Influence of Body Temperatures and Hypercapnia on Pulmonary Ventilation During Hyperthermia

by

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B.Sc. (Hons.), Simon Fraser University, 2009

THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

In the Department of
Biomedical Physiology and Kinesiology

SIMON FRASER UNIVERSITY

Summer 2010

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Acknowledgements

I would have to start by acknowledging my supervisory committee in Dr. Matthew White and Dr. Michael Walsh. Without their respective intellectual guidance, my proceeding through the program at an accelerated rate would not have been possible. Dr. White spent unprecedented hours guiding me, allowing me to keep up the furious pace I had set for myself. He pushed me to excel through academia and provided me with endless opportunities to develop as a student and as an individual. My graduate student advisor deserves my thanks for always and relentlessly supporting my personal development and progress through the program even when others may not have been.

My friends and room mates have made it possible for me to survive long hours and endless days of work in the lab. Going home became an exciting event to look forward to at the end of the day. My camping, skiing, climbing (etc) mates truly made it possible for me to "work hard but play harder". They really demanded that I remained grounded and at the worst of times, physically pulled me out of a spiral of workaholic tendencies. Of this I am most grateful.

I would also like to thank all my mentors (family and friends alike) for teaching me the values of goal setting. They provided me a means by which I was able to accomplish so much while sacrificing so little. Possibly more important they taught me the importance of being mindful of what one focuses on, and the importance of the personal values upheld by those accomplishments.

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List of Definitions

Acral regions	Regions pertaining to the legs or other extremities.
Arterio-Venuous Anastomoses	A vessel joining arterioles and venules allowing blood to bypass the capillary beds.
Control or Control System	Control refers to the action of a system on the responses that oppose perturbations of a regulated variable. eg. core temperature
Cutaneous Blood Flow	The proportion of blood of, flowing through, or affecting the skin.
Eccrine Sweating	A response of eccrine sweat glands to a thermal stimulus that produces a clear aqueous secretion intended to cool the skin without releasing part of the secreting cell in the process.
Glabrous Skin	Skin that is normally smooth and devoid of hair follicles.
Non Glabrous Skin	Skin with hair follicles.
Heat Storage	Storage of body heat within the body tissues.
Latent Heat of Vaporization	The amount of energy released or absorbed by a chemical substance during the transition from liquid to gas phases.
Phase 1 Panting (Tachypnea)	A rapid respiratory frequency accompanied by an increase in respiratory minute volume and, commonly, a decrease in tidal volume, in response to a thermoregulatory need to dissipate heat. $P_{ET}CO_2$ remains unchanged.
Phase 2 Panting (Thermal Hyperpnea)	An increase in tidal volume associated with and increase in alveolar ventilation occurring during severe heat stress which "normally" has caused a large rise in core temperature. In animals capable of thermal panting the phase of thermal hyperpnea with its slower deeper breathing is also named second phase panting.
Regulation	The maintaining constant of a variable in the *milieu interieur*. The main property of a control system is that a deviation of the regulated variable triggers a correcting response which opposes the deviation.
Resonating Frequency	An inherent property describing the specific frequency at which an object vibrates.

Servomechanism	1. A feedback system that consists of a sensor, controller, and effector, used in the automatic control of a given variable. 2. A self-regulating feedback system or mechanism.
Thermosensitive Neurons	Neurons that change in firing amplitude and/or frequency in response to changes in their temperature.
$\dot{V}O_{2\ MAX}$	The maximal capacity of an organism to utilize oxygen during maximal exertion.
$\dot{V}O_{2\ PEAK}$	The maximal oxygen consumption utilized by the body during a given work period

List of Abbreviations

ANOVA	(analysis of variance)
ATP	(adenosine triphosphate)
cAMP	(cyclic adenosine monophosphate)
CF	(cystic fibrosis)
CNS	(central nervous system)
$\dot{C}_{res}$	(rate of respiratory convection)
$\dot{C}_{v}$	(rate of convection)
DRG	(dorsal respiratory group)
$\dot{E}_{res}$	(rate of respiratory evaporation)
$\dot{E}_{SK}$	(rate of skin evaporation)
$\dot{E}_{SW}$	(eccrine sweat rate)
F_R	(frequency of Respiration)
$\dot{F}_{AIR}$	(rate of air flow)
HR	(heart rate)
$\dot{K}$	(rate of conduction)
$\dot{M}$	(metabolic rate)
NO	(nitric oxide)
P_aCO_2	(arterial partial pressure of carbon dioxide)
P_aO_2	(arterial partial pressure of oxygen)
PAR-Q	(Physical Activity Readiness Questionnaire)
$P_{ET}CO_2$	(end-tidal partial pressure of CO_2)
$P_{ET}O_2$	(end-tidal partial pressure of O_2)
pH_a	(arterial pH)

POAH	(preoptic anterior hypothalamus)
$\dot{R}$	(rate of radiation)
RH	(relative humidity)
$\dot{S}$	(rate of heat storage)
SA	(surface area)
S_aO_2	(arterial hemoglobin oxygen saturation)
T_{AMB}	(temperature – ambient)
T_{CORE}	(core temperature)
T_{ES}	(temperature – esophageal)
T_{RE}	(temperature – rectal)
$\bar{T}_{SK}$	(temperature – mean skin)
$\dot{T}_{SK}$	(temperature – rate of change of skin)
T_{SK}	(temperature – skin)
$T_{SK\,L}$	(temperature – local skin)
T_{TY}	(temperature – tympanum)
$\dot{V}_E$	(rate of pulmonary ventilation)
$\dot{V}_E/\dot{V}CO_2$	(ventilatory equivalent for carbon dioxide)
$\dot{V}_E/\dot{V}O_2$	(ventilatory equivalent for oxygen)
VIP	(vasoactive intestinal peptide)
$\dot{V}O_{2\,MAX}$	(maximal oxygen use)
$\dot{V}O_{2\,PEAK}$	(peak oxygen use)
VRG	(ventral respiratory group)
V_T	(tidal Volume)
$\dot{W}$	(rate of mechanical work)
ρ_{steam}	(grams of water vapor per liter of air)

CHAPTER 1: Thesis Overview

The thesis begins in Chapter 2 with a comprehensive review of the literature surrounding topics of human thermoregulation and control of exercise ventilation in humans. This includes a general overview of the various engineering principles that physiologists use to describe and characterize the systems involved in temperature regulation and control of pulmonary ventilation. The review then progresses to describe the physiological mechanisms and components of these systems. This is followed by a description of the body's ventilatory response to exercise. Several hypotheses are proposed that attempt to describe the mechanisms underlying the paradoxical increase in ventilation relative to metabolic demands. Subsequently, an alternative hypothesis is proposed for the control of exercise ventilation by which temperature signals from the hypothalamus result in altered breathing patterns during periods of exercise and active hyperthermia.

In Chapter 3 the first study investigated: 1) if $\overline{T}_{SK}$ influences exercise ventilation and 2) if $\overline{T}_{SK}$ and $P_{ET}CO_2$ interact in their influence on exercise ventilation. The results from this study support the hypothesis that exercise ventilation is modified by $\overline{T}_{SK}$ under hyperthermic but not normothermic core temperature conditions. In this study, the results did not support the hypothesis that $\overline{T}_{SK}$ would interact with $P_{ET}CO_2$ in its influence on exercise ventilation.

In Chapter 4, in the second study of this thesis, the question addressed was if the observed rate of dynamic skin temperature changes, that are known to influence thermoregulatory responses, also influence resting pulmonary ventilation in humans.

Both pre and post exercise states were analyzed in humans with normothermic core temperatures. The results support the hypothesis that pulmonary ventilation responds in a similar manner to dynamic changes in skin temperature in normothermic resting humans, in either pre or post exercise conditions.

In Chapter 5 the responses are given for the hypotheses and testable questions from Chapters 3 and 4.

Throughout the thesis, the number of the citation refers to the number in the reference list that immediately follows each individual chapter. A complete list for all the references is presented in alphabetical order at the end of the thesis. Following the alphabetical list of references, Appendix A gives a list of calibration equations for the core and skin temperature thermocouples.

CHAPTER 2 Literature Review

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2.0 Neurophysiological Basis of Temperature Regulation in Hyperthermia

The human body's control system for defence of core temperature during hyperthermia receives information from its environment from the temperature sensitive tissues. While this information comes from a variety of tissues and organs, such as the spinal cord and abdomen (78), there are two main groups of temperature sensitive neurons that participate in the body's temperature regulation. This anatomical division gives those temperature sensitive neurons in the central nervous system including the hypothalamus and those in the periphery including the skin.

A first main group of temperature sensitive neurons in this control system, that participates in the control of thermolytic responses, the central nervous system group, is located in the pre-optic anterior hypothalamus (POAH) and spinal cord (21). These areas serve as temperature sensors themselves (26, 75, 87) as well as integrators of converging temperature signals from the rest of the body (24, 27, 74).

The second peripheral group of neurons in this anatomical division consists mainly of an intricate system of cutaneous thermosensitive neurons that sense skin temperature. These neurons are typically 0.15 to 0.20 mm below the skin surface (80). There is a highly interactive and integrated relationship between core and peripheral temperature sensitive neurons. This has increased the challenge of exemplifying the characteristics of each of these groups of temperature sensitive neurons and how each group participates in thermoregulatory responses.

There are two populations of the neurons within each of these two anatomical groups of thermosensitive neurons. They are physiologically defined and functionally distinct warm and cold-sensitive neurons. To be considered warm-sensitive, during increases in their temperature, their thermosensitivity must be at least 0.8 impulses·°C^{-1}·s^{-1} (25, 27). To be considered cold-sensitive, thermosensitivity must be at least -0.6 impulses·°C^{-1}·s^{-1} during decreases in their temperature (25, 27).

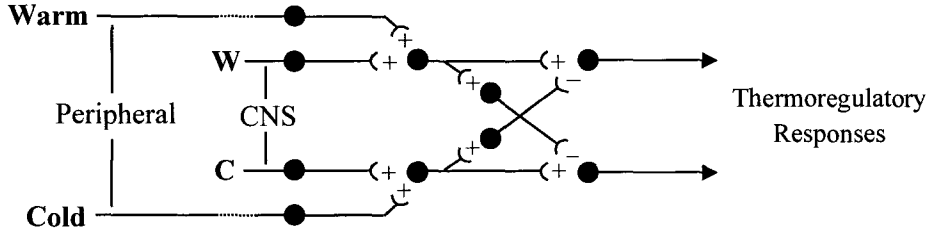

Fig 2.1: A diagrammatic representation of reciprocal cross inhibition between warm and cold sensitive neurons.

The central temperature sensitive neurons receive input from δ (delta) fibers in the skin via what are likely collateral projections from the lateral spinothalamic tract (21). Neurons from these tracts have cell bodies contained within the dorsal horn of the spinal cord and where they decussate. For the most part, peripheral neurons that respond to skin cooling/ heating innervate warm- or cold-sensitive neurons in the hypothalamus (18, 21). Increased extra-hypothalamic heating stimulates the POAH warm-sensitive neurons from these peripheral neurons. Evidence suggests that there is a reciprocal cross inhibition (Fig. 2.1) observed during warming where warm-sensitive neurons receive decreasing inhibitory input from the cold-sensitive neurons (18, 21). The same mechanism of reciprocal cross inhibition applies to the pathway of cold sensitive neurons in that during

cooling, cold-sensitive neurons receive decreasing inhibitory input from the warm-sensitive neurons. In support of this view, studies have shown that presynaptically blocking synaptic transmission from the warm-sensitive tissues within the hypothalamus greatly decreases thermosensitivity of cold-sensitive neurons (98, 99). This also supports that increases in cold-sensitive neuron sensitivity are accomplished via the relaxation of inhibitory inputs from warm-sensitive neurons (21).

There are many inputs including a combination of excitatory and inhibitory post synaptic potentials, that influence the activation level of the warm-sensitive hypothalamic neurons (23). The convergence of peripheral and central thermoregulatory inputs, for example, occurs at the aforementioned warm-sensitive neurons (21). The integrated signals are subsequently transmitted to both the cerebral cortex giving conscious awareness of these temperatures as well as to the effectors that initiate the autonomic thermoregulatory responses.

The efferent signals from the hypothalamus are sent to various brain areas so as to elicit different thermoregulatory responses. In the control of cutaneous blood flow, these signals go to the midbrain and ventral tegmental area (177). These areas receive neurons that are excited by and inhibited by hypothalamic warming respectively (91). Sweat glands are innervated by sympathetic cholinergic neurons with pre-ganglionic cell bodies located within the spinal cord. These neurons receive information from the peripyramidal and raphé areas of the medulla which are, in turn, innervated by the temperature sensitive neurons from the hypothalamus (141).

2.1 Regulation of Core Temperature

2.1.1 Heat Balance

Human beings are homeotherms that are charged with the task of regulating their own core temperature amidst a variety of environmental stresses. This temperature based control system modulates thermoeffector responses that influence body heat content. There are several specific avenues of heat transfer to and from the human body that are controlled by this system. These include metabolic rate ($\dot{M}$) which is always positive and evaporation rate ($\dot{E}$) which is always negative. The two main avenues of evaporative heat loss are from respiration ($\dot{E}_{res}$) and from sweat evaporation on the skin surface ($\dot{E}_{sk}$). Also included are rates of radiation ($\dot{R}$), conduction ($\dot{K}$), convection ($\dot{C}_v$), and respiratory convection ($\dot{C}_{res}$) as well as rates of energy lost or gained as mechanical work ($\dot{W}$). The sum of these rates is known as the rate of heat storage ($\dot{S}$) of the body (138). When the rate of heat storage equals zero, the body is in a state of thermal balance and core temperature remains constant. As mentioned above, to maintain this thermal homeostatic environment, humans defend their core body temperature within a narrow range (18, 34, 71, 119, 152). The rate of heat storage and the different avenues of heat gain or loss are described in equation 2.1, as given below:

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

2.1.2 Models of Thermoregulation in Homeotherms

As mentioned above, the human core temperature regulation circuitry is often engineered as a pseudo-servomechanism. Employing these engineering principles, two main models of human and mammalian core temperature regulation have emerged. These

are the set-point (34, 71) and null zone models of human core temperature regulation (18, 119, 152).

The set-point model functions by stabilizing core temperature about a given or desired set point of ~37.0°C with elevations or decreases as little as 0.1°C inducing elevated heat loss or gain responses (12). In response to deviations from this hypothetical set point, graded thermoregulatory responses counteract the given thermal stresses to the body. There are three main components that allow this type of control system to be effective. There are "sensors" that monitor body temperatures, "controllers" which integrate the stimulus presented by the sensors to formulate a response, and "effectors" which receive the signal from the controllers and carry out the necessary thermoregulatory response. Information in this negative feedback circuit is constantly flowing as to maintain values as close to the desired set point as possible.

Sensors for the set point theory include warm and cold-sensitive temperature sensitive neurons that intersect at single temperature (Fig. 2.2). This suggests a case of reciprocal cross inhibition of heat loss and heat production responses thus protecting core temperature about a set point (34). Support for this model is from Hammel (71) who found heating and cooling of the hypothalamus of the dog with a thermode invoked thermoregulatory responses even though extrahypothalamic core temperatures were essentially normothermic. These thermoregulatory responses were demonstrated to be regulated about a "set point" hypothalamic temperature (71). Cabanac and Massonnet's (34) study furthered this view by showing that by heating and cooling humans in water baths, they could invoke thermoregulatory responses that again appeared

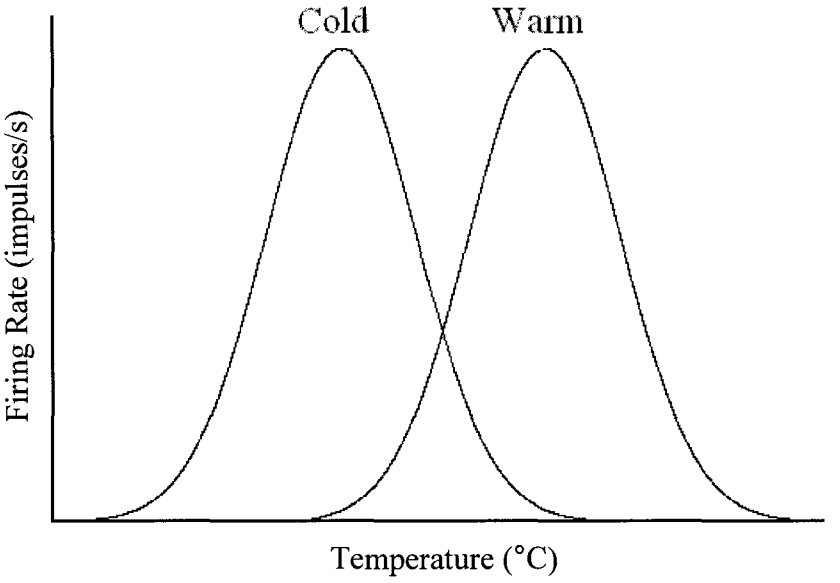

Fig 2.2: Activity profiles of warm and cold sensitive neurons

to be regulated about a given set-point esophageal temperature. In addition, a number of core temperature set-point about which the body functions (5, 63, 86). Sleep has been shown to lower the set point (63), while exercise and a fever can also alter the set point (5, 86).

In addition to the set-point model, an alternate null zone model (18, 119) or inter-threshold range (152) has been suggested for temperature regulation in humans and mammals. The null zone model supports that there is not a set-point, but a range of core temperatures that are absent of sweating or shivering responses. This zone or range was demonstrated in humans both by Mekjavic et al (119) and by Sessler's group (18, 113). It was found that an esophageal temperature difference of 0.59°C separates the onset of heat gain from heat loss responses (119). Proponents of the null zone model (18, 113) suggest that an exact set-point temperature (118) would be physiologically unreasonable to maintain when there is such a mass of inputs and effectors in the system. The view is

there is bound to be noise in any such feedback circuit making it inefficient to protect core temperature so closely that energy is constantly lost by eliciting these thermoregulatory responses, as opposed to protecting it within a range of physiologically viable values. The null zone represents a range of physiologically viable core temperatures under which the body senses no substantial threat to thermal homeostasis. A plethora of research (12, 18, 21, 119, 152) has been completed to characterize the nature and mechanisms of these two models of the thermoregulatory system. It remains to be resolved if the set-point or the null-zone model is the most appropriate model for the human or mammalian temperature regulation systems.

2.1.3 Models of Thermolytic Responses

2.1.3.1 Temperature Sensors

The eccrine sweating model developed by Nadel et al (123) characterizes the various temperature inputs that sensors convey to the central controller, thus generating the observed eccrine sweating response (Equation 2.2).

$$\text{Sweating Rate} = [\alpha(T_{ES} - T_{ES\,0}) + \beta(\bar{T}_{SK} - \bar{T}_{SK\,0} + \gamma[\dot{T}_{SK} - r_{0}])]e^{(T_{SK\,L} - T_{SK\,0})/\delta} \qquad (2.2)$$

$\alpha, \beta, \gamma, \delta$..... Individual Constants

T_{ES}..... Esophageal Temperature

$T_{ES\,0}$..... Esophageal Temperature Set Point

$\bar{T}_{SK}$..... Mean Skin Temperature

$\bar{T}_{SK\,0}$..... Mean Skin Temperature Set Point

$\dot{T}_{SK}$..... Rate of Change of Skin Temperature

r_0..... $\dot{T}_{SK}$ Set Point

$T_{SK\,L}$..... Local Skin Temperature

In Nadel's model, central warm sensitive neuron activities are represented by different levels of T_{ES} and peripheral warm sensitive neurons activities are represented by $\bar{T}_{SK}$, and $\dot{T}_{SK}$ (33, 123). From this model of eccrine sweating rate, evidence supports that there is a central controlling center for sweat secretion (3, 81) that responds to these different temperature inputs. When considering central thermoregulatory drive, local skin temperature (i.e. $T_{SK\,L}$-$T_{SK\,0}$/ δ) can be ignored as it is thought to effect sweating rate only through peripheral modifications independent of the central controller's output at the sweat glands themselves (31). As such, this model implicates increases in both body core temperature, and mean skin temperature, and changes in the rate of change in skin temperature are the signals integrated by our bodies in the control system that stimulates eccrine sweating, to help regulate core temperature.

Static Skin Temperature Changes

To examine the influence of different levels of mean skin temperature, on thermoregulatory responses including sweating, $\bar{T}_{SK}$ was altered in several studies without changing T_{ES} (32, 35, 123, 161, 162). The results for the eccrine sweating response supported that warm receptor inputs from $\bar{T}_{SK}$ occurred within a range of $\bar{T}_{SK}$ from 30°C to 50°C (51). Over this range of $\bar{T}_{SK}$ there is evidence to support a multiplicative interaction between peripheral and central temperature signals in their influence on eccrine sweating (32, 35). A number of other studies, however, suggest a

summation of the effects of core and skin temperature in their determination of efferent output to the eccrine sweat gland effectors (123, 161, 162). Changes in skin temperature have been shown to alter the core temperature thresholds for initializing thermoregulatory responses in an additive effect, as seen for eccrine sweating (11, 75). Cooling the body surface for example, raises the core temperature threshold for the onset of sweating (75). Increasing the local skin temperature was also found to have a stimulatory effect, independent of central drive or efferent output to induce eccrine sweat gland secretion, when central and mean global skin temperatures were held constant (31, 32, 116). Bullard et al. (31, 32, 116) suggested that this effect might be due to a temperature dependence of neurotransmitter release in the area of the sweat glands. This local temperature effect is supported by the resemblance to amplification/divergence models associated with molecular mechanics.

Dynamic Skin Temperature Changes

The response to dynamic changes in skin temperature has been well examined for its influence on eccrine sweating (9, 123, 176). This response, interestingly, was only observed during negative $\dot{T}_{SK}$ and was absent during positive $\dot{T}_{SK}$ (123). Hensel's work (77, 79) supported this finding by demonstrating the dynamic nature of the responses of thermosensitive nerve endings with direct recordings.

Ultimately it is still not entirely understood how information from cold and warm temperature sensitive neurons are integrated by the central controller in the control of heat loss responses (18). This central controller is reviewed in the next section where a description is given for the control of human thermolytic or heat loss responses.

2.1.3.2 Central Controller for Thermolytic Responses

As described previously, the thermoregulatory system is believed to give the integration of sensory input from both central and cutaneous temperature sensitive neurons. The thermosensitive neurons of the preoptic anterior hypothalamus (POAH) and their activity are often approximated by measuring temperature at easily accessible sites such as the esophagus (T_{ES}) and tympanum (T_{TY}). The temperature of the POAH plays a major role in the integrations of central and peripheral temperature signals. It is the crucial anatomical site and step that generates numerous thermoregulatory responses. Satinoff, however, showed that lesions in the hypothalamus and at lower spinal levels can vastly effect the nature of the thermoregulatory responses generated (144-146) and that thermoregulation continues despite these lesions. This suggests that in addition to the hypothalamus there are multiple regulatory loops at different spinal levels that are involved in the regulation of core temperature.

2.1.3.3 Thermolytic Effector Responses

During hyperthermia, to help regulate core temperature, the body initiates both conscious behavioural modifications and subconscious autonomic responses such as eccrine sweating, increased cutaneous blood flow and increased pulmonary ventilation. Each of these responses is described below and each contributes to changes in the heat balance as described by equation 2.1.

2.1.3.3.1 Behavioral Modifications

Warming of the body core has been shown to elicit behavioural responses that contribute to temperature regulation (2). This is the most diverse of our responses to warm environments. These responses could include sitting in the shade to decrease

radiative heat gain, employing an electrical fan to increase convective heat loss, putting ice bags on the limbs to increase conductive heat loss, or crouching to reduce the exposed surface area of one's skin to decrease heat gain from radiation. These actions are all responses to the increased body temperatures. The cerebral cortex plays a primary role in this type of response. A signal is sent ascending from the "controller" in the brain stem to the cerebral cortex and allows us to consciously seek out a behavioural solution to the imposed hyperthermia. For example humans exhibit behavioural responses including "cool environment" seeking behaviour or water drinking in attempts to limit or stifle the thermal load.

2.1.3.3.2 Eccrine Sweating

Eccrine sweating is the most effective human thermolytic response resulting in heat loss due to the evaporation of sweat. Sweat, consisting of both ionic components and water, transfers energy from the skin to the molecules of water to allow them to take on a gaseous state. The amount of energy transferred to the water molecules is determined by latent heat of vaporization for sweat, which is 2,426 $J \cdot g^{-1}$ (172). Sweat glands are distributed with decreasing density from the forehead, upper limbs, trunk, to lower limbs over a range of 60 glands/cm^2 to 350 glands/cm^2 (102, 104, 133, 147). Glands consist of a secretory coil where the sweat is secreted and a reabsorptive duct that transports it directly to the skin surface. There is a positive correlation between the size of the sweat gland and the maximal secretory rate of that gland (148). Sweat glands are innervated by post-ganglionic sympathetic neurons that release acetylcholine that acts on muscarinic receptors (65, 105, 135, 165). Individual sweat glands discharge periodically, with the discharge frequency increasing with greater neural stimulation from the central nervous

system (3). Direct recordings of skin sympathetic nerve activity (47) have shown that 80% of bursts in neuronal firing rates are synchronized with pulsatile sweat secretion (16, 163). While α and β adrenergic agonists have been shown to elicit sweating responses, administration of atropine, which is a muscarinic receptor antagonist, greatly diminishes the sweating response (56, 97, 101, 112, 116). This supports the control of eccrine sweating occurs via a sympathetic cholinergic pathway.

Additional to the primary inputs from temperature sensitive neurons, neuronal components implicated to modify stimulation of the sweating response during exercise include the central motor command (157, 169) and the exercise pressor reflex of active muscles (155, 156). Other influences on eccrine sweating include strong positive and negative correlations between the level of dehydration and both the core temperature threshold (122) and rate of secretion of sweat respectively(150). High plasma osmolarity also attenuates sweating responses independent of blood volume changes(55, 164).

Eccrine sweat glands show each of continuous, intermittent secretion (110) and cyclic activation of certain glands (134). There is incredible variation in maximal sweat rates of ~1-3 L/hour (106). This appears to be due to the decreased cholinergic sensitivity of receptors, the decreased size of sweat glands, and decreased secretory activity per unit volume of the gland in poor sweaters (148).

2.1.3.3.3 Increased Cutaneous Blood Flow

During hyperthermia, the body maintains a remarkable ability to increase the rate of blood flow to the skin in excess of 7-8 L/min (142). There are 3 vasodilatation responses that need to be described to understand the contribution of cutaneous blood

flow to thermoregulation during hyperthermia. They are sympathetic withdrawal, dilatation of AVA's and active cutaneous vasodilation. First, peripheral vasodilatation in non-acral, non-glabrous skin occurs in two stages, the first of which is a sympathetic withdrawal. Sympathetic release of noradrenaline, that acts on α-adrenergic receptors, normally induces a vasoconstriction of peripheral blood vessels (94). However, during passive heating of core temperatures by 0.5-1.0°C, an increase in cutaneous blood flow occurs in conjunction with a removal of this sympathetic vasoconstrictor tone (94). Secondly, when experiencing hyperthermia, in glabrous skin in the acral regions in the soles of the feet, nose, and ears vessels known as arterio-venous anastomoses (AVA's) also dilate so as to increase blood flow to the skin surface in an attempt to dissipate heat (69, 159, 160). During these hyperthermic states, decreased sympathetic activity gives less norepinephrine release and this reduces binding to the α-receptors of AVA's in acral skin (69). This decreased stimulation results in the vasodilatation of the AVA. Third, in non-acral, non-glabrous skin that covers most of the body's surface, after further increases in core temperature, this results in an active cutaneous vasodilation (94, 140). The mechanism of this third form of active vasodilatation is currently under investigation and remains to be completely resolved.

This mechanism of this active cutaneous vasodilation is said to be active and sympathetic as various methods of removing sympathetic input such as surgical sympathectomies (64, 140) or various peripheral neuropathies (88) can remove or impair this response. Interestingly, however, α and β adrenergic blocking agents appear to have very little effect on this active cutaneous vasodilatation response (59, 100). These findings beg the question of what neurotransmitter, local metabolite, or chemical

modulator might elicit this response. Because the onset of the vasodilator and sweating responses occur at a similar time in body heating (140), it was originally thought that a sympathetic release of acetylcholine might stimulate muscarinic cholinergic receptors similarly to the mechanism involved in the control of eccrine sweating (101, 140). The administration of atropine, however, resulted in a delay of the onset and moderately decreased the magnitude of active cutaneous vasodilation (97, 140, 154). There were also suggestions that an indirect mechanism via the release of an enzyme that cleaves bradykinin was responsible for active cutaneous vasodilation (57). However, that receptor specific blockade of B_2, G-protein coupled bradykinin receptors in the skin does not abolish vasodilation has proven that this hypothesis cannot be correct (96). Recently nitric oxide (NO) has been investigated for its role in active cutaneous vasodilation. The administration of L-arginine analogues to inhibit NO synthase activity has shown that 20-30% of the body's active cutaneous vasodilator response can be removed with inhibition of NO synthesis (93, 153, 154). This suggests that while NO may induce active cutaneous vasodilatation, it is by no means the primary stimulant for the response and may act as an amplifier of the response (88). Interestingly, vasodilatory responses during changes in local skin temperature are much less subject to inhibition by NO synthase inhibitors (95). This result also supports NO works as an amplifier of the vasodilator response, aside from the neural stimulation, and is perhaps temperature sensitive in its role.

The use of botulinum toxin, which acts presynaptically to block neurotransmitter release from cholinergic nerves, inhibits the vasodilator response (97). This led researchers to believe that a substance is co-released from these sympathetic cholinergic neurons that initiate this active cutaneous vasodilation in response to whole body heat

stress (82, 88). Vasoactive intestinal peptide (VIP) is one suggested cotransmitter for active cutaneous vasodilation (82). VIP is a cAMP mediated vasodilator localized in both sweat glands (167) and blood vessels (72). A VIP peptide fragment (VIP_{10-28}), that inhibits VIP receptors, was found to diminish the vasodilator response to heat stress (10). Alternatively, it was found that patients with cystic fibrosis (CF), that have markedly decreased VIP levels in the skin, still retained their active cutaneous vasodilation response (149). These conflicting studies support a complex mechanism of cholinergic co-transmission which underlies active cutaneous vasodilatation with the role of VIP or other co-transmitters yet to be elucidated.

2.1.3.3.4 Pulmonary Ventilation Response to Changes in Body Temperatures

a) During Cold Stress

The gasp response is a ventilatory response following rapid, large decreases in peripheral or surface skin temperatures. The gasp response is quantified measuring inspiratory pressures or ventilatory responses upon skin cooling. Using this method, Keatinge and Nadel (92) discovered that there is an increased sensitivity to changes in skin temperatures in the face and trunk as opposed to the upper and lower limbs. This variance in the sensitivity of the gasping response to skin temperature changes over the surface of the body has been well supported in the literature (33, 43, 124). In addition, inspiratory pressures were found to be directly related to negative rates of changes of skin temperature with increased sensitivity of this response in the torso relative to the upper and lower limbs (33, 92).

b) During Heat Stress

Hyperthermia-induced hyperventilation is a most perplexing of the responses elicited by humans to hyperthermic conditions. The hyperthermic-induced hyperventilation is also known as 'thermal hyperpnea' and is accomplished by compensatory increases in frequency of breathing and/or tidal volume (174). Humans and other homeotherms including pigs and rats do not, however, use panting as the primary heat loss mechanism (139). The effectiveness of hyperthermic-induced hyperventilation or thermal hyperpnea in humans for cranial heat loss and thermoregulation has sparked many debates (139, 174).

It is accepted that elevations in pulmonary ventilation cause more heat to be lost from the upper airways including the trachea and bronchi (137); however, it is debated if the magnitude of this heat loss is significant and if the response participates in thermoregulation. Evidence supports that this response influences cranial temperature during hyperventilation, causing heat loss in the upper airways and tracts, while giving direct cranial cooling (117, 170). With this excess ventilation the musculature of the chest and lungs must endure higher work rates. These work rates generate metabolic heat production, thus at least partly counteracting the heat lost via respiration. Proponents of hyperthermia-induced hyperventilation participating in thermoregulation argue that even at maximal respiration only 10-15% of $\dot{V}O_2$ max is due to respiratory work and the corresponding additional heat gain is marginal. To further complicate the potential physiological benefits, this response produces a respiratory alkalosis as a result of CO_2 being blown off during this hyperventilation, which appears to paradoxically remove a main input to breathing.

While it is clear there is an increased respiratory drive during hyperthermia, it is unclear as to what causes the increased ventilation. Studies have shown that cerebrovascular responsiveness to CO_2 remains unchanged during hyperthermia (54, 114). Normally, hypercapnia dilates cerebral blood vessels in normothermic humans. If CO_2 and temperature positively interacted in their influence on pulmonary ventilation (54, 114), this could have helped serve for an explanation for the paradoxical increase in ventilation relative to reduced $P_{ET}CO_2$ levels that accompany hyperthermia-induced hyperventilation. The assumption underlying these cerebrovascular studies is that the diameter of the middle cerebral artery remains the same when trans cranial doppler sonography is employed to quantify cranial blood flow. This suggests that the same or reduced volume of CO_2 is reaching cerebral tissues and the respiratory control center in the medulla oblongata during hyperthermia (129). As such, the input for the additional pulmonary ventilation remains unexplained. In the non-panting rat, passively increasing core temperature caused an increased respiratory drive despite reduced P_aCO_2 levels (20). Boden et al. (19)showed that in the rat, removing neural connections between the hypothalamus, that contains the preoptic thermosensitive areas, and the caudal brainstem abolished the increased ventilatory drive incurrent with increased core temperatures. This supports hyperthermia-induced increases in breathing are a thermoregulatory response. Research is ongoing to resolve the mechanism(s) of control of this hyperthermic-induced hyperpnea or thermal hyperpnea response in humans.

2.2 Panting Animal Responses to Regulate T_{CORE} in Hyperthermia

Panting animals undergo some similar thermoregulatory responses to changes in body temperatures as do humans. Many animals regulate their core temperatures in hot

ambient environments by facilitating evaporative heat loss through panting. Evaporative heat loss during panting, as it is during eccrine sweating, is mainly due to the latent heat of vaporization of water. When the liquids evaporate, energy is transferred from the animal's tissues to the air borne water molecules effectively removing energy from the body.

There are three primary methods or responses many homeotherms employ to harness this latent heat of vaporization so as to deal with elevated body temperatures. These methods or responses are sweating, saliva spreading, and panting. Each share a common principle in that if increased amounts of fluid evaporate, the organism increases heat dissipation. While sweating and saliva spreading both function by increasing the amount of liquid available on the body surface to evaporate, panting works by a different mechanism that includes a biphasic alteration in breathing patterns. In Phase 1 or thermal tachypnea, breathing frequency is dramatically increased and tidal volume decreases relative to resting values so as to maintain $P_{ET}CO_2$. Phase 1 occurs before the elevation of core temperature and typically follows increases in skin temperature. During Phase 2 or thermal hyperpnea, both breathing frequency and tidal volume are increased relative to resting values. This second phase is typically initiated after an increase in core temperature and results in a decrease in $P_{ET}CO_2$. Phase 2 is similar to the human pattern of ventilation observed under hyperthermic conditions, once a threshold core temperature is reached (36, 175). The increased flow rate of air within the extremely well vascularized, large surface area of the upper ventilatory passages induces an increase in the rate of evaporation and heat dissipation as long as drying or dehumidification of the upper airways does not occur (151).

There are a number of responses that panting animals have made use of in order to maintain a generalized homeostatic internal environment. Due to the increased frequency of breathing, there is the risk of hypocapnia and losing consciousness as would occur in humans experiencing severe hyperpnea. In mammals during Phase 1 panting, however, the tidal volume is sufficiently decreased so as to mainly ventilate the physiological dead space in the upper airways (70, 139). Conveniently, it is in these passages where there is warming and humidification of the incoming air. This allows the evaporation and heat loss to occur, whilst still maintaining the normal resting partial pressures of CO_2 or O_2 within the diffusion-capable regions of the lung. To deal with the increased work normally required to maintain an increase in ventilation, panting animals have a number of clever adaptations that allow them to increase the ventilatory frequency in an extremely efficient manner (67, 68). Firstly, they tend to skip right from resting frequencies to higher frequencies that are at the same as the resonating frequencies of the upper airways down which the air travels (42). This greatly decreases the amount of work that the respiratory muscles must do to ventilate the passages. Next, the addition of respiratory work gives increases in cardiac output to meet the demands of the active tissues. Along with the increase in cardiac output to the respiratory muscles, the animals conversely decrease the portions of cardiac output to non-respiratory muscles as to ensure that cardiac output remains the same throughout the transition from resting to panting (66). Both of these aspects of their respiratory responses allow animals to drastically increase the amount of air that they can ventilate through the upper airways, without suffering the detriments of the increased energy and heat production.

2.3 Selective Brain Cooling

Selective brain cooling has been extensively studied in panting and nonpanting mammals as well as humans (8, 29, 89, 171, 174). It is shown in panting mammals that warm blood from the carotid arteries is carried to the cavernous sinus, where in the *carotid rete*, it is cooled and then routed to the vasculature of the brain in a counter current system of heat exchange (7, 48, 117). This appears to be a survival mechanism allowing the organism to endure higher thermal loads and conserve fluids whilst still protecting the delicate integrity of the brain. Again, there has been much debate as to whether humans utilize a similar mechanism to selectively cool the blood flowing past the trachea via the use of a counter current flow system of energy exchange (36, 175). Research of selective brain cooling in humans is ongoing.

2.4 Human Control of Ventilation and Regulation of pH at Rest

Two main requirements for human breathing are based on the need to acquire O_2 and extrude CO_2. The systems of control that humans have over their breathing are based on ensuring that adequate amounts of these two gases are constantly flowing into and out of the body. Carbon dioxide is transported in the blood as carbamino groups attached to proteins, dissolved CO_2, but predominantly as H^+ and HCO_3^-. This method of CO_2 transport links the pulmonary ventilation system with pH balance in the blood. There are chemosensitive tissues in the body that sense the arterial partial pressures of CO_2 and O_2 as well as pH and these modulators play a role in the control of breathing. The main chemosensitive tissues are present in the carotid and aortic bodies in the periphery and on the ventral surface of the medulla oblongata in the brain stem (111, 120). While both central and peripheral chemosensitive tissues respond to increases in PCO_2 and decreases

in pH, only peripheral chemosensitive tissues respond to acute decreases in PO_2. These chemosensitive tissues relay information to the integration site in the respiratory control center on the ventral surface of the medulla oblongata. Here peripheral and central chemical information is integrated, after which an efferent signal is sent via the phrenic nerve to the main muscle of respiration, the diaphragm. The resulting increase in pulmonary ventilation feeds back negatively on the central and peripheral chemosensors by blowing off, and lowering arterial partial pressure of CO_2 (P_aCO_2), while increasing both arterial blood pH (pH_a) and arterial partial pressures of O_2 (P_aO_2). Equation 2.3 is the Henderson-Hasselbalch equation central to the understanding of the regulation of pH_a through the control of resting pulmonary ventilation. Equation 2.4 describes the equilibrium equation equating CO_2 concentration with HCO_3^- and H^+.

$$pH = pKa + \log([HCO_3^-]/[CO_2]) \tag{2.3}$$

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+ \tag{2.4}$$

2.4.1 Peripheral Chemoreceptors

Peripheral chemoreceptors are clusters of chemosensitive cells located in the walls of the carotid bodies and the aortic arch (37, 62, 83). These chemoreceptors are innervated by the glossopharyngeal and vagus cranial nerves respectively. They sense the partial pressures of O_2, CO_2, as well as the pH_a and send the information to the Ventral Respiratory Group (VRG) in the medulla oblongata. This was shown by attenuating the carotid bodies activity by subjecting them to dopamine and this decreased the response to hypoxia (46). Also, when humans have undergone a bilateral carotid body resection, there is a noticeable decrease in the ventilatory response to hypoxia (84). Under hypoxic

conditions, the partial pressure of arterial O_2 drops resulting in a signal from the peripheral chemoreceptors to the medulla oblongata to increase ventilation and help increase the supply of O_2 to the body. As was shown in cats breathing isocapnic/isooxic gases, the carotid bodies are also important sensors in the response to metabolic acidosis (17).

The carotid bodies represent 90 % of chemosensory input to the respiratory control center in the medulla oblongata in response to hypoxia, whereas only 10 % of input comes from the aortic bodies (84). Information from the carotid bodies contributes to about 30 % of the ventilatory response to hypercapnia (13, 84), where the rest comes from central chemosensitive tissues (120).

2.4.2 Central Chemosensitive Tissues

The central tissues include cells clustered around the ventral wall of the medulla oblongata (30, 111, 120). These cells are thought to monitor the partial pressure of CO_2 and the pH within cerebrospinal and medullary fluid (107, 111, 120). Within these sensory cells the equilibrium in equation 2.4 lies decidedly to the right resulting in the dissociation of carbonic acid into HCO_3^- and H^+. Hydrogen stimulates the cells to send a signal to the integrating centre in the respiratory group in the medulla oblongata (52). While hyperventilating and blowing off CO_2, the resulting hypocapnia is sensed primarily by the central chemosensitive tissues and results in a decreased ventilatory drive (111). However, as is experienced during a breath hold, when the arterial and cerebrospinal fluid CO_2 partial pressures increase, these tissues initiate an increased ventilatory drive (38). These central chemosensitive tissues play a key role in controlling pulmonary ventilation and maintaining cerebrospinal fluid as well as blood pH in humans.

2.4.3 Central Respiratory Pattern Generator

The CNS control of ventilation occurs via a number of centers or collections of neurons within the brain stem which regulate both inspiration and expiration. One of these centers, the medullary center, can be divided into two groups. As mentioned above the VRG also controls respiration through increasing expiratory muscle recruitment when necessary (14). The other group, the dorsal respiratory group (DRG), is the generator of normal inspiratory rhythms and processor of sensory information from around the body. The apneustic center, which signals the end of inspiration, is located within the pons (132, 173). Another CNS region involved with signalling ventilation includes the pneumotaxic center of the pons (121), which is thought to regulate inspiratory duration and thus respiratory rate. Descending inputs from the cortex also modify brain stem activity allowing for conscious control of ventilation. If and how these centers are modified by temperature is incompletely understood (39).

2.5 Human Control of Ventilation and Regulation of pH During Exercise

It is not completely resolved how the body controls ventilation during exercise. What is interesting is that at the low and moderate intensities, where a large increase in ventilation is observed, the values of the main modulators for resting pulmonary ventilation remain stable. Evidently some other modulators of ventilation play important roles in regulating ventilation during exercise. Even at high intensity exercise, a non-linear increase in ventilation to maximum values relative to metabolic needs results in hypocapnia and mild hyperoxia (20, 49). As CO_2 is blown off and P_aO_2 rises, there is a paradoxical continued increase of ventilation. As a consequence of the onset of blood

lactate accumulation, blood pH was thought to signal ventilation during exercise. However, glycogen depletion studies dissociated the onset of the decrease in blood pH with the ventilatory threshold (73) demonstrating the ventilatory threshold was not tied to the onset of blood lactate accumulation.

One proposal for the control of exercise ventilation is that the increased mechanical motion of the limbs increases efferent motor output allowing mechanoreceptor sensory information to cause an increase in ventilation (50). It is believed that during this 'passive exercise', the condition under which these experiments were performed (50), are not representative of true exercise conditions as no excess energy is expended to complete the exercise. Although this interferes with the view that mechanical motion plays a role in the stimulation of exercise ventilation, there is no active force development and few metabolites are produced which greatly limits the number of metabolic variables that could have additionally influenced ventilation. While it is clear that mechanoreceptors in the body are stimulating pulmonary ventilation, their contribution as inputs to ventilation during exercise remains controversial (50, 90).

Studies show that with increasing exercise intensity there are increased metabolite concentrations in the blood such as potassium, norepinephrine, lactate, and nonesterified fatty acids (60, 108, 158). Evidence suggests that these metabolites stimulate ventilation via a muscle chemoreflex that supplements the chemoreceptors responses to hypoxia (90, 130). This muscle chemoreflex suggests that altered metabolite production stimulates ventilation during exercise. The metabolite concentrations remain disrupted upwards of 10 minutes post exercise, continuing to influence ventilation (60, 108, 109). Since there are a number of possible influences on ventilation that simultaneously change during

exercise, it makes discovering the primary modulator(s) and their respective contributions to exercise ventilation quite difficult.

With humans, similar to active heating studies, passive heating studies of humans show increases in pulmonary ventilation in response to increases in skin and core temperatures. This hyperventilation occurs without limb movement or metabolite build up in the body that is evident during exercise (28, 41, 58, 103). These changes in body temperatures need to be considered as a possible mechanism contributing to the increased ventilation exhibited during exercise.

2.6 Ventilatory Response to Exercise-Induced Hyperthermia

Some researchers advocate that core temperature has multiplicative effects/ interactions with the resting modulators of ventilation (6, 44, 174). Sensitivity to P_aCO_2 has been shown to increase by up to 2 fold during hyperthermia, supporting the multiplicative model for the effect of core temperature on pulmonary ventilation (6, 44). In addition, the ventilatory responses to hypoxia at rest (45, 125) and during exercise (40, 125) were further elevated in hyperthermic relative to normothermic humans.

Some evidence suggests that core temperature has additive effects on the modulators of ventilation. These studies have shown that at rest under hyperoxic hypercapnic stresses, there were increases in pulmonary ventilation but no change in slope of the ventilation vs. CO_2 response curve (85, 168). Directly heating the VRG to 40°C induced a respiratory frequency up to 4 times that at 30°C in mice (166). A similar study found that the temperature of the ventral surface of the medulla at different PCO_2's (39) gave proportional increases in phrenic nerve firing rates with fixed alveolar PCO_2's

at temperatures ranging from 25-42°C. According to Nybo and Nielsen (129), an exercise induced hyperthermia supplemented with an additional hyperthermia resulted in an increase in human exercise ventilation by 40%. Abbiss et al. (1) found that there was a hyperthermic induced hyperventilation associated with a rise in skin temperature during prolonged exercise.

In these aforementioned studies, it is unclear if the temperature input to the respiratory control center is from central or peripheral tissues. Central chemoreceptors respond to increases in their temperature by increasing ventilation (39, 136). It has also become evident that altering the temperature of the carotid body in the periphery gives proportionate changes in its rate of firing (4, 61). Resolving the influences of peripheral and core temperatures on ventilation during exercise is an important step in characterizing the contribution of body temperatures in the control of thermal hyperpnea or hyperthermia-induced hyperventilation and exercise ventilation.

2.7 Summary and Rationale for Proposed Studies

The literature suggests combinations of skin and core thermoreceptors interact in the stimulation of the hypothalamus to elicit thermoregulatory responses. It is well demonstrated that increased body temperatures cause increased pulmonary ventilation. Evidence supports that a myriad of other modulators including P_aCO_2 stimulate human resting and exercise ventilation (22, 36, 76, 115, 129, 131). It remains to be determined if and how skin and core temperatures individually contribute to the control of human resting and exercise ventilation. As well, it remains to be determined if skin temperature and CO_2 interact in their influence on pulmonary ventilation. To make this assessment, steady state core and skin temperature need to be studied so as to allow an establishment

of their individual contributions to the net human pulmonary ventilatory response (1, 174). To allow the study of the interaction between mean skin temperature, core temperature and hypercapnia, exercise studies during eucapnia and hypercapnia are needed. To examine if rates of skin temperature change influence pulmonary ventilation, studies are needed that examine the influence of rate of change of skin temperature on resting ventilation.

During exercise in a temperate environment, increases in core temperature result mainly from significant increases in metabolic heat production in the working muscles (15, 53, 127). As such, core temperature increases are proportional to exercise intensity (126, 128, 143). If volunteers exercise at a given percentage of their pre-determined $\dot{V}O_{2\,PEAK}$ in different ambient temperature environments, this is reasoned to result in core temperatures being clamped at a consistent level within a narrow range. If the ambient temperature is also varied, this gives proportionate changes to surface skin temperature and provides a protocol to assess if steady state peripheral or skin temperatures will result in a change in ventilation independent of core temperature changes. Also if during these exercise sessions, hypercapnic challenges are induced, whilst core temperature is stabilized and skin temperatures are varied to different stable values, this allows the study of the potential interaction of hypercapnia and skin temperature in their influence on ventilation. Ultimately these studies will give insights into the control mechanisms underlying an exercise induced hyperthermic ventilatory response and shed light as to how ventilation is controlled during exercise.

Evidence is split as to whether thermal hyperpnea or hyperthermia induced hyperventilation is indeed a thermoregulatory response to hyperthermia, or whether its

benefits are outweighed by the increased work of breathing. It is clear that peripheral afferent inputs interact with central inputs in the control of eccrine sweating. Sweating rate responds to the level and rate of changes in both skin and core temperatures. To date, it is evident there is increased pulmonary ventilation following increases in core temperature (174) but it is not evident if it is influenced by $\dot{T}_{SK}$. Aside from clarifying its purpose and function of increasing heat loss via the upper airways, it is within reason to characterize thermal hyperpnea as a true thermoregulatory response should it elicit similar response dynamics as other thermoregulatory responses such as sweating rate (121) and peripheral cutaneous vasodilatation (95). Using Nadel's model (121) of eccrine sweating provides an opportunity to comprehensively investigate if and how thermoregulatory inputs influence pulmonary $\dot{V}_E$. The results could support or refute that there are inputs from the thermoregulatory control center that play a role in the observed thermal hyperpnea during actively induced hyperthermia as illustrated in Fig. 2.3.

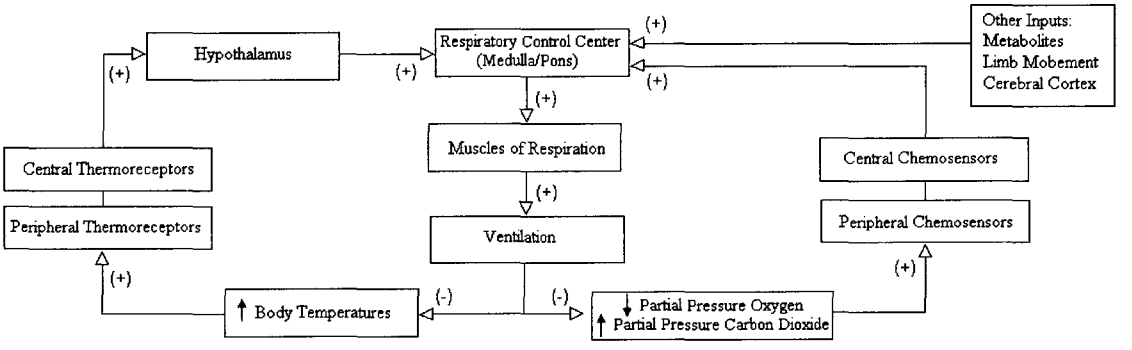

Fig 2.3: Diagram showing hypothesized integration between regulatory systems of thermoregulation and pulmonary ventilation.

2.8 Hypotheses

Chapter 3

Hypothesis 1 - Ventilation will increase proportionately to skin temperature during steady state exercise with a stable hyperthermic core temperature.

Hypothesis 2 – Mean skin temperature will positively interact with hypercapnia in its influence on exercise ventilation during steady state exercise with a stable hyperthermic core temperature.

Chapter 4

Hypothesis 3 – Peak ventilation will increase proportionately to the rate of change of skin temperature with a stable normothermic core temperature in pre- and post-exercise sessions.

Hypothesis 4 – Peak ventilation response to rate of change of skin temperature will remain the same between pre- and post-exercise tests.

2.9 Testable Questions

Chapter 3

1) Mean skin temperature will vary proportionately to ambient temperature.

2) Esophageal temperature will remain at a steady state level close to resting values of ~37.0°C during ~27% $\dot{V}O_{2\ PEAK}$ and at ~38°C during 53% $\dot{V}O_{2\ PEAK}$ exercise intensity.

3) Ventilation will increase proportionately to levels of end-tidal partial pressure of carbon dioxide while exercising at ~53% $\dot{V}O_{2\ PEAK}$.

Chapter 4

4) Rate of change of skin temperature will be elevated during radiant heating and cooling.

5) Positive and negative rate of change of skin temperature will positively influence peak ventilation responses.

6) Exercise state will not influence the relationship between rate of skin temperature change and peak ventilation responses.

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CHAPTER 3: Study 1

Influence of Skin Temperature and Hypercapnia on Exercise Ventilation during Hyperthermia

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Running Head: Skin Temperature and Hypercapnia

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3.1 Abstract

It remains unresolved how mean skin temperature ($\bar{T}_{SK}$) and end-tidal partial pressure of CO_2 (P_{ETCO2}) contribute to exercise ventilation. HYPOTHESIS: Exercise ventilation will increase proportionately to skin temperature and positively interact with $P_{ET}CO_2$ with a stable hyperthermic core temperature. METHODS: Eight participants (1.74±0.11m tall, 73.0±12.1kg, 23.0±3.1years of age;mean ± SD) exercised during eucapnia or elevations of $P_{ET}CO_2$ by +4 or +8 mm Hg during three 1h trials at T_{AMB} of 25, 30, or 35°C. Exercise trials were on separate days at ~27% (T_{ES}~37°C, normothermic) or ~53% $\dot{V}O_{2PEAK}$ (T_{ES}~38°C, hyperthermic). RESULTS: During hyperthermic exercise, there were significant main effects but no interactions for T_{AMB} and $P_{ET}CO_2$ on $\dot{V}_E$, $\dot{V}_E/\dot{V}O_2$, and $\dot{V}_E/\dot{V}CO_2$. CONCLUSION: The results support that with hyperthermic T_{ES}, skin temperatures between ~33 and 36°C positively influences pulmonary ventilation during steady state exercise.

3.2 Introduction

The physiological mechanisms controlling resting pulmonary ventilation are fairly well understood (17, 25, 27, 30). Uncovering the modulators of exercise ventilation has proven to be more difficult. Evidence has consistently shown during exercise there are substantial increases in ventilation despite little to no changes to the known modulators of resting ventilation (12).

Following core temperature thresholds, both during passive (7, 11) and active (20, 21, 33, 36) whole body warming, there are proportionate increases in ventilation and core temperature. This evidence supports that these temperature increases contribute to the ventilatory response to exercise (35). This thermal hyperpnea persists despite some studies suggesting that there is decreased cerebral blood flow during hyperthermia (28, 33) and consequently less CO_2 reaching central chemosensitive tissues. This suggests a reduced importance of CO_2 and pH in the control of exercise ventilation in these hyperthermic conditions (14, 28, 33). A growing body of evidence suggests that hyperthermia increases the activity of chemosensitive tissues in the carotid bodies and on the ventral surface of the medulla (9, 16). In addition, Boden et al. (2) showed that in rats, lesions between the respiratory control center in the pons and the hypothalamus successfully abolished the effects of hyperthermia on ventilation. Although the mechanisms of the control of thermal hyperpnea remain to be resolved, collectively these results suggest that hypothalamic tissues and hyperthermia-induced increases in chemosensitivity play an important role in modulating the exercise ventilation response. It was recently demonstrated that steady state elevations in $\bar{T}_{SK}$ did not influence exercise ventilation when core temperatures were stable and normothermic (19). The potential

interaction between peripheral and central temperatures in the control of exercise ventilation in humans has yet to be examined when core temperatures are stable and hyperthermic (20).

The purpose of this study was to assess the separate and combined influences of the body temperature and $P_{ET}CO_2$ inputs on exercise ventilation. A novel experimental design was employed that allowed assessment of steady state T_{ES} and $\overline{T}_{SK}$ inputs to exercise ventilation with and without periods of hypercapnia. It was hypothesized that for a given stable hyperthermic T_{ES} during steady state exercise: 1) ventilation will increase proportionately to skin temperature during steady state exercise and, 2) skin temperature will positively interact with hypercapnia in its influence on exercise ventilation. To make this assessment, core temperature was held constant at either a normothermic or hyperthermic level during steady state submaximal exercise. Three ambient temperature conditions (25, 30, 35°C) were employed to give 3 steady state skin temperatures. This allowed the assessment of the influence of steady state $\overline{T}_{SK}$ on exercise ventilation and provided the conditions to test if $\overline{T}_{SK}$ and $P_{ET}CO_2$ interact in their influence on exercise ventilation.

3.3 Methods

The following study was conducted at Simon Fraser University's Department of Biomedical Physiology and Kinesiology in the Laboratory for Exercise and Environmental Physiology. Ethical approval was obtained for the study from the Office of Research Ethics at Simon Fraser University and the study conformed to the Helsinki Declaration.

3.3.1 Participants

A power calculation was employed using a difference worth detecting of 7.0 ± 4.5 L/min in $\dot{V}_E$ and 3.0 ± 1.5 (unitless) in $\dot{V}_E/\dot{V}O_2$ based on pilot data collected from the lab. It was determined that a sample size of 8 control volunteers was sufficient to give a power of 0.90 and an α of 0.05. Each participant was moderately fit and between the ages of 19 and 28 years old (Table 3.1). They were all non-smokers and had no acute or chronic pulmonary deficiencies. They were asked to abstain from alcohol, caffeine, or intense exercise in the 24 hr preceding their scheduled test date. Each prospective volunteer, before accepting to participate in the study, was given an orientation session in the laboratory to explain potential risks, and protocols employed in this study. Following the introduction and a 24 h reflection period, the participant was asked to fill out a Physical Activity Readiness Questionnaire (PAR-Q), a Laboratory for Exercise and Environmental Physiology Confidential Health Screen Questionnaire, and an informed consent form to participate in the study.

3.3.2 Instrumentation

3.3.2.1 Ventilatory/ Metabolic Responses

During all ventilatory tests or measurements, the participant wore a nose clip. The breathing apparatus consisted of a mouthpiece connected to a two-way flow sensor measuring ventilation and a two-way non-rebreathing valve (NRB 2700, Hans Rudolph Inc, Kansas City, MO, USA). The 2-way flow sensor was calibrated using a 3 L standardized volume syringe (Sensormedics, Yorba Linda, CA, USA). A sample line for oxygen and carbon dioxide measurements was also connected to this breathing apparatus. The sample line removes a volume of ~500 $mL \cdot min^{-1}$ on a breath-by-breath basis for measurement by a Sensormedics Vmax 229c metabolic cart (Sensormedics, Yorba Linda, CA, USA). The CO_2 partial pressures were obtained using a non-dispersive infrared spectroscopy whereas O_2 partial pressures were measured using a paramagnetic sensor. Both sensors were calibrated prior to each trial using air and 2 gases of known concentrations (20.93 % O_2 and 0.05 % CO_2 with balance N_2; 26 %O_2 with balance N_2; 4 % CO_2 and 16 % O_2 with balance N_2).

The inspired air, during the three trials, was composed of a mixture of compressed air, CO_2 and N_2. A LabVIEW software program (National Instruments, Austin, TX, USA, Version 7.1) and end-tidal forcing system (26) controlled the opening time of electronic solenoid valves attached to the three gas cylinders. Based on the measured values from the expired air of the breath immediately preceding it, the end-tidal forcing program altered the time each valve stayed open to stabilize end tidal concentrations of various gasses. In this way, it was assured that the end-tidal partial pressures of CO_2 and O_2 remained constant at the desired values over the course of the prescribed hypercapnic

periods. The breathing apparatus was connected to a humidifier via 250 cm of 3.8 cm diameter corrugated Collins tubing. The humidifier moistens air being fed to the participant from the cylinders of compressed gas. This end-tidal forcing system is described in detail by Koehle et al. (26). Variables measured in this study included exercise ventilation ($\dot{V}_E$), tidal volume (V_T), breathing frequency (F_R), oxygen consumption ($\dot{V}O_2$), CO_2 production ($\dot{V}CO_2$), ventilatory equivalents for O_2 ($\dot{V}_E/\dot{V}O_2$) and CO_2 ($\dot{V}_E/\dot{V}CO_2$), inspiratory time (Ti), expiratory time (Te), and total breath time (Ttot).

3.3.2.2 Cardiovascular Responses

Heart rate (HR) and arterial hemoglobin saturation (S_aO_2) were measured continuously using a pulse oximeter (Masimo Radical, Irvine, CA, USA) attached to one of the participants' distal phalanxes.

3.3.2.3 Thermal Responses

Skin and core temperatures were continuously recorded throughout each experiment. Core temperatures were measured with rectal (T_{RE}) and esophageal (T_{ES}) probes, whereas skin temperatures were measured at 5 locations and expressed as their un-weighted mean value ($\overline{T}_{SK}$). These 5 locations included forehead (T_{fh}), upper arm (T_{ua}), thigh (T_{th}), chest (T_{ch}), and lower back (T_{lb}). Esophageal temperature was sampled with a pediatric sized nasopharyngeal esophageal temperature thermocouple (9 FR, Mallinckrodt Medical Inc., St. Louis, MO, USA) positioned at the T8/T9 level. This location was found using Mekjavic and Rempel's equation for standing height (29).

$$L = 0.228 \bullet (\text{standing height (cm)}) - 0.194 \quad \text{.....(2)}$$

Rectal temperature was sampled from a sheathed thermocouple inserted 15 cm into the rectum (12 FR, Mallinckrodt Medical Inc., St. Louis, MO, USA). Skin temperatures were recorded by T-type, copper/constantan thermocouples (Omega Engineering Inc., Stanford, CT, USA) placed all on the left side of the participant's body and taped down to prevent deviations from true skin temperature values. Calibrations of T_{ES}, T_{RE} , and $\overline{T}_{SK}$ thermocouple probes were completed in a regulated temperature water bath over the range of expected values (VWR International, Model 1196 West Chester, Pensylvania, USA). See Appendix A for these calibration equations.

3.3.2.4 Work Rate

Exercise work rates were performed on an electrically braked cycle ergometer (Lode 91100 V2.23, Groningen, Netherlands).

3.3.2.5 Climate Chamber

Desired climatic conditions were obtained within a 5.08 m by 3.75 m by 2.49 m high walk-in climatic chamber (Tenney Engineering Inc., Union, NJ, USA).

3.3.2.6 Data Acquisition

Ventilatory data were measured and sampled by the metabolic cart on a breath-by-breath basis. The flow signal from the metabolic cart was also used to trigger LabVIEW to sample all temperature and physiological sensors (National Instruments, Austin, TX, USA, Version 7.1). Upon triggering by the flow sensor, these data were sampled and recorded by the data acquisition system.

3.3.3 Protocol

Each volunteer was asked to participate in 3 normothermic and 3 hyperthermic exercise trials over the course of two days. These trials were conducted at the pre-specified time of day for each volunteer. Each volunteer was prehydrated prior to their exercise session by drinking 0.5L ± 0.2L before instrumentation began (33). Water was made available *ad libitum* to the volunteers over all the trials.

The following exercise trials were presented in a randomized and counter balanced order. Each trial began by collecting 10 min of resting data while the volunteer sat resting at room temperature (21°C, ~25% RH). Following this period, the volunteer was relocated to a climatic chamber, controlled at a RH of ~25% and one of 25, 30, or 35°C. In the climatic chamber, the participant rode on a cycle ergometer at 70 rpm and at a power of 27% (Normothermic trials) or 53% $VO_{2\,PEAK}$ (hyperthermic trials). The exercise intensity in the hyperthermic trial was chosen (Table 3.2) to ensure participants remained below their anaerobic threshold (Table 3.2). Each participant breathed ambient air until the T_{ES} had stabilized at ~37°C ± 0.1°C in Normothermic trials, and to ~38°C ± 0.1°C in hyperthermic trials. A rain coat was employed as needed to increase the rate of increase of T_{ES} in the hyperthermic trials. Once the desired T_{ES} had been reached the rain coat was removed. Once T_{ES} and T_{SK} stabilized a series of hypercapnic challenges were administered to the volunteer. These hypercapnic challenges were presented in a randomized and counterbalanced order and consisted of 5 to 10 min of steady state hypercapnia with a $P_{ET}CO_2$ clamped at ~+4.0 mm Hg CO_2 or ~+8.0 mm Hg CO_2 above the preceding eucapnic level. These two challenges were always separated by a 5 to 10

min period of steady state clamped $P_{ET}CO_2$ at eucapnic levels relative to the last 2 min of the T_{ES} stabilization period during exercise.

3.3.4 Statistical Analyses

In normothermic and hyperthermic conditions, a 2-way repeated measures ANOVA was conducted with the factors of ambient temperature (T_{AMB}; Levels: ~25, 30 and 35°C) and partial pressure of end-tidal CO_2 (Levels: 0.0, +4.0, and +8.0 mmHg $P_{ET}CO_2$). A second 2-way repeated measures ANOVA was conducted with factors of Core Temperature (Levels: Normothermic and Hyperthermic) and activity level (Levels: Rest and Exercise) so as to assess the effect of elevated T_{ES} on the dependant outcome variables. Dependent outcome variables included T_{ES}, T_{RE}, $\overline{T}_{SK}$, $\dot{V}_E$, V_T, F_R, Ti, Te, Ttot, HR, SaO_2, $\dot{V}_E/\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$, $\dot{V}O_2$, and $\dot{V}CO_2$. If there was a significant main effect or interaction effect of ambient temperature or $P_{ET}CO_2$, paired t-tests were employed for means of comparison. The level of significance was set at 0.05.

3.4 Results

Ambient Temperature was varied to 3 different levels of 25, 30 and 25°C to give 3 significantly different $\bar{T}_{SK}$ (Fig. 3.1) in the normo- and hyperthermic conditions. Main effects of T_{AMB} were evident for $\bar{T}_{SK}$ in the normo- ($F=28.8$, $p < 0.001$) and hyperthermic ($F=51.9$, $p < 0.001$) conditions. For T_{ES} there were no main effects of T_{AMB} in normo- ($F=0.7$, $p = 0.51$) or hyperthermic ($F=3.5$, $p < 0.06$) conditions (Fig. 3.1). During the hyperthermic trials the grand mean for T_{ES} was significantly elevated ($F=46.7$, $p < 0.001$) relative to the grand mean for T_{ES} in the normothermic conditions. The $\Delta P_{ET}CO_2$ (Fig. 3.2) was the same at each level of T_{AMB} in normo- ($F=2.8$, $p = 0.14$) and hyperthermia ($F=4.7$, $p = 0.068$). The grand means across levels of T_{AMB} for $P_{ET}CO_2$ were not significantly different between the normothermic and hyperthermic trials. For HR in the normothermic condition there was a main effect of T_{AMB} ($F=5.0$, $p = 0.03$) such that at T35 it increased by ~ 5 bpm relative to HR at T25 ($P<0.05$). In the hyperthermic condition there was no main effect of T_{AMB} on HR that had a grand mean of ~170 bpm that was significantly elevated ($F=165.8$, $p < 0.001$) relative to the normothermic HR.

There was no significant main effect of T_{AMB} on $\dot{V}_E$ ($F=1.8$, $p=0.20$) with a normothermic core temperature (Fig. 3.3A) but there was a significant ($F=4.1$ $p=0.04$) main effect of T_{AMB} with hyperthermic core temperatures as $\dot{V}_E$ increased from 71.1 ± 11.6 to 72.6 ±11.0 and 76.9 ± 14.3 L/min across the three T_{AMB} conditions (Fig. 3.3B). There were significant main effects of $P_{ET}CO_2$ on $\dot{V}_E$ in both normothermic ($F=138.3$ $p < 0.001$) and hyperthermic ($F=99.3$ $p < 0.001$) conditions (Fig. 3.3C/D). In the hyperthermic trials, the grand means of $\dot{V}_E$ were significantly greater than that in the normothermic trials across levels of T_{AMB} and $P_{ET}CO_2$. There were no significant

interactions between T_{AMB} and $P_{ET}CO_2$ in their effects on $\dot{V}_E$ during normothermic (F=0.5, p=0.76) and hyperthermic (F=1.1 p=0.39) conditions (Fig. 3.3E/F).

There was no significant main effect of T_{AMB} on $\dot{V}_E/\dot{V}O_2$ (unitless) (F=0.4, p=0.65) with a normothermic core temperature (Fig. 3.4A) but there was a significant (F=7.5 p=0.006) main effect with hyperthermic core temperatures as $\dot{V}_E/\dot{V}O_2$ increased from 32.1 ± 4.2 to 33.1 ±3.7 and 34.2 ± 4.6 across the three T_{AMB} conditions (Fig. 3.4B). There were significant main effects of $P_{ET}CO_2$ on $\dot{V}_E/\dot{V}O_2$ in both normothermic (F=25.9 $p < 0.001$) and hyperthermic (F=30.8 $p < 0.001$) conditions (Fig. 3.4C/D). Between normothermic and hyperthermic trials, $\dot{V}_E/\dot{V}O_2$ was not significantly different for grand means of T_{AMB} or $P_{ET}CO_2$. There were no significant interactions between T_{AMB} and $P_{ET}CO_2$ in their effects on $\dot{V}_E/\dot{V}O_2$ during normothermic (F=0.2, p =0.91) and hyperthermic (F=1.3 p=0.31) conditions (Fig. 3.4E/F).

There was no significant main effect of T_{AMB} on $\dot{V}_E/\dot{V}CO_2$ (unitless) with a normothermic core temperature (Fig. 3.5A) but there was a significant (F=4.5 p=0.03) main effect with hyperthermic core temperatures as $\dot{V}_E/\dot{V}CO_2$ increased significantly from 34.4 ± 4.2 and 34.2 ±4.2 in 25 and 30°C conditions to 35.9 ± 5.1 in the 35 °C condition (Fig. 3.5B). There were significant main effects of $P_{ET}CO_2$ on $\dot{V}_E/\dot{V}CO_2$ in both normothermic (F=16.7 $p < 0.001$) and hyperthermic (F=32.3 $p < 0.001$) conditions (Fig. 3.5C/D). Between normothermic and hyperthermic trials $\dot{V}_E/\dot{V}CO_2$ was not significantly different for grand means of T_{AMB} or P_{ETCO2}. There were no significant interactions between T_{AMB} and $P_{ET}CO_2$ in their effects on $\dot{V}_E/\dot{V}CO_2$ during normothermic (F=1.3, p =0.30) and hyperthermic (F=1.2 p=0.34) conditions (Fig. 3.5E/F).

There was no significant main effect of T_{AMB} on F_R (F=1.3, 0.32) with a normothermic core temperature (Fig. 3.6A) but there was a significant (F=5.2 p=0.02)

main effect with hyperthermic core temperatures as F_R started at 34.0 ± 5.1 breaths/min in T_{AMB} of 25°C, decreased to 33.6 ± 4.5 breaths/min in T_{AMB} of 30°C, and then increased to 35.8 ± 5.2 breaths/min in T_{AMB} of 35°C (Fig. 3.6B). There were no significant main effects of $P_{ET}CO_2$ on F_R in both normothermic (F=2.8 p=0.10) and hyperthermic (F=1.6 p=0.24) conditions (Fig. 3.6C/D). The grand mean of F_R significantly increased (F=53.3, $p < 0.001$) from the normothermic to hyperthermic trial. From the normo- to hyperthermic trials, the grand means of F_R increased from ~24 bpm to ~33 bpm (F=55.0, $p < 0.001$). There were no significant interactions between T_{AMB} and $P_{ET}CO_2$ in their effects on F_R during normothermic (F=0.6, p =0.69) and hyperthermic (F=0.4 p=0.84) conditions (Fig. 3.6E/F).

There was no significant main effect of T_{AMB} on V_T in the normothermic (F=0.5, p=0.61) or hyperthermic (F=0.4 p=0.68) conditions (Fig. 3.7A/B). There were significant main effects of $P_{ET}CO_2$ on V_T that increased from 1.2 ± 0.2 L to 1.6 ± 0.3 L and 1.5 ± 0.3 L in normothermic (F=37.2 $p < 0.001$) conditions and from 1.8 ± 0.4 L to 2.0 ± 0.5 L and 2.1 ± 0.5 L hyperthermic (F=17.2 $p < 0.001$) conditions (Fig. 3.7C/D). The grand mean of V_T across 3 levels of T_{AMB} significantly increased (F=5.3, $p = 0.05$) from the normothermic to hyperthermic trial. There were no significant interactions between T_{AMB} and $P_{ET}CO_2$ in their effects on V_T during normothermic (F=0.4, p=0.84) and hyperthermic (F=1.4 p=0.27) conditions (Fig. 3.7E/F).

There was no significant order effect of the trials on T_{ES} (F=1.2 p=0.34), heart rate (F=0.5 p=0.6), $P_{ET}CO_2$ (F=2.9 p=0.09), $\dot{V}_E$ (F=1.5 p=0.27), or $\dot{V}_E/\dot{V}O_2$ (F=3.1 p=0.08).

There was no significant main effect of T_{AMB} on Ti in the normothermic (F=0.6, p=0.54) or hyperthermic (F=1.1, p=0.35) conditions (Table 3.4/3.5). Likewise, there was

no significant main effect of $P_{ET}CO_2$ on Ti in normothermic (F=1.4, p=0.29) or hyperthermic (F=2.4, p=0.13) conditions. There was no significant main effect of T_{AMB} on Te in the normothermic (F=1.4, p=0.30) or hyperthermic (F=1.8, p=0.21) conditions. There was also no significant main effect of $P_{ET}CO_2$ on Te in hyperthermic (F=0.4, p=0.71) conditions but there was for normothermic (F=4.5, p=0.04) conditions. There was no significant main effect of T_{AMB} on Ttot in the normothermic (F=1.1, p=0.25) or hyperthermic (F=1.9, p=0.18) conditions. There was no significant main effect of $P_{ET}CO_2$ on Ttot in normothermic (F=2.0, p=0.18) or hyperthermic (F=0.5, p=0.62) conditions. There was no main effect of $\overline{T}_{SK}$ on V_T/Ti in hyperthermic (F=0.9, p=0.44) or normothermic (F=0.1, p=0.91) trials. There was no main effect of $\overline{T}_{SK}$ on Ti/Ttot in hyperthermic (F=1.7, p=0.22) or normothermic (F=1.8, p=0.2) trials.

3.5 Discussion

As hypothesized exercise ventilation increased in proportion to $\overline{T}_{SK}$ in hyperthermic conditions with T_{ES} of ~37.9°C (Fig. 3.1) but this was not evident in the normothermic condition (T_{ES} ~ 37.1°C). This is evidence to support our first hypothesis that ventilation, during a given steady state exercise with an elevated core temperature is modulated by changes in $\overline{T}_{SK}$. Our second hypothesis was rejected, however, as the factors of T_{AMB} and $P_{ET}CO_2$ did not interact in their effect on exercise ventilation at either level of core temperature.

Previously it was reasoned that body temperature helps modulate the ventilatory response to steady state low intensity exercise (35). Greiner et al. (18) found that with normothermic core temperatures, however, that skin temperature did not modulate the ventilatory response during steady state exercise. The present study shows with a steady state hyperthermic core temperature that $\overline{T}_{SK}$ does modulate the ventilatory response to steady state exercise (20). It is suggested that this response is in fact similar to other thermoregulatory response patterns as for thermoregulatory responses such as eccrine sweating (1, 31). In a normothermic condition, the core temperature was not high enough to reach a threshold of activation of ~37.6°C to observe a thermal hyperpnea as reported by White and Cabanac (36). However with elevated core temperatures (Fig. 3.1D) the thermal stress was great enough so as to demonstrate changes in $\overline{T}_{SK}$ had an influence on exercise ventilation.

Under resting conditions the peripheral chemosensitive areas in the carotid bodies and aortic arch are sensitive to pH, $P_{ET}CO_2$, and $P_{ET}O_2$ (8, 17, 24) while the ventral surface of the medulla (27, 30) is sensitive to changes in $P_{ET}CO_2$ and pH. During

hyperthermia, however, despite suspected decreases in cerebral perfusion (15, 33), it is evident in both passive (7, 11) and active (20, 21, 33, 36) whole body heating that there are proportionate increases in ventilation and core temperature. It follows that the chemosensitive tissues in the carotid bodies (16) and ventral medulla (9) exhibit intrinsic thermosensitive characteristics. Boden et al.'s work in the non-panting rat, revealed that the ventilatory response to hyperthermia is removed by lesions between the pre-optic area of the hypothalamus and the respiratory control center in the brainstem. This suggests the hypothalamus is the predominant site of an additional respiratory drive in non-panting animals during hyperthermia (2). There is exhaustive evidence that core and peripheral temperatures interact in their influence on various thermoregulatory responses that are modulated by the hypothalamus (3, 5, 22). To date it was not evident if this skin to core temperature interaction also applied to exercise ventilation. Together these results suggest that the observed responses are the result of distinct thermoregulatory efferent neurons from the thermoregulatory center in the hypothalamus to the respiratory control center in the medulla. This suggests that the ventilatory response to hyperthermia may result from stimulation of both the peripheral and central thermosensitive neurons (4, 34).

In this current study the low and moderate intensity exercise in a climate chamber at different ambient temperatures succeeded in producing significantly different skin temperatures (Fig. 3.1 A/B) as well as steady state normothermic and hyperthermic core temperatures (Fig. 3.1 C/D). The hyperthermic T_{ES} was ~37.9°C and this is above the core temperature threshold for thermal hyperpnea during exercise, as demonstrated by White and Cabanac (36). This clamping of core temperature was successful because of the increased heat production associated with the increased muscular work performed by

participants and by the addition as well as removal of the vapour impermeable rain coat (13, 32).

Some limitations to this study could include the use of the rain suit during the development of hyperthermic core temperatures. This helps to induce hyperthermia but it did cause a drop in skin temperature as sweat begins to evaporate following its removal. To address this, the participant cycled for a further 5 min until the skin temperatures had stabilized at this new level so as to avoid this potential pitfall. There are possible effects of increasing fatigue between normothermic and hyperthermic core temperatures, however, this effect was balanced across the different skin temperature and hypercapnia conditions by randomizing order of presentation within each core temperature condition. Additionally, because only 5 different measurements of skin temperature were employed at various sites (forehead, thigh, chest, lower back and shoulder) it can only be assumed that these data are indicative of the overall body skin temperature. The density of thermosensitive neurons in the skin varies quite dramatically from site to site (4, 23). Therefore three $\overline{T}_{SK}$ measurements were taken from the surface of the body core, which has been shown to be more sensitive to thermal stimuli in the cold (6). Lastly it cannot be entirely excluded that in sequential hypercapnic periods, although $P_{ET}CO_2$ was clamped, that the same physiological stimulus was given to the ventral surface of the medulla. During intense exercise the body is charged with the task of transporting large amounts of CO_2 between the working muscles and the lungs. It is possible that pools of CO_2 buffers become saturated during the first hypercapnic period and are unable to relinquish this CO_2 back to pre-hypercapnic levels during the 5 min eucapnia period separating the 2

hypercapnic trials. To address this possibility, we randomized the order of hypercapnic trials so as to remove any potential effect of this nature.

Tidal volume (Fig. 3.7) was consistently modified by $P_{ET}CO_2$ in both core temperature conditions; where as the F_R (Fig. 3.6) appears to be modified by increasing skin temperature only with hyperthermic core temperatures (10, 11). This result mirrors patterns of ventilation similar to the phase 2 panting, thermal hyperpnea. This response suggests that when exposed to the heat, humans may elicit a hyperthermic-induced hyperventilation as a mechanism of heat loss similar to panting animals. When the components of ventilation were examined in terms of mean inspiratory flow (V_T/Ti) and proportion of total breath time in inspiration (Ti/Ttot) there were no significant differences evident for different levels of T_{AMB} or $P_{ET}CO_2$ nor between core temperature in the normothermic and hyperthermic trials. This suggests that the drive to ventilate and the timing of breathing were unchanged in these conditions.

In view of the current evidence, more work needs to be done to fully understand the mechanisms underlying this response of resting and exercise ventilation to variations of static $\overline{T}_{SK}$. Potential future studies include measuring the influence of skin temperatures on exercise ventilation following heat acclimation.

In conclusion, mean skin temperature was altered in proportion to changes in ambient temperature, while core temperature remained at ~37°C during light exercise or was elevated to ~37.9°C during steady state moderate intensity exercise. With hyperthermic core temperatures, exercise ventilation increased relative to normothermic exercise ventilation and did so in proportion to mean skin temperature. For each 1°C increase in $\overline{T}_{SK}$, $\dot{V}_E$ increased by ~1.2 L/min. The ventilatory equivalent responses for

CO_2 and O_2 during this protocol were similar to those for $\dot{V}_E$. Hypercapnia and skin temperature did not interact in their effect on exercise ventilation.

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3.7 Tables

Table 3.1: Age, gender, physical characteristics and body mass index (BMI) of each participant.

Participant	Age (y)	Gender	Height (m)	Weight (kg)	BMI (kg/m^2)
1	19	M	1.64	75.0	27.9
2	24	M	1.87	87.0	24.9
3	23	F	1.71	72.0	24.6
4	28	F	1.61	54.0	20.8
5	22	M	1.88	91.8	26.0
6	23	M	1.86	72.4	20.9
7	26	F	1.68	63.0	22.3
8	19	F	1.70	69.0	23.9
Mean	23	-	1.74	73.0	23.9
SD	3	-	0.11	12.1	2.5

Table 3.2: Peak $\dot{V}O_2$, percentage of $\dot{V}O_{2\ PEAK}$ at anaerobic threshold and relative work rates for each participant during exercise trials in T_{AMB} of 25 (T25), 30 (T30) and 35°C (T35).

			Normothermic			Hyperthermic		
Particip.	$\dot{V}O_{2\ PEAK}$ ($L \cdot min^{-1}$)	Anaerobic Threshold (%)	T25 $\dot{V}O_{2PEAK}$ (%)	T30 $\dot{V}O_{2PEAK}$ (%)	T35 $\dot{V}O_{2PEAK}$ (%)	T25 $\dot{V}O_{2PEAK}$ (%)	T30 $\dot{V}O_{2PEAK}$ (%)	T35 $\dot{V}O_{2PEAK}$ (%)
1	4.1	60.2	24.3	28.2	27.8	52.9	52.4	49.7
2	5.7	52.1	24.4	24.3	24.1	49.0	48.5	51.5
3	4.0	62.8	38.4	21.6	22.1	48.6	48.6	53.8
4	2.8	70.3	33.9	38.6	41.0	59.1	60.2	56.8
5	5.2	64.6	22.7	24.8	25.6	50.2	46.9	46.0
6	5.4	71.1	21.8	20.8	21.3	46.8	49.1	44.9
7	3.5	67.7	30.5	31.0	27.8	62.5	57.2	61.9
8	3.3	72.7	27.2	27.4	27.8	60.7	56.4	58.5
Mean	4.2	65.2	27.9	27.1	27.2	53.7	52.4	52.9
SD	1.1	6.8	5.9	5.7	6.2	6.1	4.9	6.0

Table 3.3: Maximal HR, $\dot{V}_E$, $\dot{V}_E/\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$, F_R, and V_T values attained during $\dot{V}O_{2\ PEAK}$ trials.

Subject	HR_{max} (beats /min)	$\dot{V}_{E\ max}$ (L/min)	$\dot{V}_E/\dot{V}O_{2\ max}$ (Unitless)	$\dot{V}_E/\dot{V}CO_{2\ max}$ (Unitless)	$F_{R\ max}$ (breaths/min)	$V_{T\ max}$ (L)
1	192	178	55	42	65	3.0
2	163	182	38	35	62	3.4
3	205	131	52	33	61	3.1
4	173	100	33	30	58	1.7
5	192	169	36	31	61	3.3
6	191	192	38	30	56	4.4
7	189	132	41	35	60	2.4
8	202	154	45	38	57	2.9
Mean	188	155	42	34	60	3.0
SD	14	32	8	4	3	0.8

Table 3.4: Timing components of pulmonary ventilation for each participant with a normothermic esophageal temperature, during each of the three 27% $\dot{V}O_{2\ PEAK}$ exercise trials in different climatic chamber ambient temperature (T_{AMB}) conditions of 25 (T25), 30 (T30), and 35°C (T35).

Participant number	Ti (s)			Te (s)			Ttot (s)			V_T/Ti ($L \cdot s^{-1}$)			Ti/Ttot (unitless)		
	T25	T30	T35	T25	T30	T35	T25	T30	T35	T25	T30	T35	T25	T30	T35
1	0.89	0.88	0.89	1.44	1.27	1.29	2.33	2.15	2.18	1.51	1.60	1.53	0.38	0.41	0.41
2	1.03	1.11	1.03	1.43	1.73	1.50	2.46	2.84	2.53	1.73	1.70	1.76	0.42	0.39	0.41
3	1.71	1.39	1.26	2.56	2.05	1.46	4.27	3.45	2.72	1.33	1.34	1.15	0.39	0.40	0.46
4	0.78	0.73	0.78	1.07	1.05	1.10	1.86	1.78	1.88	1.34	1.49	1.52	0.42	0.41	0.42
5	0.90	0.90	0.90	1.29	1.35	1.25	2.19	2.25	2.15	1.61	1.62	1.70	0.41	0.40	0.42
6	1.19	1.33	1.25	1.72	1.80	1.69	2.90	3.13	2.94	1.43	1.29	1.38	0.41	0.43	0.43
7	0.97	1.11	0.98	1.28	1.36	1.26	2.25	2.48	2.24	1.44	1.36	1.37	0.43	0.45	0.44
8	1.10	1.05	1.06	1.49	1.39	1.40	2.58	2.44	2.46	1.34	1.44	1.44	0.42	0.43	0.43
Mean	1.07	1.06	1.02	1.53	1.50	1.37	2.60	2.56	2.39	1.47	1.48	1.48	0.41	0.41	0.43
SD	0.29	0.23	0.17	0.45	0.33	0.18	0.74	0.55	0.34	0.14	0.15	0.20	0.02	0.02	0.02

Table 3.5: Timing components of pulmonary ventilation for each participant with a hyperthermic esophageal temperature, in each of the three 53% $\dot{V}O_{2\ PEAK}$ exercise trials in different climatic chamber ambient temperature (T_{AMB}) conditions of 25 (T25), 30 (T30), and 35°C (T35).

Participant number	Ti (s)			Te (s)			Ttot (s)			V_T/Ti ($L \cdot s^{-1}$)			Ti/Ttot (unitless)		
	T25	T30	T35	T25	T30	T35	T25	T30	T35	T25	T30	T35	T25	T30	T35
1	0.80	0.79	0.81	1.07	1.08	0.96	1.92	1.89	1.77	1.02	1.03	1.01	0.42	0.42	0.45
2	0.94	0.96	0.97	1.06	1.29	1.10	1.77	2.41	2.00	0.88	0.84	0.84	0.53	0.40	0.49
3	0.92	0.87	0.85	0.95	0.84	0.84	1.94	1.80	1.77	0.89	0.94	0.96	0.48	0.49	0.48
4	0.70	0.76	0.67	0.75	0.87	0.75	1.42	1.60	1.43	1.17	1.07	1.22	0.49	0.47	0.47
5	0.75	0.64	0.72	0.84	0.71	0.82	1.57	1.38	1.47	1.09	1.27	1.14	0.48	0.47	0.49
6	1.00	0.95	0.92	1.17	1.09	1.07	2.16	1.96	2.04	0.81	0.86	0.89	0.46	0.48	0.45
7	0.83	0.81	0.76	0.87	0.85	0.75	1.71	1.70	1.49	0.98	1.00	1.08	0.49	0.48	0.51
8	0.80	0.85	0.78	0.97	1.05	0.97	1.76	1.88	1.74	1.02	0.96	1.05	0.45	0.45	0.45
Mean	0.84	0.83	0.81	0.96	0.97	0.91	1.78	1.83	1.71	0.98	1.00	1.02	0.47	0.46	0.47
SD	0.10	0.10	0.10	0.14	0.19	0.14	0.23	0.30	0.23	0.12	0.13	0.12	0.03	0.03	0.02

3.8 Figures

Fig 3.1: Normothermic (A,C) and hyperthermic (B,D) mean skin temperature ($\bar{T}_{SK}$;A,B) and esophageal temperature (T_{ES};C,D) responses to sub-maximal exercise at ~53% $\dot{V}O_{2\,PEAK}$ in three ambient temperatures of 25, 30, and 35°C (T_{AMB}); † $p<0.001$; a: 3 means not significantly different; b: 2 means not significantly different; c: normothermic- is not different from hyperthermic-grand mean across 3 levels.

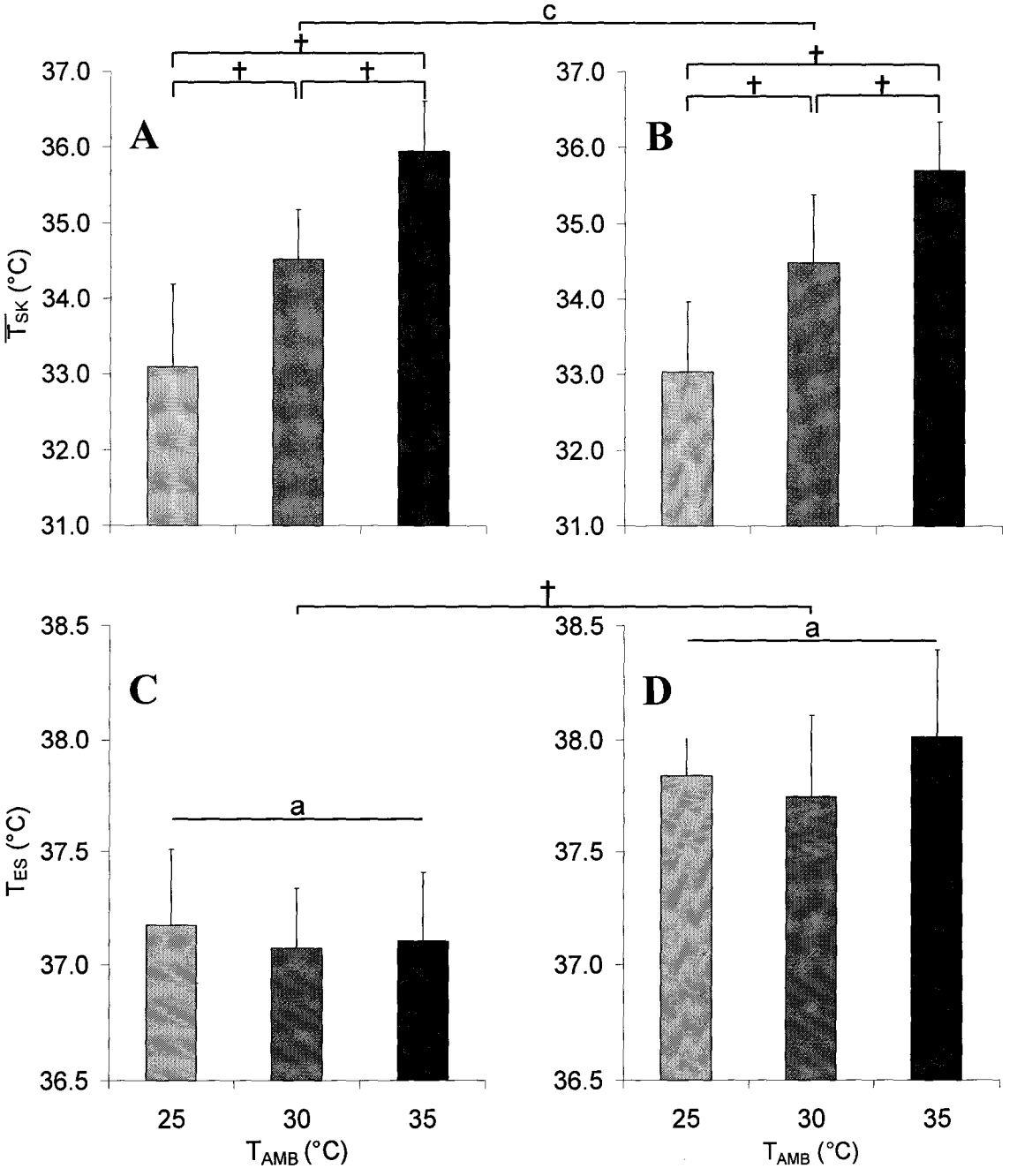


Fig 3.2: Normothermic (A,C) and hyperthermic (B,D) end-tidal partial pressure of carbon dioxide across 3 levels of $P_{ET}CO_2$ ($P_{ET}CO_2$;A,B) and heart rate (HR;C,D) responses to sub-maximal exercise at ~ 53% $\dot{V}O_{2\ PEAK}$ in three ambient temperatures of 25, 30, 35°C (T_{AMB}). * $p<0.05$; a: 25=30=35; b: 2 means not significantly different; c: normothermic-is not different from hyperthermic-grand mean across 3 levels.

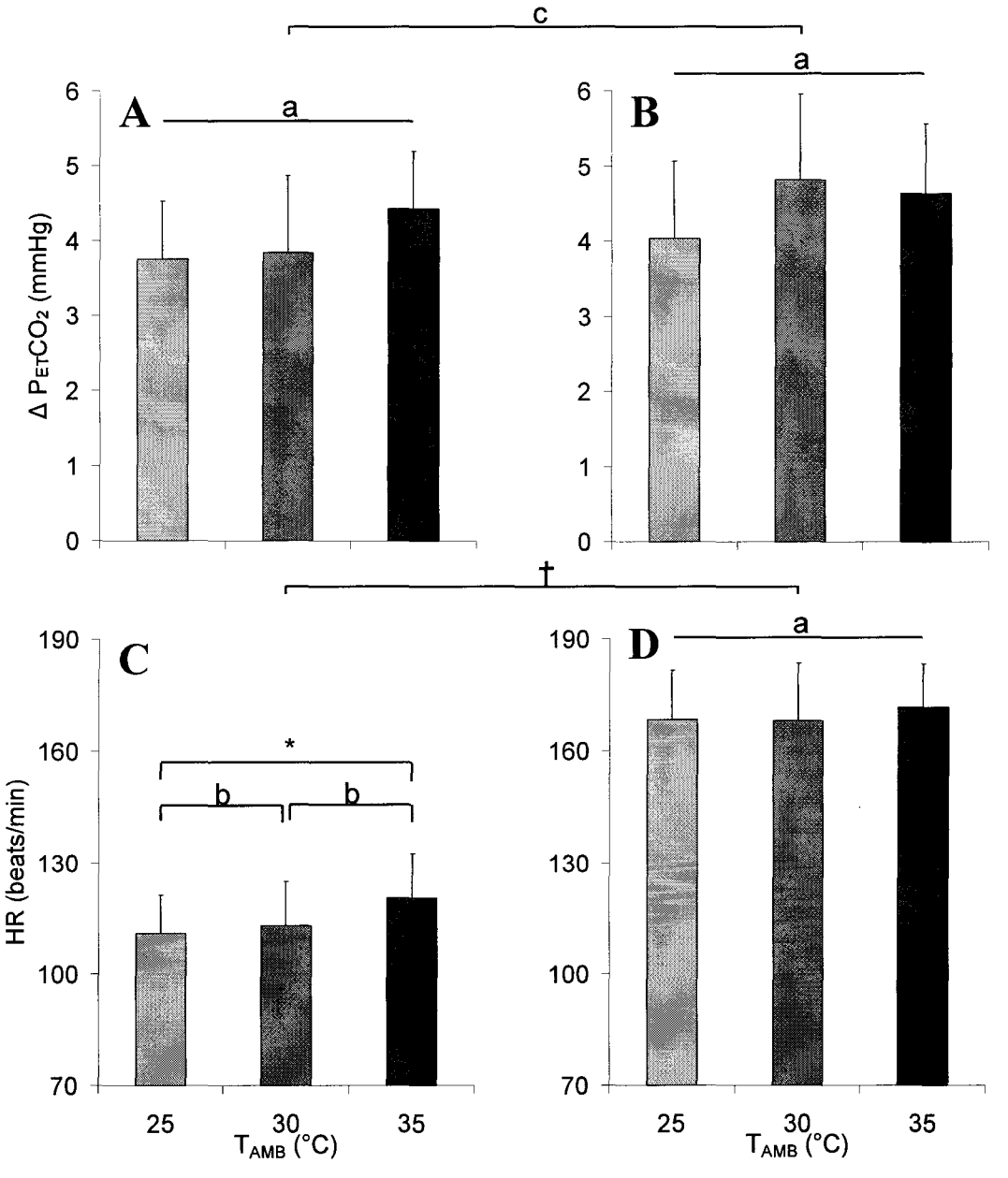


Fig 3.3: Normothermic (A,C,E) and hyperthermic (B,D,F) exercise ventilation at three different ambient temperatures (A,B) and at two levels of hypercapnia that were each preceded by a eucapnia period (C,D). Interaction plots for $\dot{V}_E$ shown for $P_{ET}CO_2$ and T_{SK} (E,F); E = preceding eucapnia, H4 = + 4 mmHg hypercapnia, H8 = + 8 mmHg hypercapnia. Symbol shades in E/F correspond to bar fills in A/B. * $p<0.05$; † $p<0.001$; a: 3 means not significantly different; b: 2 means not significantly different; c: normothermic- is not different from hyperthermic-grand mean across 3 levels.

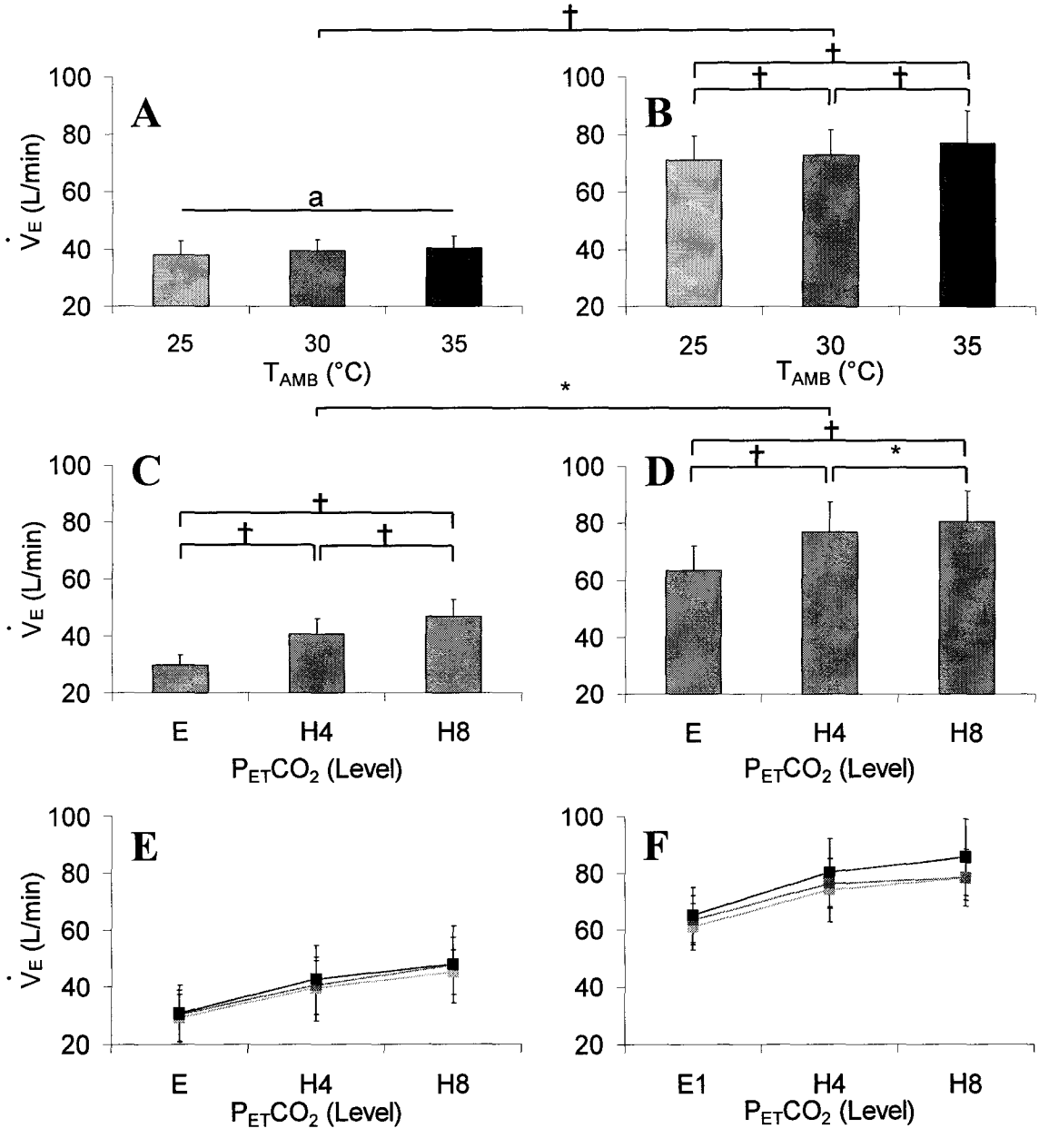


Fig 3.4: Normothermic (A,C,E) and hyperthermic (B,D,F) ventilatory equivalent for oxygen ($\dot{V}_E/\dot{V}O_2$) at three different ambient temperatures (A,B) and at two levels of hypercapnia that were each preceded by a eucapnia period (C,D). Interaction plots for $\dot{V}_E/\dot{V}O_2$ shown for $P_{ET}CO_2$ and T_{SK} (E,F); E = preceding eucapnia, H4 = + 4 mmHg hypercapnia, H8 = + 8 mmHg hypercapnia. Symbol shades in E/F correspond to bar fills in A/B. * $p<0.05$; † $p<0.001$; a: 3 means not significantly different; b: 2 means not significantly different; c: normothermic- is not different from hyperthermic-grand mean across 3 levels.

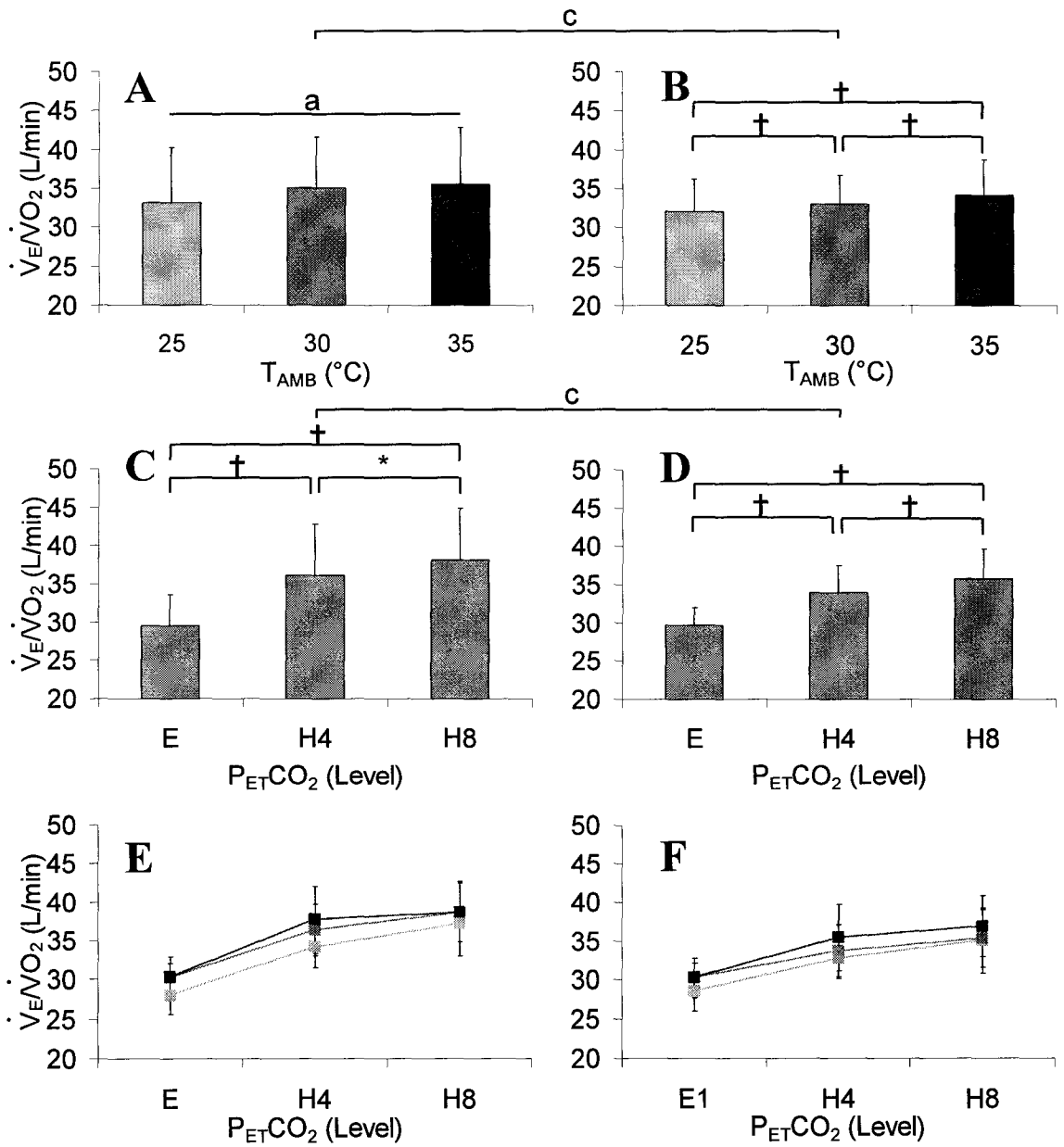


Fig 3.5: Normothermic (A,C,E) and hyperthermic (B,D,F) ventilatory equivalent for carbon dioxide (V_E/VCO_2) at three different ambient temperatures (A,B) and at two levels of hypercapnia that were each preceded by a eucapnia period (C,D). Interaction plots for $\dot{V}_E/\dot{V}CO_2$ are shown for $P_{ET}CO_2$ and T_{SK} (E,F); E = preceding eucapnia, H4 = + 4 mmHg hypercapnia, H8 = + 8 mmHg hypercapnia. Symbol shades in E/F correspond to bar fills in A/B. * $p<0.05$; † $p<0.001$; a: 3 means not significantly different; b: 2 means not significantly different; c: normothermic- is not different from hyperthermic-grand mean across 3 levels.

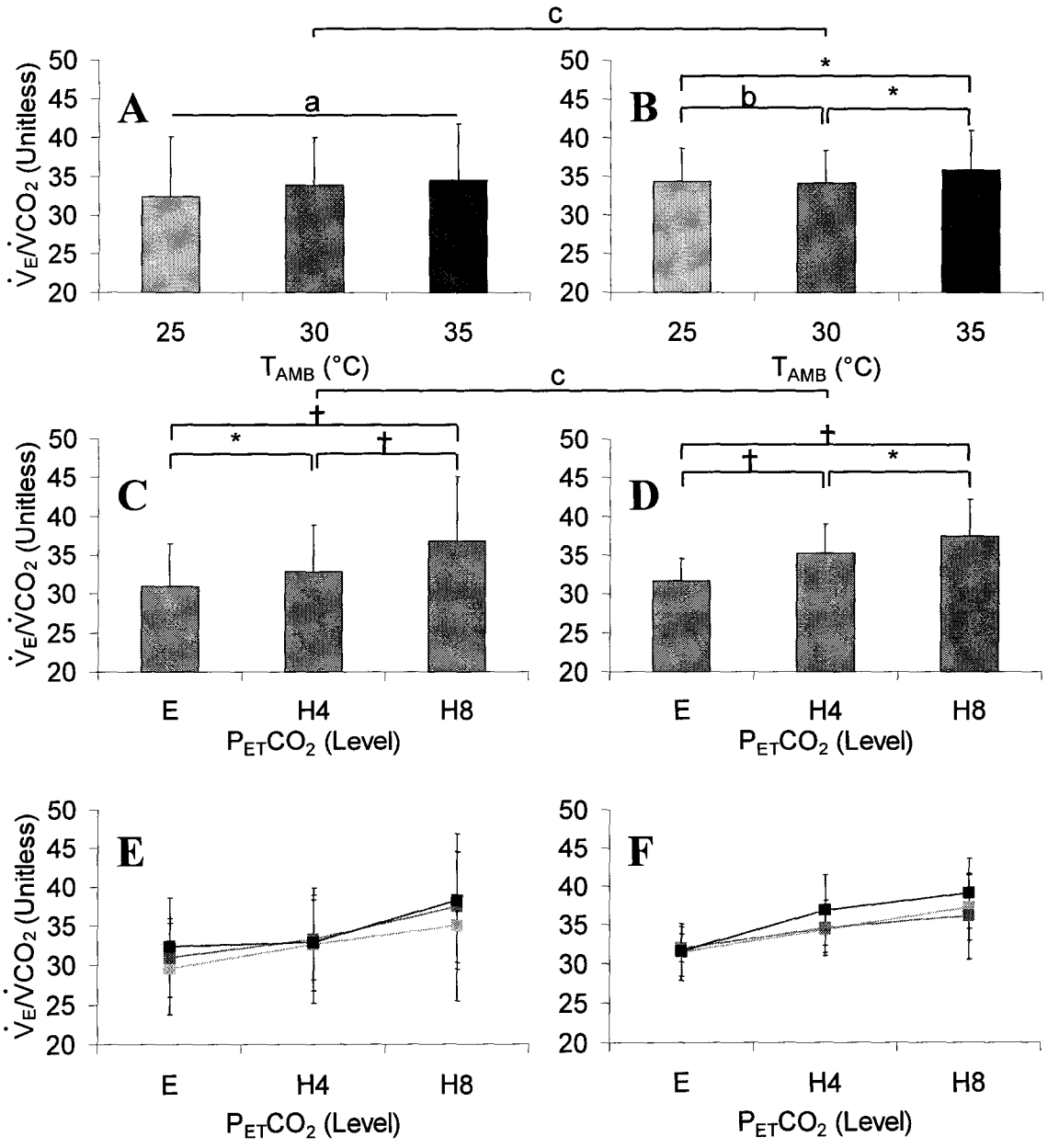


Fig 3.6: Normothermic (A,C,E) and hyperthermic (B,D,F) frequency of respiration (F_R) at three different ambient temperatures (A,B) and at two levels of hypercapnia that were each preceded by a eucapnia period (C,D). Interaction plots for F_R are shown for $P_{ET}CO_2$ and T_{SK} (E,F); E = preceding eucapnia, H4 = + 4 mmHg hypercapnia, H8 = + 8 mmHg hypercapnia. Symbol shades in E/F correspond to bar fills in A/B. * $p<0.05$; † $p<0.001$; a: 3 means not significantly different; b: 2 means not significantly different; c: normothermic- is not different from hyperthermic-grand mean across 3 levels.

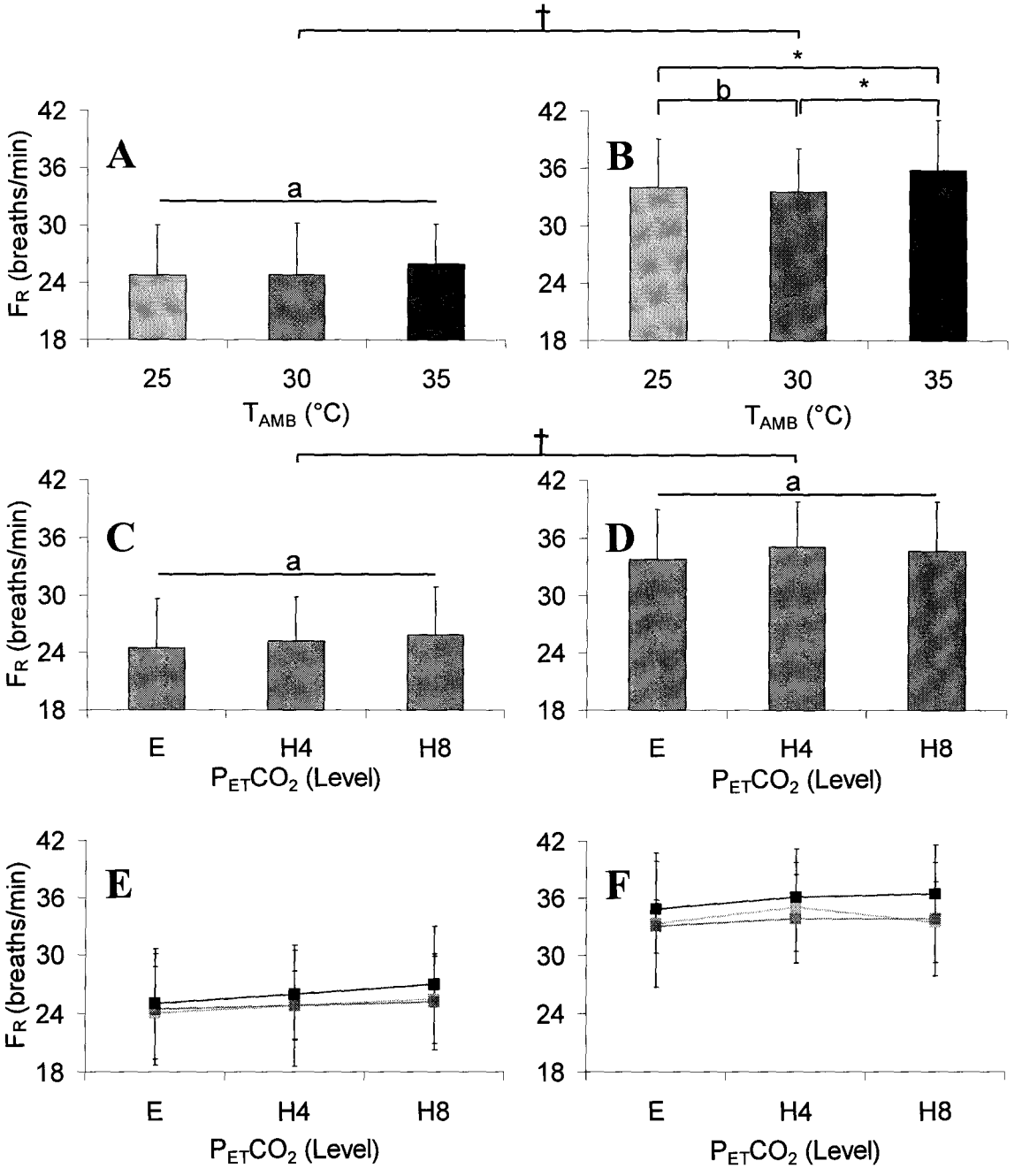
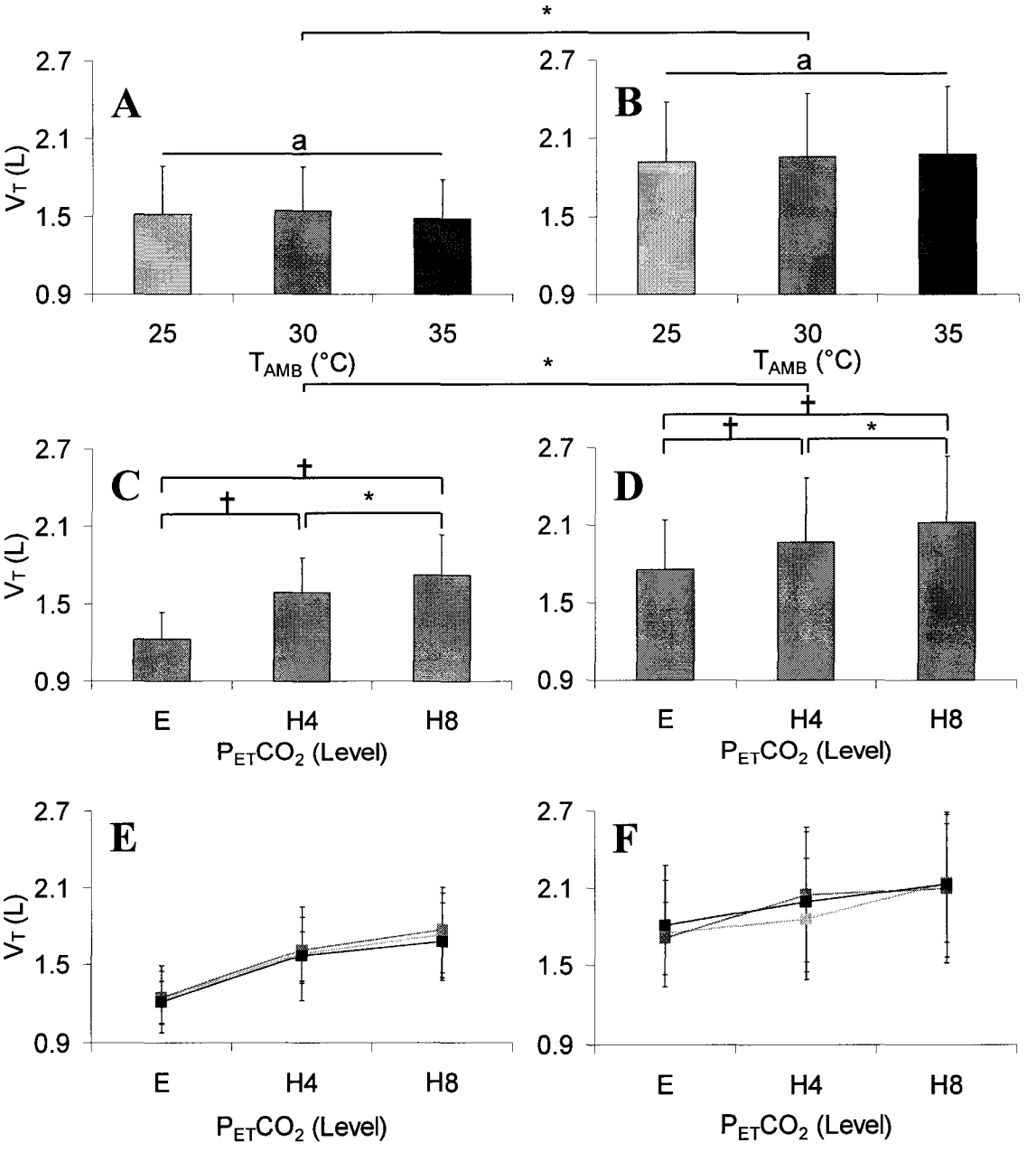


Fig 3.7: Normothermic (A,C,E) and hyperthermic (B,D,F) tidal volume (V_T) at three different ambient temperatures (A,B) and at two levels of hypercapnia that were each preceded by a eucapnia period (C,D). Interaction plots for V_T are shown for $P_{ET}CO_2$ and T_{SK} (E,F); E = preceding eucapnia, H4 = + 4 mmHg hypercapnia, H8 = + 8 mmHg hypercapnia. Symbol shades in E/F correspond to bar fills in A/B. * $p<0.05$; † $p<0.001$; a: 3 means not significantly different; b: 2 means not significantly different; c: normothermic- is not different from hyperthermic-grand mean across 3 levels.



CHAPTER 4: Study 2

Influence of the Rate of Change of Skin Temperature on Maximal Pulmonary Ventilation Before and Following Exercise

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Running Head: Skin Temperature and Ventilation

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4.1 Abstract

It remains unresolved if dynamic ($\dot{T}_{SK}$) skin temperature changes contribute to thermal hyperpnea. HYPOTHESIS: Peak $\dot{V}_E$ responses will increase proportionately to $\dot{T}_{SK}$ with a stable normothermic core temperatures in pre- and post-exercise sessions. METHODS: Six participants (1.68±0.06 m, 67.2±11.9 kg, and 23.2±3.9 yoa;mean±SD) were irradiated with heat lamps for a 10 min period followed by no irradiation for 5 min before and after exercise at 62.4% $\dot{V}O_{2\ PEAK}$. RESULTS: There was no main effect of exercise state for peak $\dot{V}_E$, $\dot{V}_E/\dot{V}O_2$, or $\dot{V}_E/\dot{V}CO_2$ responses, but there was a main effect of $\dot{T}_{SK}$ on peak $\dot{V}_E$, $\dot{V}_E/\dot{V}O_2$, and $\dot{V}_E/\dot{V}CO_2$ responses. There was no interaction between pre- and post-exercise conditions and $\dot{T}_{SK}$ in their influence on peak $\dot{V}_E$ response. CONCLUSION: Both increases and decreases in $\dot{T}_{SK}$ result in proportional increases in resting peak pulmonary ventilation.

4.2 Introduction

The thermoregulatory system defends changes in hypothalamic temperatures by generating thermoregulatory responses to changes in skin (10, 12, 15) and core temperatures (4, 5, 14, 23, 35, 40). The thermoregulatory system is sensitive to both static (27, 29) and dynamic (2, 13, 31, 36, 42) changes in skin and core temperature. A number of studies have characterized the temperature sensitive nature of the neurons in the pre-optic anterior hypothalamus and spinal cord (6, 9). This is the anatomical site where the integration of both central and peripheral thermal inputs is thought to occur (8, 26). Studies in our lab have characterized the patterns of the ventilatory response to dynamic increases of central (16, 41), as well as static increases of central (17), and peripheral (19, 22) temperatures. In addition, some evidence during cool to warm immersions has suggested that dynamic peripheral temperature changes also influence pulmonary ventilation (13, 31). A series of experiments in rats by Boden et. al (6, 7) show there are synaptic connections between the hypothalamus and the respiratory control centers in the medulla oblongata that initiate a temperature dependant input to pulmonary ventilation during hyperthermia.

It is known that core temperatures can contribute to increases in exercise ventilation but the influence of skin temperature on this response remains to be resolved (24). The rate of core temperature change (24, 41) has been assessed for its influence on exercise $\dot{V}_E$, but it is not evident if and how $\dot{T}_{SK}$ influences this response. In addition, some studies have shown an increased chemosensitivity of pulmonary ventilation during hyperthermia (1, 18, 19, 30, 37) and consequently controlling end-tidal gasses is needed in studies of ventilation and body temperatures. Changes in metabolite concentrations

concurrent with exercise (3, 33, 39) could potentially interact with the influences of body temperatures on stimulating exercise ventilation. As such it is important to assess if exercise metabolites (i.e. muscle chemoreflex) influences peak ventilation responses during periods of dynamic skin temperature changes.

This study was conducted to explore the influence of dynamic changes in skin temperature on resting ventilation. It was hypothesized that peak pulmonary ventilation responsewill increase proportionately to rate of change of skin temperature in humans with a stable normothermic core temperature. We further hypothesized that the response of peak pulmonary ventilation to the rate of skin temperature change will remain unchanged between pre- and post-exercise tests despite metabolites remaining elevated post exercise (3, 39). The dynamic influence of skin temperature on peak pulmonary ventilation was examined by irradiating the trunk and head of participants with radiant heat lamps in a climatic chamber held at 25°C before and after steady state exercise. The post exercise test was completed after core temperature had returned to a resting value and during a period when metabolites from exercise are known to remain elevated (3, 33, 20).

4.3 Methods

The following study was conducted in Simon Fraser University's Department of Biomedical Physiology and Kinesiology in the Laboratory for Exercise and Environmental Physiology. Ethical approval was obtained for the study from the Office of Research Ethics at Simon Fraser University.

4.3.1 Participants

A power calculation was done to determine sample size using a difference worth detecting of 9 ± 4.9 L/min in maximum pulmonary $\dot{V}_E$ based on pilot data collected in the lab. Six volunteers were used to achieve a power of 0.90 and an α of 0.05. Each participant was moderately fit and between the ages of 19 and 29 years old (Table 4.1). They were all non-smokers and had no acute or chronic pulmonary deficiencies. They were asked to abstain from alcohol, caffeine, or intense exercise in the 24 hr preceding their scheduled test date. Each prospective volunteer, before accepting to participate in the study, was given an orientation session in the laboratory to explain potential risks and protocols employed by this study. Following the introduction and a 24 h reflection period, the participant was asked to fill out a Physical Activity Readiness Questionnaire (PAR-Q), a Laboratory for Exercise and Environmental Physiology Confidential Health Screen Questionnaire, and an informed consent form to participate in the study.

4.3.2 Instrumentation

4.3.2.1 Ventilatory/ Metabolic Variables

During all ventilatory tests or measurements the participant wore a nose clip. The breathing apparatus consisted of a mouthpiece connected to a two-way flow sensor measuring ventilation and a two-way non-rebreathing valve (NRB 2700, Hans Rudolph Inc, Kansas City, MO, USA). The 2-way flow sensor was calibrated using a 3 L standardized volume syringe (Sensormedics, Yorba Linda, CA, USA). The sample line for oxygen and carbon dioxide gas partial pressure measurements was also connected to this breathing apparatus. The sample line removes a volume of ~500 $mL \cdot min^{-1}$ during breath by breath measurement of respiratory gases by a Sensormedics Vmax 229c metabolic cart (Sensormedics, Yorba Linda, CA, USA). The CO_2 partial pressures were assessed with non-dispersive infrared spectroscopy and O_2 partial pressures were quantified with a paramagnetic sensor. Both sensors were calibrated prior to each trial using air and 2 gases of known concentrations (20.93% O_2 and 0.05% CO_2 with balance N_2; 26% O_2 with balance N_2; 4% CO_2 and 16% O_2 with balance N_2).

The inspired air, during the three trials, were composed of a mixture of compressed air, CO_2 and N_2. A LabVIEW software program (National Instruments, Austin, TX, USA, Version 7.1) and end-tidal forcing system (32) controlled the opening time of electronic solenoid valves attached to the three gas cylinders. Based on the measured values from the expired air of the immediately preceding breath, LabVIEW altered the time each valve was open to stabilize end tidal concentrations of various gases. In this way, it was assured that the end-tidal partial pressures of CO_2 and O_2 remained constant at the desired values over the course of the prescribed temperature

stresses. The breathing apparatus was connected to a humidifier via 250 cm's of 3.8 cm diameter corrugated Collins tubing. The humidifier moistened air being fed to the participant from the cylinders of compressed gas. This end-tidal forcing system is described in detail by Koehle et al. (32). Variables followed included exercise ventilation ($\dot{V}_E$), oxygen consumption ($\dot{V}O_2$), CO_2 production ($\dot{V}CO_2$), ventilatory equivalents for O_2 ($\dot{V}_E/\dot{V}O_2$) and CO_2 ($\dot{V}_E/\dot{V}CO_2$), and respiratory exchange ratio (RER).

4.3.2.2 Cardiovascular Variables

Heart rate (HR) and arterial hemoglobin saturation (S_aO_2) were measured continuously using a pulse oximeter (Masimo Radical, Irvine, CA, USA) attached to one of the participants' distal phalanxes.

4.3.2.3 Body Temperatures

Skin and core temperatures were continuously recorded throughout the test. Core temperatures were measured esophageal (T_{ES}) probes, whereas skin temperatures were averaged over 8 locations and expressed as their un-weighted mean value ($\bar{T}_{SK}$). These 8 locations included forehead (T_{fh}), chest (T_{ch}), upper abdomen (T_{abup}), lower abdomen (T_{ablo}), neck (T_{neck}), Trapeziums (T_{trap}), upper back (T_{baup}), lower back (T_{balo}). Esophageal temperature was sampled with a pediatric sized nasopharyngeal esophageal temperature thermocouple (9 FR, Mallinckrodt Medical Inc., St. Louis, MO, USA) placed at the T8/T9 level. This location was found using Mekjavic and Rempel's equation for standing height (34).

$$L = 0.228 \bullet (\text{standing height (cm)}) - 0.194 \quad \text{.....(2)}$$

Rectal temperatures were sampled from a sheathed thermocouple inserted 15 cm into the rectum (12 FR, Mallinckrodt Medical Inc., St. Louis, MO, USA). Skin temperatures were recorded by T-type, copper/constantan thermocouples (Omega Engineering Inc., Stanford, CT, USA) taped down to prevent deviations from true skin temperature values. Calibrations of T_{ES}, T_{RE}, and $\overline{T}_{SK}$ thermocouple probes were completed in a regulated temperature water bath over the range of expected values (VWR International, Model 1196 West Chester, Pensylvania, USA).

4.3.2.4 Radiant Heating

Increases in skin temperature were achieved by using 8 heat lamps (General Electric lighting Inc., heat lamp red, 250 W, Cleveland, Ohio, USA). The 8 lamps were evenly distributed to project light on the entire ventral (4 lamps) and dorsal (4 lamps) surfaces of the body above the waist as skin below the waist was shown to be of lower thermosensitivity (13).

4.3.2.5 Eccrine Sweating

Forehead eccrine sweat rate ($\dot{E}_{SW}$) was measured using the ventilated capsule method. A forearm band was worn to secure a capsule (surface area of 5.31 cm^2) to the forearm. The capsule was flushed at a rate of 1 $L \cdot min^{-1}$ by an anhydrous compressed air source. Changes in the humidity of the air were measured by a resistance hygrometer before (RH-200, Omega, Laval, Quebec) and a capacitance hygrometer after (HMT337, Vasaila, Helsinki, Finland) being directed, via PVC tubing, into a capsule (volume of 15.6 cm^3) positioned on the forearm. Sweating rate was calculated using Bullard's equation taking into account the surface area of the capsule (11).This is given in equation 4.1 below:

$\dot{E}_{SW}$ (mg·m^{-2}·s^{-1}) = [$\dot{F}_{AIR}$ (L·s^{-1}) · (ΔRH/100) · ρ_{steam} (mg·L^{-1})] / SA (m^2).....(4.1)

$\dot{F}_{AIR}$ is the rate of air flow, ΔRH is the change in relative humidity, ρ_{steam} is the density of water vapor, and SA is the surface area under the capsule.

4.3.2.6 Work Rates

Exercise was performed on an electrically braked cycle ergometer (Lode 91100 V2.23, Groningen, Netherlands).

4.3.2.7 Climate Chamber

Desired climatic conditions were obtained within a 5.08 m by 3.75 m by 2.49 m high walk-in climatic chamber (Tenney Engineering Inc., Union, NJ, USA).

4.3.2.8 Data Acquisition

Ventilatory data were sampled on a breath-by-breath basis by the metabolic cart. The recording rate was on a breath-by-breath basis. The flow signal from the metabolic cart was used to trigger LabVIEW to sample and record all temperature as well as physiological sensors (National Instruments, Austin, TX, USA, Version 7.1).

4.3.3 Protocol

Testing commenced between 6:00 am and 10:00 am for each participant with the climate chamber set at 25°C and 20 % RH. First the volunteer was instrumented for body temperature and ventilatory responses. The chamber fans were then turned off just prior to turning the heat lamps on to minimize air circulation and convective heat loss at the skin surface. Within the chamber, the participant stood 45 cm from the heat lamps in a control period for 10 min at rest without any radiant heating. The last 2 min of this rest

period was analyzed for zero rate of change of $\bar{T}_{SK}$ data. The participant was then exposed to radiant heating bulbs for 10 min followed by a 5 min nonheated period. The periods when $\dot{T}_{SK}$ were changing were analyzed for (+) and (-) $\dot{T}_{SK}$ data. During both the heating and nonheating periods end-tidal CO_2 and O_2 were clamped at eucapnic and euoxic levels. With the chamber fans turned on again, the participant then exercised at about ~62.4% $\dot{V}O_{2\ PEAK}$ until their core temperature stabilized at ~38°C. Following a rest period allowing ventilation and T_{ES} to drop back to resting values for 5 min, and cessation of the chamber fans once again, the identical radiant heating procedure was repeated.

During all experiments care was taken to distract the volunteer by means of visual or oral stimuli so as to protect against a variable volitional response of breathing and each volunteer was naïve to the objectives of the experiment.

4.3.4 Statistical Analyses

Results were analyzed using peak values for $\bar{T}_{SK}$, $\dot{T}_{SK}$, $\dot{E}_{SW}$, $\dot{V}_E$, $\dot{V}_E/\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$, HR, and $\dot{V}O_2$, while mean values were used for $P_{ET}CO_2$ and $P_{ET}O_2$. A 2-way ANOVA for repeated measures was employed with factors of Dynamic Skin Temperature change (levels: zero, positive, negative) and Exercise State (levels: pre and post). If there was a significant main effect of rate of either factor, one-tailed paired t-tests were employed on pooled means between levels for means comparison. Dependent outcome variables included T_{ES}, $\bar{T}_{SK}$, $\dot{T}_{SK}$, $\dot{E}_{SW}$, $\dot{V}_E$, $\dot{V}_E/\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$, HR, $\dot{V}O_2$, RER, $P_{ET}O_2$, and $P_{ET}CO_2$. If there was a significant main effect or interaction effect of Dynamic Skin Temperature or Exercise State, single-tailed, paired t-tests were employed for means of comparison. The level of significance was set at 0.05.

4.4 Results

An example participant's rate of change of skin temperature ($\dot{T}_{SK}$), mean skin temperature ($\overline{T}_{SK}$), sweating rate ($\dot{E}_{SW}$), ventilation ($\dot{V}_E$) and ventilatory equivalents for oxygen ($\dot{V}_E/\dot{V}O_2$) and carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) are given in Fig. 4.1A-F.

Irrespective of Exercise State ($F=0.9$, $p = 0.39$) there was a main effect ($F=10.5$, $p < 0.001$) of Dynamic Skin Temperature change on $\dot{T}_{SK}$. This main effect was explained by significant changes from 0 to + 0.14 or from 0 to -0.14 °C/s (Fig. 4.2A). There was a main effect of Dynamic Skin Temperature change on $\overline{T}_{SK}$ ($F=164.4$, $p < 0.001$) and T_{ES} ($F=19.5$, $p < 0.001$) (Fig. 4.2B/C). The pooled means of $\overline{T}_{SK}$ were 30.7 ± 1.3°C at rest, 41.5 ± 2.8°C during a positive $\dot{T}_{SK}$, and 43.0 ± 1.7°C during a negative $\dot{T}_{SK}$. The pooled means of T_{ES} were 36.8 ± 0.6°C at rest, 36.8 ± 0.5°C during positive $\dot{T}_{SK}$, and 37.0 ± 0.5°C during negative $\dot{T}_{SK}$. There was no effect of Exercise State on $\overline{T}_{SK}$ ($F=5.4$, $p=0.07$) or T_{ES} ($F=5.0$, $p=0.08$).

There was a main effect of Dynamic Skin Temperature change on peak $\dot{V}_E$ ($F=28.8$, $p < 0.001$) but no main effect ($F=2.4$, $p=0.18$) of Exercise State (Fig. 4.3A). The peak $\dot{V}_E$ increased from 13.2 ± 2.8 at rest to 21.3 ± 4.9 during positive $\dot{T}_{SK}$ and 22.0 ± 5.0 L/min during negative $\dot{T}_{SK}$. There were main effects of both Dynamic Skin Temperature change ($F=19.5$, $p < 0.001$) and Exercise State ($F=8.4$, $p=0.03$) on peak $\dot{E}_{SW}$ (Fig. 4.3B). The peak $\dot{E}_{SW}$ increased from ~5 to 10 mL/m^2/min ($p=0.03$) between pre- and post-exercise trials. The peak $\dot{E}_{SW}$ increased from ~4 mL/m^2/min at rest to ~8 mL/m^2/min during positive $\dot{T}_{SK}$ and ~11 mL/m^2/min ($P<0.001$) during negative $\dot{T}_{SK}$.

There were main effects of both Dynamic Skin Temperature change ($F=33$, $p < 0.001$) and Exercise State ($F=33.6$, $p=0.02$) on peak heart rate (Fig. 4.4A). Irrespective of

Dynamic Skin Temperature change level, peak heart rate increased significantly from 97.6 ± 19.9 to 114.9 ± 20.4 beats/min (p=0.02) between pre- and post-exercise trials. It also increased from 95.4 ± 19.6 at rest to 108.6 ± 22.0 during positive $\dot{T}_{SK}$ and 114.7 ± 20.6°C (p<0.001) during negative $\dot{T}_{SK}$. There was a significant positive interaction (F=6.1, p=0.02) between Dynamic Skin Temperature change and Exercise State in their influence on peak heart rate. Relative to peak heart rate at rest, the difference in this response between pre- and post-exercise was diminished in the (-) and (+) dynamic skin temperature changes. There was no effect of Exercise State on either peak $\dot{V}O_2$ (F=1.3, p=0.31) or peak RER (F=0.02, p=0.90). There was a main effect of Dynamic Skin Temperature change on both peak $\dot{V}O_2$ (F=20.2, p < 0.001) and peak RER (F=6.0 p=0.02) (Fig. 4.4B/C). The peak $\dot{V}O_2$ increased from 0.3 ± 0.1 at rest to 0.7 ± 0.3 during positive $\dot{T}_{SK}$ and to 0.6 ± 0.2 L/min (p<0.001) during negative $\dot{T}_{SK}$. The peak RER increased from 0.9 ± 0.0 at rest to 1.1 ± 0.3 during positive $\dot{T}_{SK}$ and to 1.22 ± 0.4 (p=0.02) during negative $\dot{T}_{SK}$.

There were main effects of Dynamic Skin Temperature change on peak $\dot{V}_E/\dot{V}O_2$ (unitless) (F=25.1, p < 0.001) and peak $\dot{V}_E/\dot{V}CO_2$ (unitless) (F=36.1, p < 0.001); (Fig. 4.5A/B). The peak $\dot{V}_E/\dot{V}O_2$ increased from 43.9 ± 5.7 at rest to 69.8 ± 12.9 during positive $\dot{T}_{SK}$ and 75.9 ± 15.7 (p<0.001) during negative $\dot{T}_{SK}$. The peak $\dot{V}_E/\dot{V}CO_2$ increased from 52.7 ± 6.4 at rest to 86.0 ± 17.0 during positive $\dot{T}_{SK}$ and 87.2 ± 12.4 (p<0.001) during negative $\dot{T}_{SK}$. There was no effect of Exercise State on peak $\dot{V}_E/\dot{V}O_2$ (F=0.8, p=0.42) or peak $\dot{V}_E/\dot{V}CO_2$ (F=0.8, p=0.40).

There was no main effect of Exercise State (F=0.1, p=0.73) on mean $P_{ET}CO_2$ (Fig. 4.7A) but there was a main effect of Exercise State (F=9.0, p=0.03) on mean $P_{ET}O2$ (Fig. 4.7B). Resting values increased from 101.8 ± 2.8 to 106.2 ± 3.5 mm Hg and from 102.0 ±

2.9 to 108.0 ± 2.6 mm Hg (p,0.001) during positive $\dot{T}_{SK}$ between pre- and post-exercise trials. There was no main effect of Dynamic Skin Temperature change on mean $P_{ET}CO_2$ (F=0.1, p=0.91) or $P_{ET}O_2$ (F=3.0, p=0.77).

4.5 Discussion

It was hypothesized that maximal pulmonary ventilation would increase proportionately to rate of change of skin temperature with a stable normothermic core temperature. It was also hypothesized that rate of change of skin temperature would not interact with exercise state in its influence on peak ventilation. Indeed the peak ventilation response was modulated by changes in the rate of change of skin temperature (Fig. 4.3A) and was not modulated by changes in exercise state. Similar response patterns were observed for peak $\dot{V}_E/\dot{V}O_2$ (Fig. 4.5A) and peak $\dot{V}_E/\dot{V}CO_2$ (Fig. 4.5A) as those evident for peak $\dot{V}_E$. This evidence supported our first hypothesis that ventilation would increase proportionately to rate of change of skin temperature.

The thermoregulatory system defends changes in hypothalamic temperatures by generating thermoregulatory responses to changes in skin (10, 12, 15) and core temperatures (4, 5, 14, 23, 35, 40). The thermoregulatory system is sensitive to both static (27, 29) and dynamic (2, 13, 31, 36, 42) changes in skin and core temperature. Studies by Nadel et al. (36), using radiant heat lamps to impose a thermal challenge, showed eccrine sweating was sensitive to rates of change of skin temperature. Together this supports sweating (36) as well as peak pulmonary ventilation (Fig. 4.4A, Fig. 4.5 A,B) can be modulated by $\dot{T}_{SK}$ during skin warming or skin cooling, when $\overline{T}_{SK}$ is at a hyperthermic value >40°C.

Turning on the radiant heating lamps succeeded in producing a positive rate of change of skin temperature while turning them off produced a similar magnitude of negative rate of change of skin temperature (Fig. 4.2A). Profiles of the rise and decay of mean skin temperature were constant (Fig. 4.1B). The $\dot{T}_{SK}$ induced an apparent increase

in sympathetic output as increases were evident in peak oxygen consumption, heart rate, respiratory exchange ratio, ventilation, and sweating rate responses. Following exercise, radiant heating began once ventilation and T_{ES} dropped to pre-exercise values. Radiant heating was successful in activating whole body thermoregulatory responses.

Passive (16, 19) and active (24, 25, 38, 41) whole body heating have been shown to elicit increases in ventilation above core temperature thresholds. As such, a series of studies have characterized the patterns of the ventilatory response to dynamic central (16, 41), static central (17), and static peripheral (22) thermal stimuli. Additional evidence from Boden et al. (6) revealed that in the non-panting rat, thermal hyperpnea can be blunted by introducing lesions between the hypothalamus and the respiratory control center in the brain stem. This suggested that a main drive to ventilate during hyperthermia is coming from temperature control centers in the hypothalamus. The results presented in the current study support that neurons in the skin, that are sensitive to rates of their temperature change, can stimulate pulmonary ventilation. The thermal hyperpnea induced by increases and decreases in $\dot{T}_{SK}$ (Fig. 4.4A) exhibits similar stimulus/response patterns as other classical thermoregulatory responses including eccrine sweating and cutaneous blood flow. This current research provides more evidence to suggest that thermal hyperpnea is controlled by similar mechanisms as other thermoregulatory responses that are generated after integration of temperature signals in the hypothalamus. This new evidence supporting the influence of dynamic temperature changes on peak $\dot{V}_E$ suggests this change in pulmonary ventilation may act as a thermoregulatory response generated from the integration of skin and core temperatures.

We conducted the current pre- and post-exercise trial to investigate the combined metabolic and thermoregulatory influences on ventilation responses. If exercise metabolites (i.e. the muscle chemoreflex) were responsible for or contributed to the effects on ventilation, one would expect the response to be potentially exaggerated during post-exercise radiant heating. This is a period when altered metabolite concentrations such as lactate, K^+ or norepinephrine circulating in the blood could influence ventilation (20, 21). During intense exercise plasma norepinephrine and lactate become elevated to ~521 pg/mL and 92 mg/100mL respectively (3, 39). The time constant for the decay of plasma norepinephrine was over 100 s (39) and upwards of 30 min for lactate removal (3). Although K^+ recovers quickly, there is a prolonged depression of plasma K^+ concentrations by ~0.5 mmol/L up to 10 minutes post exercise (33). Despite heart rate and sweating rate being further increased, all pulmonary ventilation responses increased by similar amounts in pre- and post-exercise trials. This suggests the ventilatory response to Dynamic Skin Temperature changes is primarily the consequence of the cutaneous thermal stimulation and not influenced by the muscle chemo-reflex. It appears the elevated HR in the post exercise condition follows from the cutaneous vasodilation that lowers central blood volume and through a baro-reflex induced response increases HR to maintain cardiac output and mean arterial pressure.

Some limitations to this study include there was a small but not significant increase in T_{ES} between the pre- and post-exercise trials. This increase in T_{ES} was, however, still at normothermic levels much below thresholds of thermal hyperpnea that are ~37.6°C during exercise (41) and 38.5°C during passive hyperthermia (16). Each of $P_{ET}CO_2$ and $P_{ET}O_2$ were clamped at eucapnic and euoxic levels during pre- and post-

exercise trials so as to standardize chemical drives by the chemosensitive tissues on ventilation. The radiant heat lamps were distributed with 4 lamps in front and 4 lamps behind, located on the midline and evenly spaced. As such the same rate of skin temperature stimulus was not observed uniformly over the entire surface of the body. While the density of skin temperature sensitive neurons in the skin can vary quite dramatically (8, 28), they are highest in the core and face over which the lamps were evenly distributed.

In conclusion, both positive and negative rates of change of skin temperature were altered by radiant heating. These positive and negative rates of change of skin temperature resulted in similar, significant, pre- and post-exercise increases in resting peak responses of pulmonary ventilation, respiratory exchange ratio, and the ventilatory equivalents for oxygen and carbon dioxide.

4.6 References

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4.7 Tables

Table 4.1: Age, gender, body mass index (BMI), physical characteristics, $\dot{V}O_{2\ PEAK}$ and % $\dot{V}O_{2\ PEAK}$ of each participant.

Participant	Age (y)	Gender	Height (m)	Weight (kg)	BMI (kg/m^2)	$\dot{V}O_{2\ PEAK}$ ($L*min^{-1}$)	% $\dot{V}O_{2\ PEAK}$
1	26	M	1.71	63	21.5	5.0	52.0
2	19	M	1.64	75	27.9	4.1	61.0
3	23	M	1.73	85	28.4	4.6	63.0
4	19	F	1.70	69	23.9	3.3	63.6
5	29	F	1.57	51	20.7	2.1	61.9
6	23	M	1.73	60	20.0	3.3	72.7
mean	23.2	-	1.68	67.2	23.7	3.8	62.4
SD	3.9	-	0.06	11.9	3.7	1.2	6.6

4.8 Figures

Fig 4.1: A sample participant's rate of change of skin temperature ($\dot{T}_{SK}$; A), mean skin temperature ($\overline{T}_{SK}$;B), sweating rate ($\dot{E}_{SW}$;C), ventilation (10 s avg) (D), ventilatory equivalent for oxygen ($\dot{V}_E/\dot{V}O_2$;E) and carbon dioxide ($\dot{V}_E/\dot{V}CO_2$;F) responses to radiant heating. Vertical arrows in panel A indicate the onsets of radiant heating.

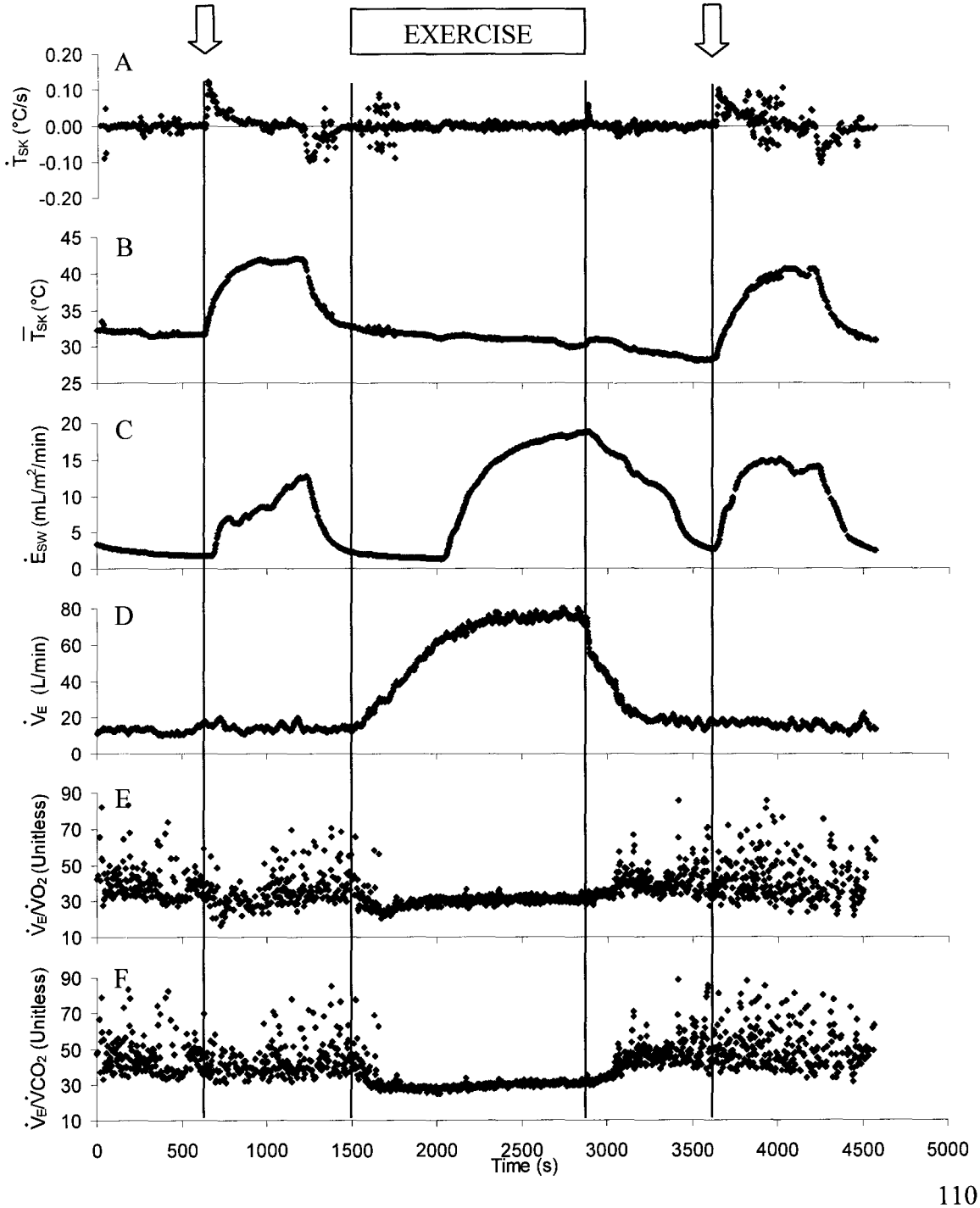


Fig 4.2: Peak values for each of rate of change of skin temperature ($\dot{T}_{SK}$;A), mean skin temperature ($\overline{T}_{SK}$; B), and esophageal temperature (T_{ES};C) responses to changes in Exercise State and Dynamic Skin Temperature change. 0 = no rate of change, (+) = positive rate of change, (-) = negative rate of change. Grey = pre-exercise; Black = post-exercise conditions. * $p<0.05$; † $p<0.001$; a: pre = post; b: pooled pre-post exercise means not significantly different.

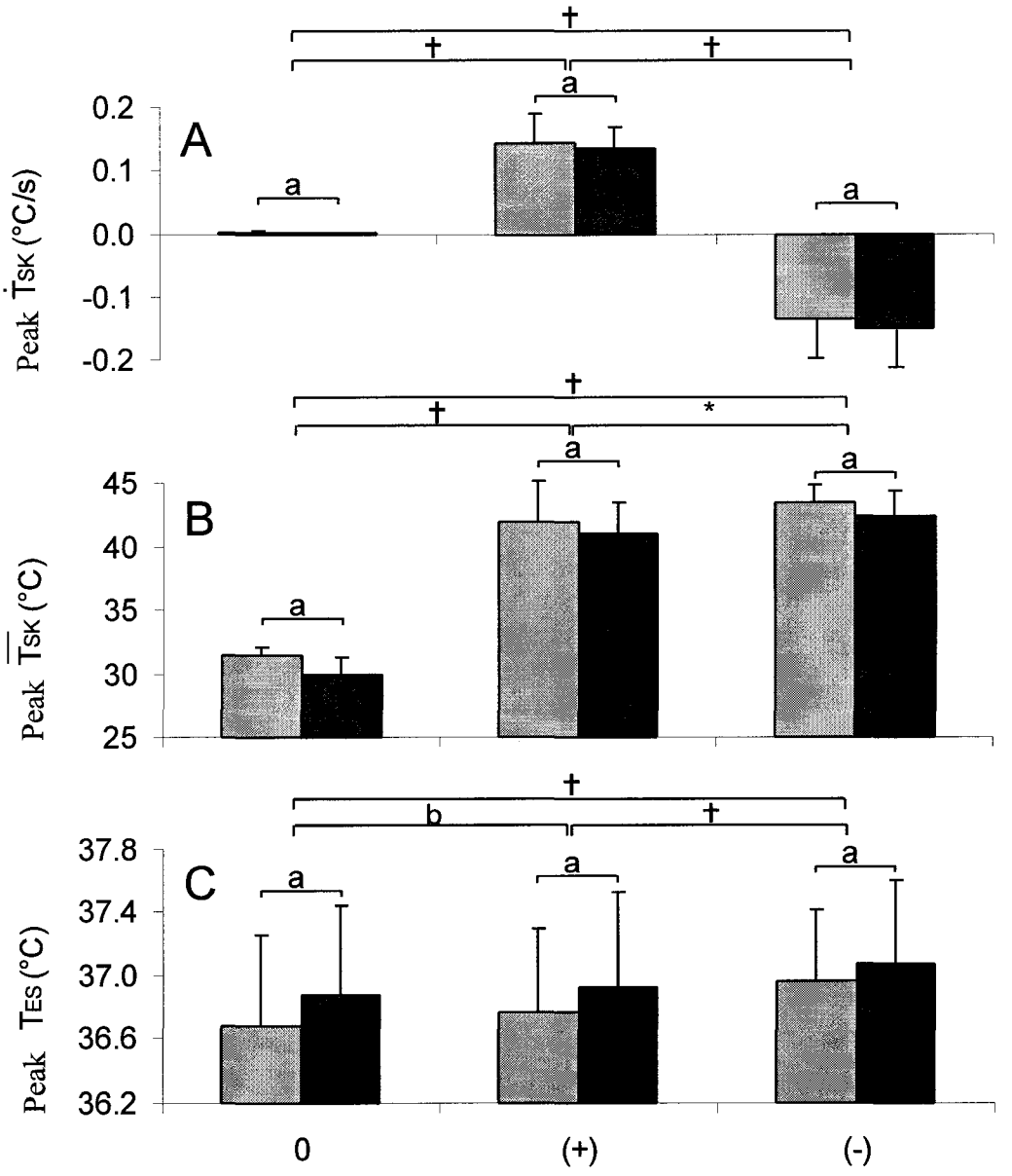


Fig 4.3: Peak values for each of ventilation ($\dot{V}_E$;A) and sweating rate ($\dot{E}_{SW}$;B) responses to change in Exercise State and Dynamic Skin Temperature change. 0 = no rate of change, (+) = positive rate of change, (-) = negative rate of change. Grey = pre-exercise; Black = post-exercise conditions. * $p<0.05$; † $p<0.001$; a: pre = post; b: pooled pre-post exercise means not significantly different.

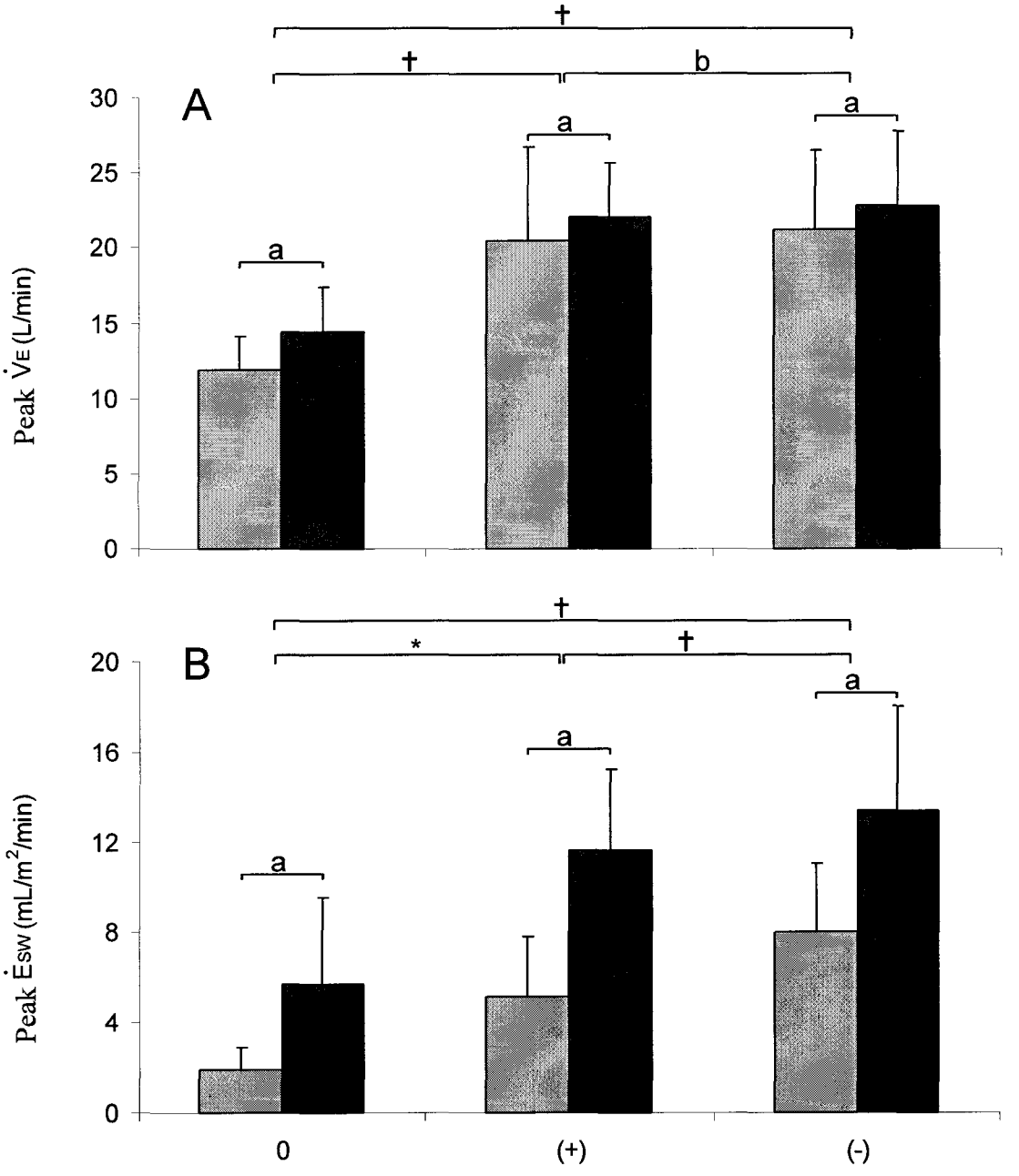


Fig 4.4: Peak values for each of heart rate (HR;A), oxygen consumption ($\dot{V}O_2$;B), and respiratory exchange ratio (RER;C) responses to changes in Exercise State and Dynamic Skin Temperature change. 0 = no rate of change, (+) = positive rate of change, (-) = negative rate of change. Grey = pre-exercise; Black = post-exercise conditions. * $p<0.05$; † $p<0.001$; a: pre = post; b: pooled pre-post exercise means not significantly different.

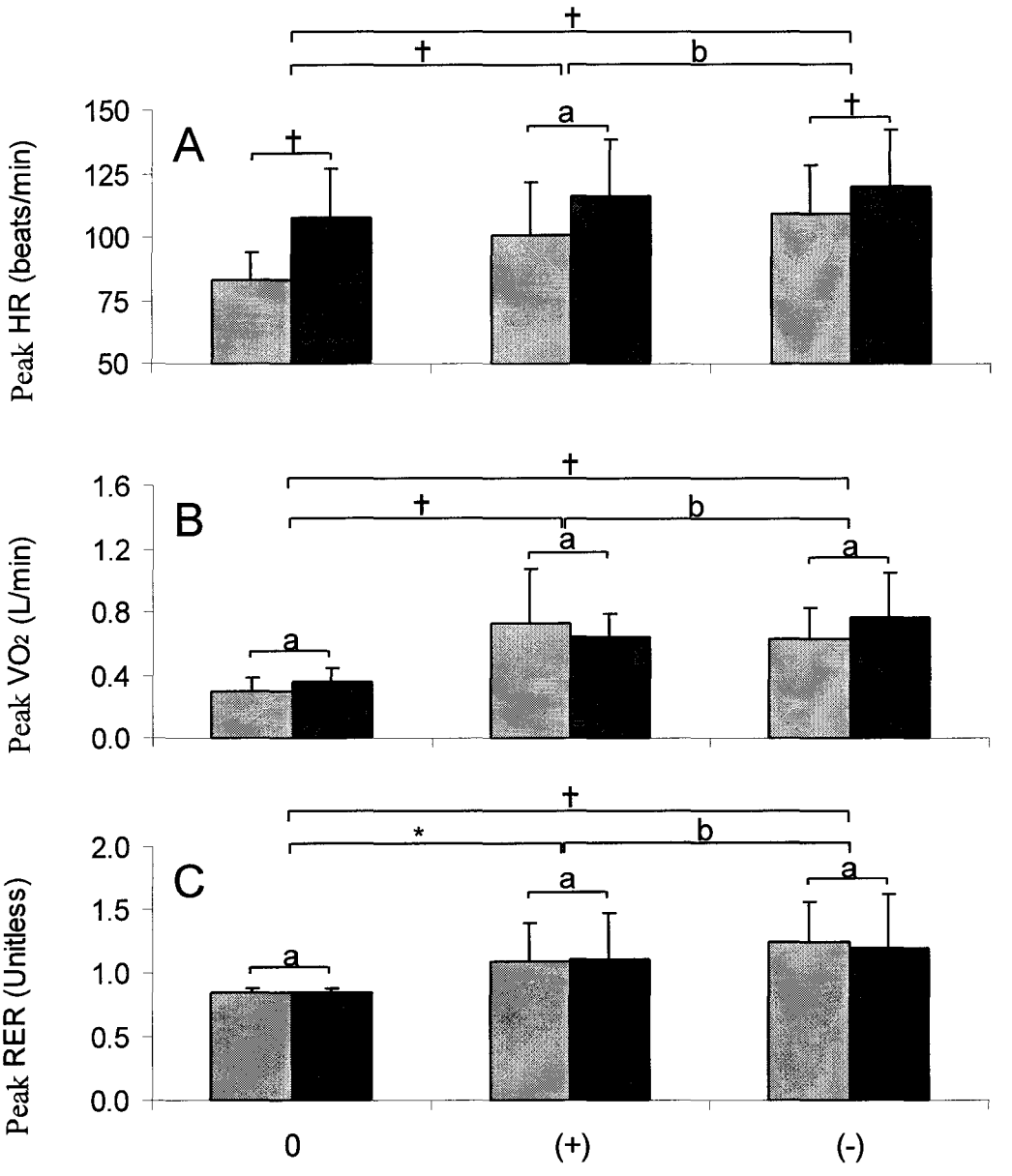


Fig 4.5: Peak values for each of ventilatory equivalent for oxygen ($\dot{V}_E/\dot{V}O_2$;A) and carbon dioxide ($\dot{V}_E/\dot{V}CO_2$;B) responses to changes in Exercise State and Dynamic Skin Temperature change. 0 = no rate of change, (+) = positive rate of change, (-) = negative rate of change. Grey = pre-exercise; Black = post-exercise conditions. † $p<0.001$; a: pre = post; b: pooled pre-post exercise means not significantly different.

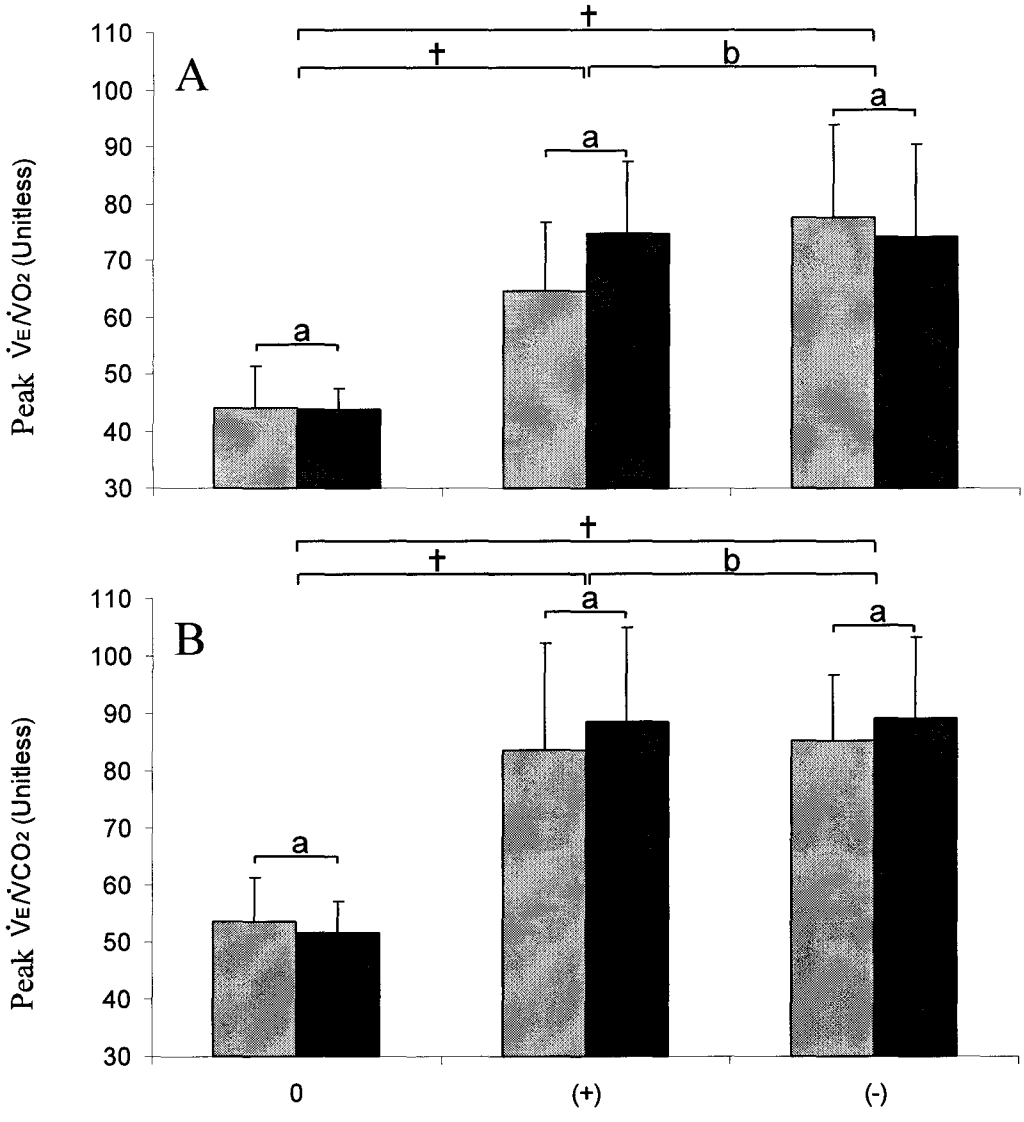
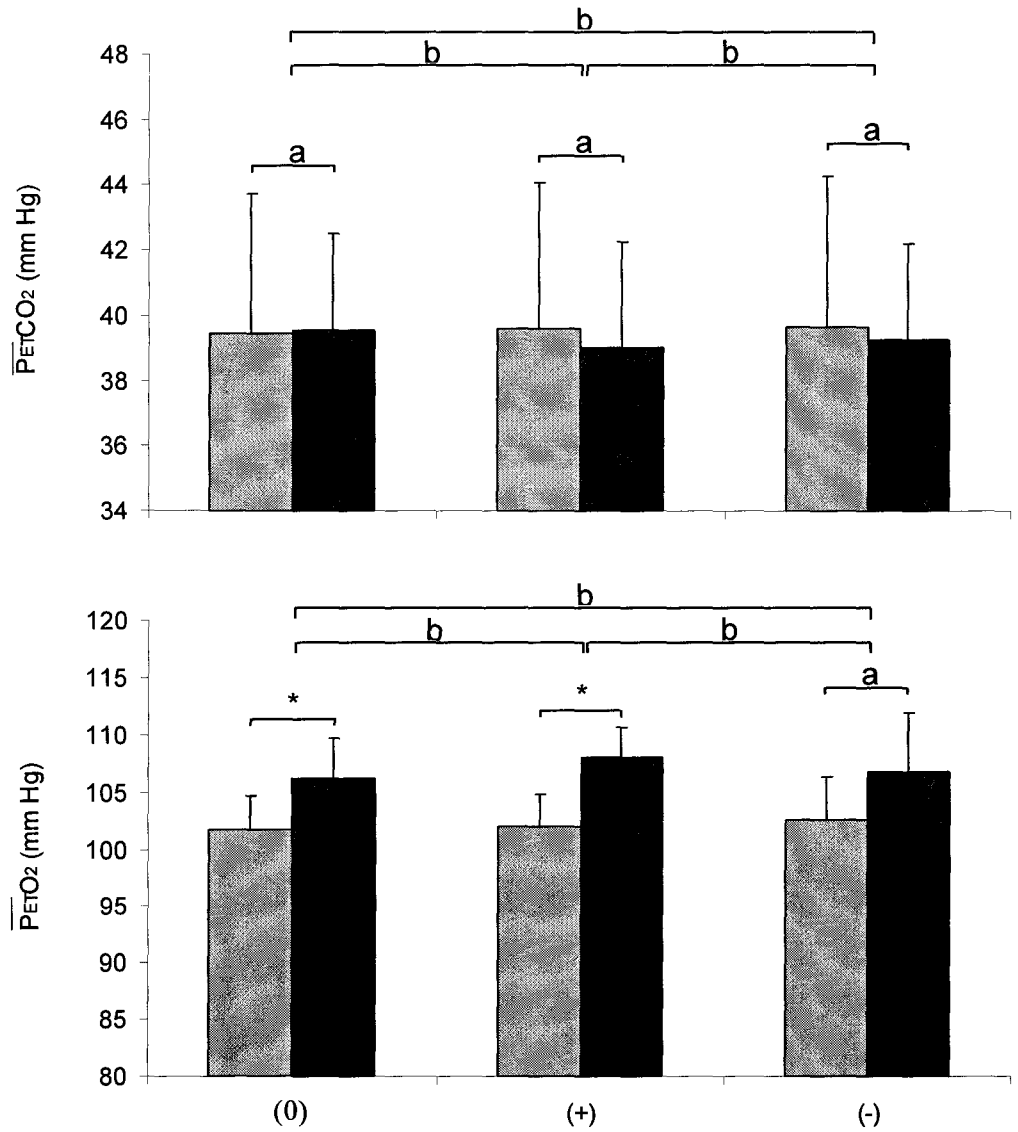


Fig 4.6: Both mean $P_{ET}CO_2$ and mean $P_{ET}O_2$ responses to changes in Exercise State and Dynamic Skin Temperature change. 0 = no rate of change, (+) = positive rate of change, (-) = negative rate of change. Grey = pre-exercise; Black = post-exercise conditions. * $p<0.05$; a: pre = post; b: pooled pre-post exercise means not significantly different.



CHAPTER 5: Thesis Summary

5.1 Hypotheses

Chapter 3

Hypothesis 1 - Ventilation will increase proportionately to skin temperature during steady state exercise with a stable hyperthermic core temperature.

- Ventilation did increase proportionately to skin temperature during steady state exercise with a stable hyperthermic core temperature

Hypothesis 2 – Mean skin temperature will positively interact with hypercapnia in its influence on exercise ventilation during steady state exercise with a stable hyperthermic core temperature.

- Skin temperature did not positively interact with hypercapnia in its influence on exercise ventilation during steady state exercise with a stable hyperthermic core temperature.

Chapter 4

Hypothesis 3 – Peak ventilation will increase proportionately to the rate of change of skin temperature with a stable normothermic core temperature in pre- and post-exercise sessions.

- Peak ventilation did increase proportionately to the rate of change of skin temperature with a stable normothermic core temperature in pre- and post-exercise sessions.

Hypothesis 4 – Peak ventilation response to rate of change of skin temperature will remain the same between pre- and post-exercise tests.

- Peak ventilation response to rate of change of skin temperature did remain the same between pre- and post-exercise tests.

5.2 Testable Questions

Chapter 3

1) Mean skin temperature will vary proportionately to ambient temperature.

- Mean skin temperature did vary proportionately to ambient temperature

2) Esophageal temperature will remain at a steady state level close to resting values of ~37.0°C during ~27% $\dot{V}O_{2\ PEAK}$ and at ~38°C during 53% $\dot{V}O_{2\ PEAK}$ exercise intensity.

- Esophageal temperature did remain at a steady state level close to resting values of ~37.0°C during ~27% $\dot{V}O_{2\ PEAK}$ and at ~37.9°C during 53% $\dot{V}O_{2\ PEAK}$ exercise intensity.

3) Ventilation will increase proportionately to levels of end-tidal partial pressure of carbon dioxide while exercising at ~53% $\dot{V}O_{2\ PEAK}$.

- Ventilation increased proportionately to levels of end-tidal partial pressure of carbon dioxide while exercising at ~53% $\dot{V}O_{2\ PEAK}$.

Chapter 4

4) Rate of change of skin temperature will be elevated during radiant heating and cooling.

- Rate of change of skin temperature was elevated during radiant heating and cooling.

5) Positive and negative rate of change of skin temperature will positively influence peak ventilation responses.

- Positive and negative rate of change of skin temperature positively influenced peak ventilation responses.

6) Exercise state will not influence the relationship between rate of skin temperature change and peak ventilation responses.

- Exercise state did not influence the relationship between rate of change of skin temperature and peak ventilation responses.

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Appendix A

Table A1: Thermocouple location and calibration equations.

Site	Participant Number	Linear Regression Equation	R^2	P value
[1]T_{ES}	1	y = 1.0348x - 2.1258	1.00	P<0.01
T_{ES}	2	y = 1.3244x - 13.596	1.00	P<0.01
T_{ES}	3	y = 1.0107x - 1.272	1.00	P<0.01
T_{ES}	4	y = 0.9962x + 0.8013	1.00	P<0.01
T_{ES}	5	y = 0.9931x + 0.939	1.00	P<0.01
T_{ES}	6	y = 1.3862x - 15.891	1.00	P<0.01
T_{ES}	7	y = 1.0958x - 4.5647	1.00	P<0.01
[2]T_{ES}	8	y = 1.0484x - 2.6612	1.00	P<0.01
T_{ES}	1	y = 1.0487x - 2.487	1.00	P<0.01
T_{ES}	3	y = 1.0484x - 2.6612	1.00	P<0.01
T_{ES}	5	y = 1.1755x - 7.6441	1.00	P<0.01
T_{ES}	6	Y = 0.9952x + 0.8323	1.00	P<0.01
T_{RE}	1-8	y = 0.956x + 0.9678	1.00	P<0.01
[3]T_{SK}	1-8/1-6	y = 0.9402x+0.7809	1.00	P<0.01
[3]T_{SK}	1-8/1-6	y = 0.942x+1.9769	1.00	P<0.01
[3]T_{SK}	1-8/1-6	y = 1.0036x-0.3581	1.00	P<0.01
[3]T_{SK}	1-8/1-6	y = 1.0159x-0.4383	1.00	P<0.01
[3]T_{SK}	1-8/1-6	y = 1.5638x - 15.183	1.00	P<0.01
[3]T_{SK}	1-8/1-6	y = 1.0012x - 0.2582	1.00	P<0.01
[3]T_{SK}	1-8/1-6	y = 1.0013x - 0.4239	1.00	P<0.01
[3]T_{SK}	1-8/1-6	y = 1.0049x - 0.8361	1.00	P<0.01

[1] Participant 1 is participant 2 in study 2.

[2] Participant 8 is participant 4 in study 2.

[3] Skin temperature calibration equations correspond to skin temperature sites as given in the database for this thesis.