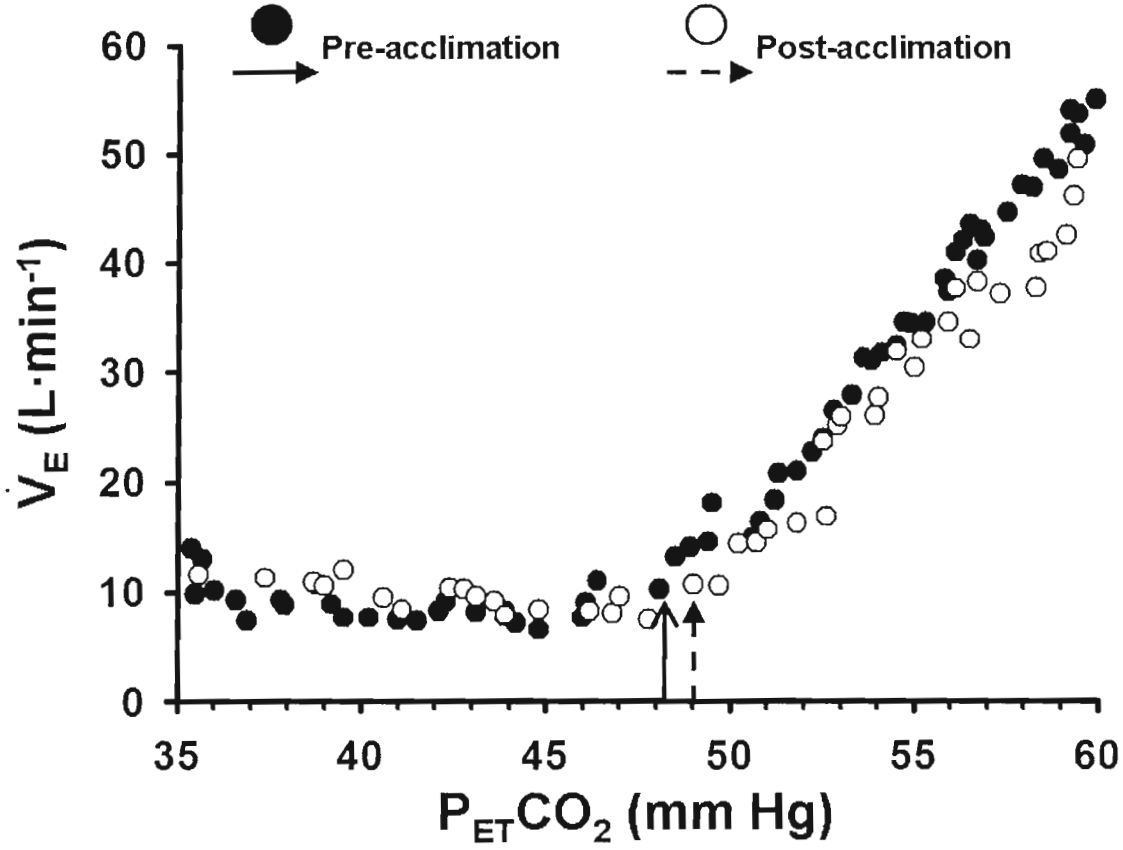


Figure 5.3 Mean pulmonary ventilation ($\dot{V}_E$; **A**), tidal volume (V_T; **B**), breathing frequency (f; **C**), total breath time (T_{TOT}; **D**), inspiratory time (T_I; **E**), and expiratory time (T_E; **F**) at rest when T_{es} was clamped at either the normo- or hyperthermic level while immersed up to the shoulders (iREST) and when $P_{ET}CO_2$ was at 40, 45 50 and 55 mm Hg while breathing from the re-breathing bag. Squares are the normothermic pre- (■, solid line) and post-acclimation (□, dashed line) trials and the circles are the hyperthermic pre- (●, solid line) and post-acclimation (○, dashed line) trials. Error bars in A represent ±SD, but were excluded from the remaining plots for clarity. Symbols represent comparisons between the normo- and hyperthermic trials. * and ** represents a significant difference during the pre- and post-acclimation trials, respectively, with a $p \leq 0.05$; † and †† represents a significant difference during the pre- and post-acclimation trials with a $p \leq 0.01$; ‡ and ‡‡ represents a significant during the pre- and post-acclimation trials with a $p \leq 0.001$; and ¥ and ¥¥ represents a trend during the pre- and post-acclimation trials with a $0.05 < p \leq 0.10$.

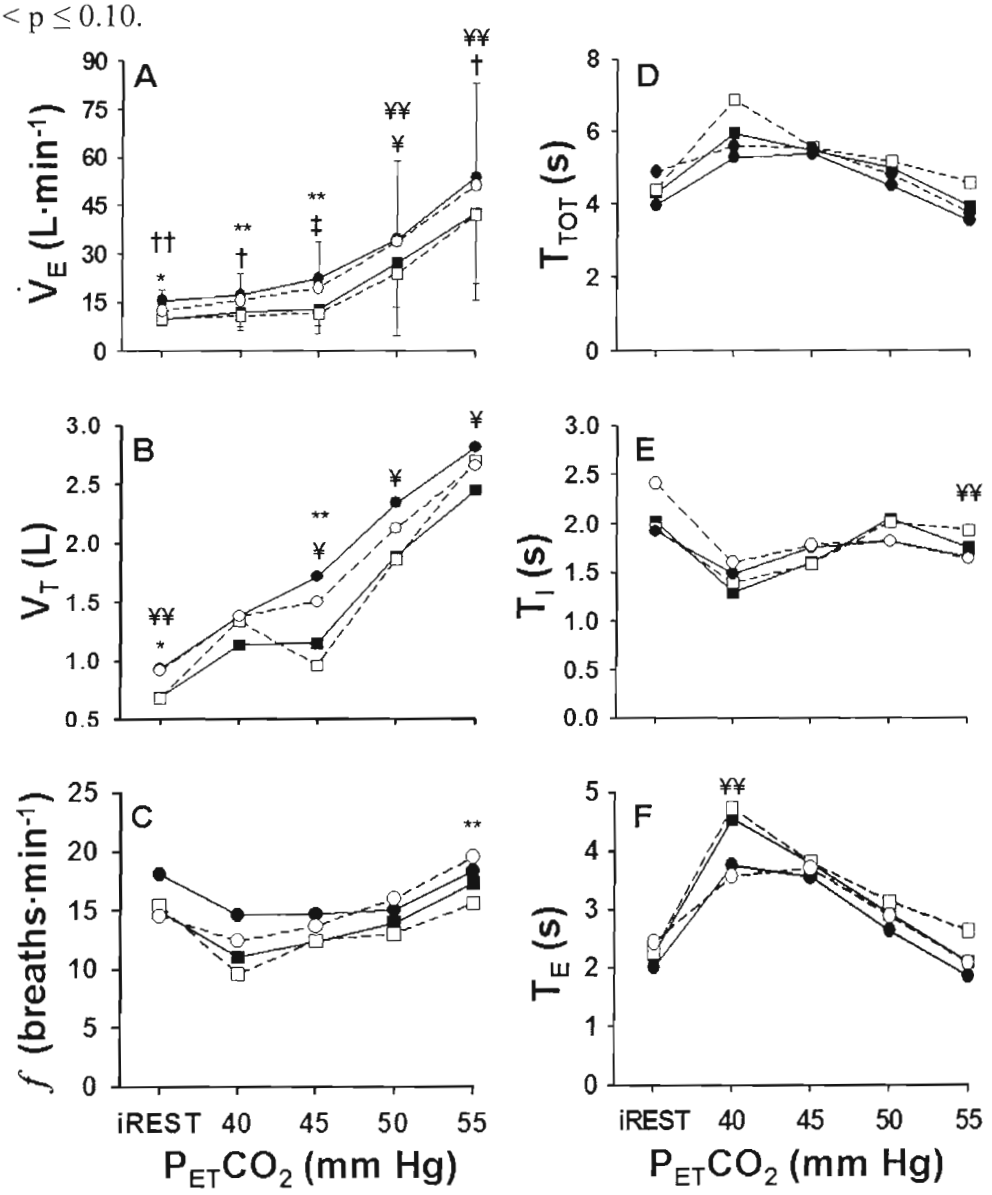
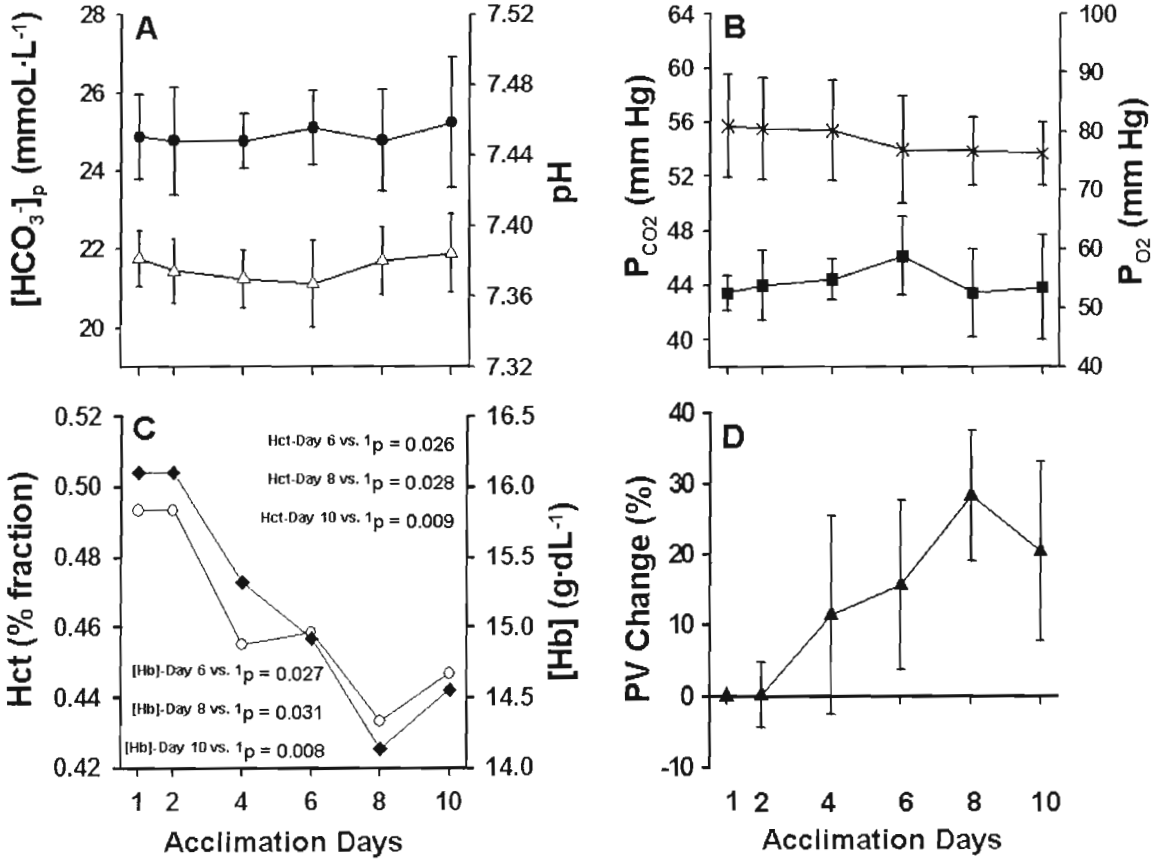


Figure 5.4 Normothermic, resting arterialized blood plasma bicarbonate concentration ($[HCO_3^-]_p$; ●) and pH (Δ; A), partial pressure of CO_2 (P_{CO2}; ■) and O_2 (P_{O2}; ×; B), haematocrit (Hct; ○) and haemoglobin concentration ([Hb]; ♦; C) and the percentage change in plasma volume (PV Change %; ▲) from baseline (i.e., HA Day 1) measured on the 2nd, 4th, 6th, 8th and 10th day of acclimation prior to instrumentation. Error bars represent ±SD and have been omitted from C for clarity. Only significant p-values are shown for the comparisons between Hct and [Hb] values on HA days 2, 4, 6, 8 and 10 to baseline measures on day 1. Mean $[HCO_3^-]_p$, P_{CO2} and P_{O2} are for n =8 and the Hct, [Hb] and PV changes are for n = 7. Hct and [Hb] were significantly decreased by Day 6 of the HA protocol compared to Day 1.



Chapter 6 – Thesis Summary

6.1 Research Hypotheses

1. **Acclimation to a hot environment will result in adaptation of ventilation and its components observed during a passively and actively-induced hyperthermia.**

This hypothesis was accepted as the T_{es} threshold at which $\dot{V}_E$ began to increase was significantly decreased within, both, the passive and active heating protocols following HA. Additionally, the hypothesis was validated as V_T was higher and f was lower at all levels of T_{es} examined during the post-acclimation passive heating protocol. The T_{es} threshold for the plateau in V_T and the increase in f were also significantly lower during the active heating protocol following HA.

2. **Heat acclimation will increase the sensitivity of the central chemoreflex ventilatory response to CO_2 during a passive hyperthermia. In addition, it is hypothesized heat acclimation will also modify the central chemoreflex ventilatory response to CO_2 during normothermia.**

The first hypothesis was not validated as the sensitivity of the hyperoxic central chemoreflex ventilatory response to CO_2 during a passive-induced hyperthermia was not significantly different following HA. The second hypothesis

was also rejected as the normothermic sensitivity of the hyperoxic central chemoreflex ventilatory response to CO_2 was not altered by HA.

3. **Arterialized P_{CO2}, plasma bicarbonate concentration ($[HCO_3^-]_p$) and pH will not be modified following acclimation to a hot environment.**

This third hypothesis was validated as the arterialized P_{CO2}, P_{O2}, $[HCO_3^-]_p$ and pH were not significantly affected by the HA protocol.

6.2 Testable Questions

1) **Following acclimation to a hot environment, will the onset of increase in cutaneous blood flow and the initiation of eccrine sweating occur at a lower core temperature during, both, a passive and active heating protocol? Additionally, will there be a greater gain in cutaneous blood flow and eccrine sweating for a given change in T_c?**

The T_{es} for the initiation of cutaneous vasodilatation and eccrine sweating were both significantly lower during the passively- and actively-induced hyperthermia following HA. The gain for both CBV_{TEMPLE} and $\dot{E}_{sw}$ (i.e., τ) were not significantly different following HA during either, the passive or active heating protocols.

2) **Following acclimation to a hot environment, will the core temperature threshold for thermally-induced increase in ventilation shift to a lower value and will the gain of the $\dot{V}_E$:T_c relationship be augmented during a passively and actively induced hyperthermia? Will the absolute levels of $\dot{V}_E$, V_T and *f* change during an acute heat stress following heat acclimation?**

The T_{es} threshold for the passively- and actively-induced hyperthermic increase in $\dot{V}_E$ was significantly lower following HA, but the gain of the $\dot{V}_E$:T_{es} relationship was not significantly different during either, the passive or active heating protocol. The post-acclimation $\dot{V}_E$ was not significantly different at the same T_{es} during the passive heating protocol, but was significantly higher at all levels of mean T_{es} during the active heating trials. Following HA, within the

passive heating trials, V_T was significantly higher and there was a trend for f to be lower at the same levels of T_{es}. For the active heating protocol, V_T was significantly higher at the lowest T_{es} and f was significantly higher at the two highest levels of T_{es} during the post-acclimation trials.

3) Will heat acclimation modify the $P_{ET}CO_2$ threshold and the sensitivity of the central chemoreflex ventilatory response to CO_2 during a normothermic- or hyperthermic-hyperoxic hypercapnic ventilatory response test measured by a modified Read re-breathing test?

Passive heat acclimation did not modify the $P_{ET}CO_2$ threshold (VRT) or the chemosensitivity of either the normo- or hyperthermic hyperoxic central chemoreflex ventilatory response to CO_2 assessed by a modified Read re-breathing test. Within, both the pre- and the post-acclimation re-breathing trials core temperature significantly interacted with $P_{ET}CO_2$ level so that there was a greater $\dot{V}_E$ at a given level of $P_{ET}CO_2$ within the hyperthermic trials, compared to the normothermic trials.

4) **Will the pattern of ventilation observed during normothermic- and hyperthermic-hyperoxic hypercapnic ventilatory response tests be modified by acclimation to hot environment?**

The ventilatory pattern observed during both the normo- and hyperthermic hyperoxic central chemoreflex ventilatory response to CO_2 trials was not significantly different following HA.

5) **Will the arterialized P_{CO2}, bicarbonate concentration ($[HCO_3^-]_a$) and pH_a be modified following acclimation to a hot environment.**

The 10-day passive heat acclimation protocol did not have a significant effect on arterialized levels of P_{CO2}, $[HCO_3^-]_a$ or pH_a. Following HA, arterialized P_{CO2}, $[HCO_3^-]_a$, pH_a were not different from the pre-acclimation levels measured prior to the start of the normo- and hyperthermic hyperoxic-central chemoreflex ventilatory response tests. Additionally, pre- and post-acclimation levels of arterialized P_{CO2}, $[HCO_3^-]_a$ and pH_a measure during the hHHCVR trials when T_{es} was clamped at the hyperthermic level were not significantly different.

6.3 Thesis Summary and Future Directions

Overall, the hyperthermic-induced increase in $\dot{V}_E$ observed during both a passively- and actively-induce hyperthermia adapted following the passive heat acclimation in a manner expected if hyperthermic-induced increases in $\dot{V}_E$ is a human thermoregulatory heat loss response. In addition to lowering the T_{es} threshold for increases in $\dot{V}_E$ during the passive heating protocol, the pattern of $\dot{V}_E$ was modified to increase respiratory heat loss. In addition, the T_{es} threshold at which V_T began to plateau and f began to increase were also decreased a similar amount and $\dot{V}_E$ was higher for a given T_{es}. Following HA, the normo- and hyperthermic hyperoxic central chemoreflex ventilatory response to CO_2 was not modified, but irrespective of acclimation state, hyperthermia enhanced the chemosensitivity to a CO_2 stimulus over the whole range of $P_{ET}CO_2$ explored.

Future directions would be to determine how human hyperthermic hyperventilation would adapt following an active heat acclimation protocol while employing a control group to account for the possible training effect that may arise. Additionally, it would be interesting to explore whether acclimation to a hot-humid environment would produce similar adaptations to the human hyperthermic hyperventilation as it known to produce slightly different adaptations in traditional human heat loss responses. Finally, assessing chemosensitivity during exercise before and after HA may help clarify some of the ventilatory changes observed in Chapter 4.

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Appendix A

Esophageal thermocouple and rectal thermistor temperature calibrations

Participants' esophageal thermocouples and rectal thermistors were calibrated using a temperature regulated, circulating water bath (Model 1196, VWR International, Mississauga, Ont., Canada) monitored by a platinum precision thermometer (Fisherbrand Traceable RTD, Fisher Scientific, Ottawa, Ont., Canada). Probes were immersed in the water bath and the temperature was increased from approximately 36.0 to 40.0°C. For the esophageal probes, the water bath was increased in ~1.0°C increments and for the rectal thermistors the water bath temperature was increased in 0.5°C increments. At each temperature, the water bath was allowed to stabilize for a minimum of 10 min, after which the probes were immersed and connected to a SCXI-1000 data acquisition system (National Instruments, Austin, TX, USA) controlled by LabVIEW software (National Instruments, Austin, TX, USA, version 7.1) on a personal computer. Each probe was immersed at every bath temperature for at least 5 min prior to values being recorded for 3 min. Table A.1 and A.2 contain the 3 min mean temperature value for each participant's esophageal and rectal probes at all eight water bath temperatures, respectively. Figure A.1 and A.2 plots the actual temperature of the circulated water bath versus the mean of all participants' esophageal and rectal probes at each stabilized water bath temperature.

Table A.1 Mean temperature for each 3 min recording of participants' esophageal thermocouples immersed in a temperature regulated circulated water bath monitored by a precision platinum thermometer at eight stable water temperatures.

	Water Bath Temperature (°C)				
Participant	***36.05***	***37.04***	***38.05***	***39.04***	***40.07***
1	36.80	37.75	38.72	39.68	40.80
2	36.95	37.72	38.84	39.75	40.80
3	36.74	37.84	38.75	39.73	40.77
4	36.74	37.69	38.72	39.72	40.80
5	36.75	37.81	38.72	39.75	40.80
6	36.74	37.69	38.72	39.75	40.80
7	36.72	37.72	38.71	39.72	40.80
8	36.72	37.67	38.70	39.72	40.80
9	37.10	37.67	38.70	39.75	40.98
10	36.75	37.71	38.70	39.72	40.69
Mean *(SD)*	**36.81** *(0.13)*	**37.73** *(0.06)*	**38.73** *(0.04)*	**39.73** *(0.02)*	**40.80** *(0.07)*

Table A.2 Mean temperature for a 3 min recording of each participant's rectal thermistor immersed in a temperature regulated circulated water bath monitored by a precision platinum thermometer at eight stable water temperatures.

	Water Bath Temperature (°C)							
Participant	***36.02***	***36.53***	***37.03***	***37.53***	***38.03***	***38.53***	***39.04***	***39.54***
1	36.00	36.51	37.01	37.51	38.02	38.52	39.02	39.53
2	35.98	36.48	36.99	37.49	38.00	38.50	39.00	39.50
3	35.96	36.48	36.98	37.48	37.99	38.50	38.99	39.49
4	36.03	36.52	37.02	37.53	38.04	38.53	39.05	39.56
5	36.04	36.52	37.03	37.54	38.04	38.54	39.06	39.55
6	36.02	36.53	37.03	37.53	38.05	38.55	39.05	39.56
7	36.02	36.53	37.02	37.53	38.03	38.53	39.04	39.55
8	36.06	36.56	37.08	37.57	38.08	38.58	39.09	39.59
9	36.01	36.50	37.02	37.52	38.01	38.53	39.02	39.52
10	36.03	36.53	37.02	37.53	38.03	38.54	39.04	39.55
Mean *(SD)*	**36.02** *(0.03)*	**36.52** *(0.02)*	**37.02** *(0.03)*	**37.52** *(0.03)*	**38.03** *(0.03)*	**38.53** *(0.02)*	**39.07** *(0.03)*	**39.54** *(0.03)*

Figure A.1 Circulated water bath temperature monitored by a platinum thermometer plotted against the mean temperature of all participants' esophageal thermocouples at five different water temperatures. The line of identity (y = x) is indicated by the dashed line.

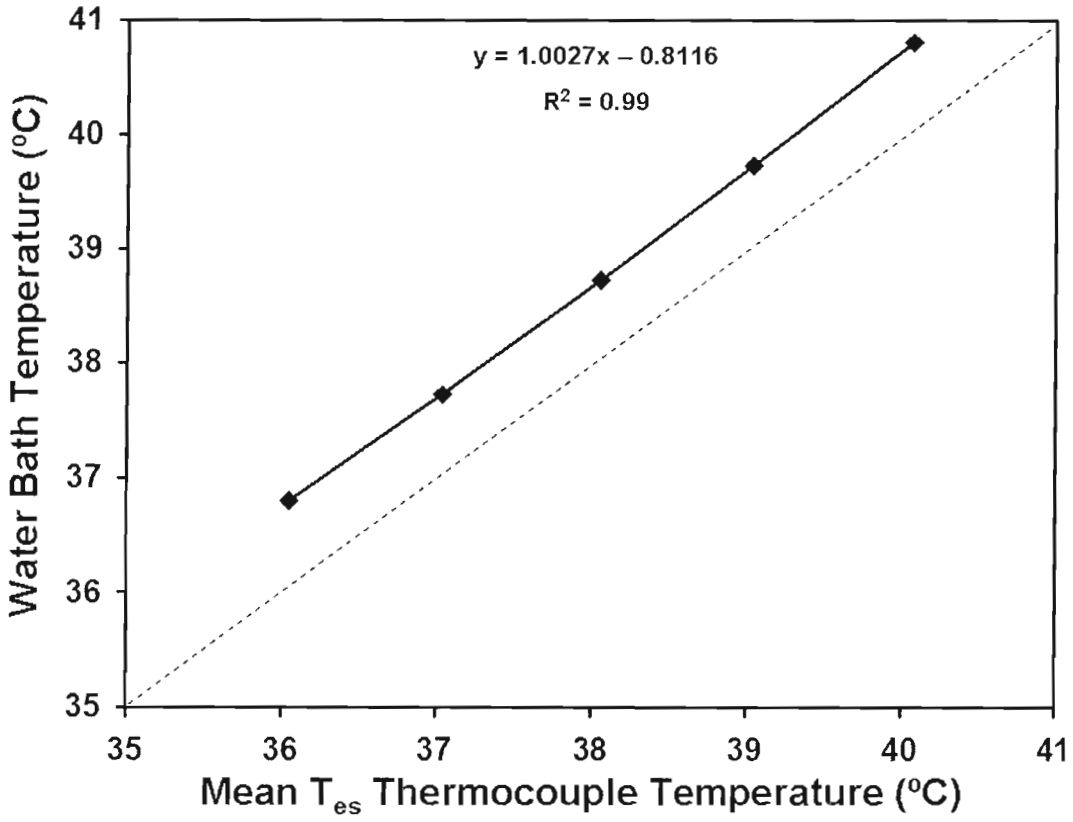
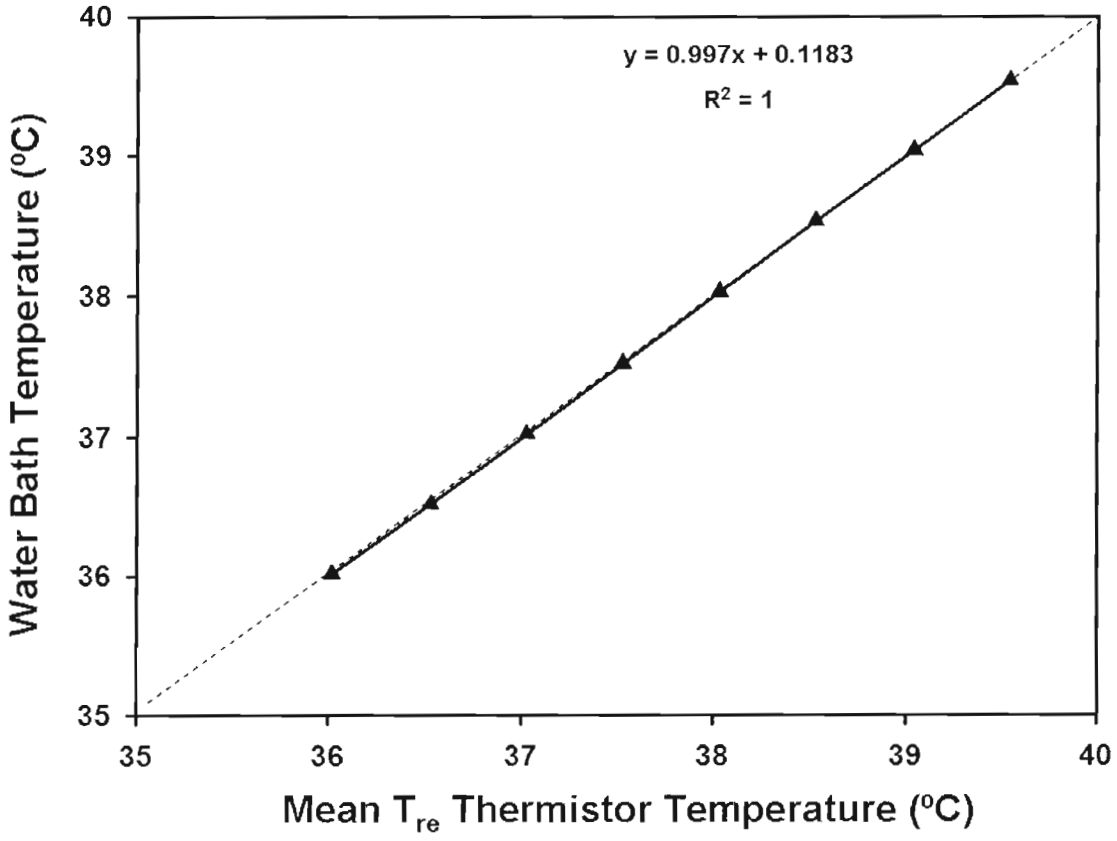


Figure A.2 Circulated water bath temperature monitored by a platinum thermometer plotted against the mean temperature of all participants' rectal thermistors at each of the eight water temperatures. Line of identity (y = x) indicated by the dashed line.



Appendix B

Time constant for eccrine sweating measurement set-up

To determine the response time of the eccrine sweating measurement set-up utilizing a capacitance hygrometer (HMT337, Vasaila, Helsinki, Finland), a water filled, sealed glass jar with a 2.4 cm diameter hole cut into the lid and covered with a piece of porous tape (3M Transpore Tape, London, ON, Canada) to simulate the skin surface was utilized. Initially, the sweat capsule was place on non-permeable clear plastic barrier covering the hole in the lid to replicate resting (non-sweating) conditions. The glass jar was then heated until the water temperature reached ~37.5 to 38.5°C, at which point the plastic barrier was removed and the capsule was placed directly over the perforated tape covered hole. It was held in place for a minimum of three minutes or until the humidity measurements plateaued. The glass jar was filled with sufficient water so that the surface of the water touched the bottom side of the porous tape when the lid was on tight and the sweat capsule was flushed with an anhydrous air source continuously at 1 $L \cdot min^{-1}$. An additional small hole was punched into the lid along its edge just large enough for the insertion of a T-type thermocouple (Omega Engineering Inc., Stanford, CT, USA).

The time constant of the system for each trial was calculated by fitting a mono-exponential curve to the relative humidity versus time plot for each trial using commercial graphing software (Sigma Plot 9.0, Systat Software Inc., Point Richmond, CA, USA) and the following equation:

$$RH_{pred} = RH(ss) + \Delta RH(ss) \times (1 - e^{(-(time\text{-}delay)/\tau)}) \quad (C.1)$$

where RH_{pred} is the predicted relative humidity at a specific "time"; RH(ss) is the baseline RH when the capsule was on the non-permeable barrier covering the hole in the jar cap; $\Delta RH(ss)$ is the maximal steady state output above the baseline levels; "delay" is the time before the plastic barrier is removed and the RH began to rise; and τ (tau) is time it takes for the RH_{pred} to reach 63.2% of the $\Delta RH(ss)$. Figure B.1 is a representative RH response fitted with the mono-exponential function used to determine τ. Table B.1 shows the mean RH(ss), $\Delta RH(ss)$, τ, and R^2 of the fitted mono-exponential function for five trials performed .

Table B.1 Individual temperature of the water within the glass jar (T_{H_2O}; °C) and the RH(ss) (%), ΔRH(ss) (%), tau (s) and R^2 values of the mono-exponential function fitted the RH vs. time plots for the 5 trials performed to determine the response of the eccrine sweat rate measurement set-up using a Vasaila HMT337 capacitance hygrometer.

Trial	T_{H2O} (°C)	RH(ss) (%)	ΔRH(ss) (%)	Tau (s)	R^2
1	37.75	0.41	23.73	18.56	0.99
2	38.04	0.71	24.17	18.98	0.99
3	38.23	1.02	17.10	13.03	0.99
4	37.51	1.43	19.64	16.23	1.00
5	37.57	0.82	17.71	13.48	0.99
Mean *(SD)*	**37.82** *(0.31)*	**0.88** *(0.38)*	**20.47** *(3.32)*	**16.06** *(2.77)*	

Figure B.1 Representative plot of relative humidity (%) vs. time (s) used to determine the tau (τ) of the eccrine sweat measurement system employing a Vasaila HMT337 capacitance hygrometer.