HUMAN THERMOREGULATORY AND PULMONARY VENTILATION RESPONSES TO ACTIVELY- AND PASSIVELY-INDUCED HYPERTHERMIA

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By

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Thesis Abstract

To explore the nature and mechanisms underlying the control of human pulmonary ventilation during hyperthermia, 2 studies in this thesis examined how esophageal temperature (T_{es}) thresholds for eccrine sweating ($\dot{E}_{SW}$) and cutaneous blood velocity (CBV) compared to those for pulmonary ventilation. In study 1 seven untrained males were rendered hyperthermic during an incremental exercise test on a seated cycle ergometer from rest to the point of exhaustion. In study 2 the same participants were passively rendered hyperthermic in a hot bath at 40°C. In both studies a piece-wise linear regression model was used to determine T_{es} thresholds. Esophageal temperature thresholds for ventilatory equivalents for oxygen consumption ($\dot{V}_E \cdot \dot{V}O_2^{-1}$), carbon dioxide production ($\dot{V}_E \cdot \dot{V}CO_2^{-1}$) in study 1 and for ventilation ($\dot{V}_E$) in study 2 were each compared to T_{es} thresholds for $\dot{E}_{SW}$ and CBV. The T_{es} thresholds for $\dot{V}_E \cdot \dot{V}O_2^{-1}$ and $\dot{V}_E \cdot \dot{V}CO_2^{-1}$ (Study 1) and for $\dot{V}_E$ (Study 2) were significantly higher ($p < 0.05$) than T_{es} thresholds for $\dot{E}_{SW}$ and CBV. The results support separate mechanisms underlie the pulmonary ventilation, eccrine sweating and cutaneous blood velocity responses to hyperthermia. In conclusion, these studies: 1) confirm an existence of core temperature thresholds for ventilation during passive and active body warming, 2) demonstrate core temperature thresholds for ventilation were affected by exercise and were at significantly higher core temperatures than those for $\dot{E}_{SW}$ and CBV, and, 3) support the mechanisms of control for $\dot{E}_{SW}$ and CBV are different from those for hyperthermic-induced hyperventilation.

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List of Abbreviations

AU	Arbitrary Units
BMI	Body Mass Index
CBV	Cutaneous Blood Velocity
C_D	Conduction
CO_2	Carbon Dioxide
C_V	Convection
E	Evaporation
E_{SW}	Eccrine Sweat
f	Frequency of Breathing
HR	Heart Rate
HR_{max}	Maximum Heart Rate (age-estimated)
LDF	Laser Doppler Flow
MR	Metabolic Rate
P_aCO_2	Arterial Partial Pressure of Carbon Dioxide
P_aO_2	Arterial Partial Pressure of Oxygen
$P_{ET}CO_2$	End-Tidal Partial Pressure of Carbon Dioxide
R	Radiation
RER	Respiratory Exchange Ratio
RQ	Respiratory Quotient
S	Rate of Heat Storage
SD	Standard Deviation
SE	Standard Error
T_a	Ambient Temperature (°C)
T_c	Core Temperature (°C)
T_{es}	Esophageal Temperature (°C)
T_{fs}	Forehead Skin Temperature (°C)
T_{re}	Rectal Temperature (°C)

T_{sk}	Skin Temperature (°C)
$\dot{V}CO_2$	Volume of Carbon Dioxide ($l \cdot min^{-1}$)
$\dot{V}_E$	Ventilation ($l \cdot min^{-1}$)
$\dot{V}_E \cdot \dot{V}CO_2^{-1}$	Ventilatory Equivalent for Carbon Dioxide
$\dot{V}_E \cdot \dot{V}O_2^{-1}$	Ventilatory Equivalent for Oxygen
$\dot{V}O_2$	Volume of Oxygen Consumption ($l \cdot min^{-1}$)
$\dot{V}O_{2max}$	Maximum Volume of Oxygen ($l \cdot min^{-1}$)
V_T	Tidal Volume (l)
W	Work Rate (W)

List of Definitions

Conduction, thermal– Is the heat transfer by conduction down a thermal gradient between two parallel surfaces in a medium when a unit temperature difference is maintained between them. Within an organism, or between an organism and its external environment the rate of heat transfer during a steady state when a temperature difference of 1°C is maintained across a layer of tissue, expressed either per unit area ($W \cdot m^{-2} \cdot °C^{1}$) or in absolute terms ($W \cdot °C^{-1}$). Also heat is transferred from one mass to another mass to another through direct molecular contact (3).

Control – Refers to the action of a system on responses that oppose perturbations. For example body temperature is regulated through the control of heat loss and heat gain (1).

Convection, forced – Movement of a fluid medium along pressure gradients induced by forces such as wind, fans pumps; it is relevant in thermal physiology as a rate of heat and water vapor transfer (3).

Convective Heat Transfer - Is the heat transfer in a moving gas or fluid (i.e. by convection) between different parts of the organism, or between the organism and its external environment; it may develop and be amplified by thermal gradients (see Forced Convection). It is usually expressed in terms of unit area of the total body surface area ($W \cdot m^{-2}$). The quantity (C) in the heat balance equation in which (-C) = heat gain and (+C) = heat loss.

Core Temperature (T_C) – Ideally the mean temperature of the thermal core. In practice it is represented by a specific core temperature. This can be the rectal, sublingual, esophageal, or tympanic temperatures. Note brain temperatures are core temperatures that may vary relative to core temperatures outside the brain during due to selective brain cooling, as is evident in a number of species. Modified from (3).

Eccrine Sweating – A response of the eccrine sweat glands to a thermal stimulus ($mg \bullet m^{-2} \bullet min^{-1}$) (3).

Evaporative Heat Loss – Is evaporative heat transfer from the body to the ambient air (i.e. loss of heat energy) by evaporation of water from the skin and the surfaces of the respiratory tract. Usually expressed in terms of heat flow (W) or ($W \bullet m^{-2}$) (3). Note, in humans evaporative heat loss has passive (e.g. water vapourizing from the respiratory tract that is insensible) and active thermoregulatory components (e.g. thermal sweating).

Frequency of Breathing (f) – The number of breathes per minute, at rest this value is approximately 12-15 per minute (3).

Hyperpnea – See Thermal hyperpnea.

Hyperthermia - The condition of a temperature regulator when the core temperature is above its set-range specified for the normal active state of the species (3). More specifically, increase of core temperature by 1°C above resting normothermic levels.

Insensible Heat Loss – Is a form of evaporative heat energy transfer that is passive such as that due to water vaporizing from the respiratory tract. It is the sum of the water lost by diffusion through the skin and water lost in breathing and excludes any water excreted (e.g. sweat, urine or feces). This form of evaporative heat loss is usually expressed in terms of energy per unit time per unit area of total body surface (3). The term evaporative heat loss is a synonym and is the preferred term.

Maximum Oxygen Consumption (O_2 max) – The maximum rate at which the organism can take up oxygen. This measure require high motivation by the participant. Expressed conventionally in $l \cdot min^{-1}$ but it is often expressed in $ml \cdot kg^{-2} \cdot min^{-1}$ (3).

Null Zone or Thermoeffector Threshold Zone (Interthreshold zone) – The temperature range between which two threshold body temperatures, for activation of any thermoeffector responses particularly of metabolic heat production (H) and evaporative heat loss when no thermal load is present. This special steady-state may be called a set-point. The null zone or thermoeffector threshold zone should be distinguished from thermoneutral zone.

Panting, thermal – Increased respiratory evaporative heat loss due to increased respiratory minute volume. It can occur in animals with an open or closed mouth. Used as a mechanism to regulate body temperature when it rises. In animals capable of thermal panting the phase of thermal hyperpnea with its slower, deeper breathing is also referred

to as second phase panting, since it is usually preceded by a first phase panting (i.e. rapid, shallow breathing with an elevated function residual capacity) (3).

Radiance, thermal – radiance of energy due to a thermal radiation [$W \cdot sr^{-1} \cdot m^{-1}$] (3).

Respiratory Quotient – The ratio between the rates of CO_2 released (CO_2) and oxygen consumed (O_2). This is a theoretical measure of activity at the tissue level (4).

Regulation – is the maintaining constant of a variable in the *milieu interieur*. The main property of a regulated system is that the deviation of the regulated variable triggers a correcting response that opposes the deviation (1).

Respiratory Exchange Ratio – The ratio between the rates of CO_2 produced (CO_2) and oxygen consumed (O_2) for non-metabolic changes (but not solely restricted to these changes) in the Respiratory Quotient. This is measured at the level of the lungs (5).

Sensible Heat Loss – Heat loss, dry or sensible. The sum of rates of heat flow or flux from radiation, convection and conduction from a body in the environment (3).

Set Point, temperature - The set-point is the value of a regulated variable which a healthy organism tends to stabilize by the processes of regulation (3). i.e. Point of core temperature about which it is regulated (2).

Skin Temperature – The sum of the products of the area of each regional surface element and its mean temperature divided by the total body (surface) area. Mean cutaneous temperature can be used as a physical variable in the calculation of heat balance or of heat content of the body. Mean skin temperature is not necessarily a good estimate of the integrated input of the cutaneous thermoreceptors, because different surface regions may differ in their importance as thermosensor sites (3).

Temperature Regulation – The maintenance of the temperature or temperatures of a body within a restricted range under conditions involving variable internal and/or external heat loads. Biologically it is the existence of some degree of body temperature regulation by autonomic or behavioral means (3).

Thermal Hyperpnea – An increase in tidal volume associated with an increase in alveolar ventilation occurring during severe heat stress which has caused a large rise in core temperature. In animals capable of thermal panting the phase of thermal hyperpnea with its slower, deeper breathing is also named second phase panting, since it is usually preceded by a phase of typical first phase panting (rapid, shallow breathing). (Greek: hyper-above, over; pnoia-breath) (3). See *Panting* above.

Thermoneutral Zone – The range of ambient temperature at which temperature regulation is achieved only by control of sensible heat loss, i.e. without changes in metabolic heat production or evaporation heat loss (3). This zone is different when insulation, posture or basal metabolic rate are varied.

Thermoreceptor – A thermosensitive neural tissue for which both its afferent function and its response characteristics are electrophysiologically identified. Also thermosensor or temperature receptor. Thermoreceptors have been unequivocally identified, so far, only in the skin & mucous surfaces as cold receptors, warm receptors and infrared receptors (3).

Thermoeffector Threshold Temperature – Describes the level of a specific body temperature (e.g. core temperature) the transgression of which in one direction either upward or downward will activate a certain thermoeffector. In other words, the temperature in which a response starts to increase (e.g. eccrine sweating and cutaneous blood flow). As a rule the threshold core temperature determined for a given effector will be a function of skin temperature and vice versa: similar interdependencies exist with and among the threshold temperatures determined for specified thermosensor regions in the body core (e.g. hypothalamus, spinal cord) (3).

Tidal Volume – The amount of air that is inspired or expired in a breath, it can reach ~50% of an individual's vital capacity, at rest this value is approximately 0.5 l(4).

Ventilation – Is the process of oxygen and carbon dioxide exchange through the common medium of inert gas, i.e. nitrogen (4). Ventilation is a rate expressed in volume of gas per unit time.

Work, positive – The rate of work done by an organism on an external force. The quantity (+ W) in the body heat balance equation (3).

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Chapter 1 Thesis Overview

1.1 Overview of Thesis

During exercise- or passively-induced hyperthermia it appears body core temperature is one afferent input for pulmonary ventilation. The mechanisms underlying this response remain to be resolved and the focus of this thesis was to establish whether thermoregulatory heat loss responses have similar or different mechanisms of control from those for body temperature induced increases in ventilation. This was assessed by comparing T_c thresholds for eccrine sweating and cutaneous blood velocity to T_c thresholds for ventilation. As well, the pattern of ventilation and end-tidal gases during passive hyperthermia were examined to further explore the nature of the ventilation response to body warming.

In Chapter 2 a review of the literature is given where it was established that core temperature thresholds for eccrine sweating, cutaneous vasodilatation and ventilation have each been demonstrated for humans. An exhaustive literature review did not uncover comparisons of these thresholds during either passive or active body warming. Although the mechanisms for control of eccrine sweating and cutaneous vasodilatation during hyperthermia are partially or completely resolved, few studies examined temperature induced increases in ventilation in humans. A substantial body of research examined panting mammals for core temperature thresholds for ventilation that are typically at about 38 to 39°C. These thresholds are substantially higher than those reported for thresholds for eccrine sweating and cutaneous vasodilatation; these 2

responses can be induced by changes in skin temperature alone or by a small increase in core temperature. If such if a vestigial panting response remains in humans, it was reasoned it should follow a similar mechanism. As such, following a summary of the literature review and the thesis rationale, it is hypothesized at the conclusion of Chapter 2 that core temperature thresholds for ventilation in humans would be initiated at higher core temperatures than those for eccrine sweating and cutaneous vasodilatation.

Chapter 3 reports the investigation of seven college aged males during actively- or exercise-induced hyperthermia where there was a comparison of the core temperature thresholds for ventilation, eccrine sweating, and cutaneous vasodilatation. Chapter 4 reports the second investigation which was conducted using the same participants but with hyperthermia induced in a 40°C-bath. The core temperature thresholds for ventilation, eccrine sweating, and cutaneous blood velocity were also compared in this second study and ,in addition, the pattern of ventilation and end-tidal gases were examined to further explore the nature of this hyperthermia-induced hyperventilation.

In Chapter 5 the responses to the research hypothesis and testable questions to both studies were answered. In addition, a brief comparison and integration is made for the results from the two studies together with a discussion of the limitations of the methods employed in these studies.

Chapters 2, 3, 4 and 5 in the thesis each has its own unique list of references and in Chapter 6 an alphabetical list of all references in the thesis is given.

1.2 Co-authorship Statement

Design and Identification of the Research Proposal:

The design and identification of my two-part research proposal was a collaborative effort between Dr. Matthew White and myself. Between September 2001 and April 2002, Dr. White and myself discussed ideas of possible areas of examination for my research proposal.

Practical Aspects of the Research:

The set-up of the equipment and fine-tuning of the protocol for the first study of my research project was a collaborative effort between Amanda Hall, Lise Petrie, and myself, with consultation by Dr. White. For the first part of my research the data collection was completed by Amanda Hall and myself. The set-up of the protocol for the second study of my research project was completed by Dr. White and by myself. Dr. White provided the necessary input and hands on technical assistance during the data collection. Both experiments were conducted in Dr. White' s Environment and Exercise Physiology Laboratory using his laboratory equipment.

Data Analysis:

The data analysis for the first study of my thesis was a collaborative effort between Amanda Hall, Dr. White and myself. The data analysis for the second study was completed by Dr. White and myself.

Manuscript Preparation:

For the two studies in my thesis, I prepared first drafts of both manuscripts and I also prepared the first draft of the review of literature. Dr. White provided the necessary feedback and corrections, as they were needed for all sections of my thesis writing.

Chapter 2 Literature Review

2.1 Overview of this Literature Review

This literature review is divided into five sections. In *Section 2.1*, the outline of the chapter is given. Next, *Section 2.2* reviews principal mechanisms of human body temperature regulation. This is followed by *Section 2.3* where the review of human thermoregulation is extended to responses during exercise and heat stress. In *Section 2.4*, the review shifts to a focus of how pulmonary ventilation is controlled in humans at rest and during exercise. This section includes the current state of knowledge on pulmonary ventilation and thermoregulatory responses during exercise and hyperthermia. *Section 2.5* provides a review on how panting is controlled in non-human mammals. The literature review concludes with the *2.6 Literature Review Summary and Thesis Rationale*, *2.7 Research Hypotheses* and *2.8 Testable Questions* addressed in the two studies in this thesis.

2.2 Human Body Temperature Regulation

Humans are constantly challenged with maintaining their core temperature. When the environment is cooler than the body, heat production is increased to maintain a stable core temperature needed for cellular metabolism (65). Conversely, when outside temperature is higher than the neutral ambient temperature, the body reacts to maintain homeostasis by dissipating heat through thermoregulatory responses of eccrine sweating and elevated cutaneous blood flow or vasodilatation. Human pulmonary ventilation is known to increase in a warm environment and may represent a vestigial or second phase panting response (22, 30, 42, 98).

Cellular function is extremely sensitive to fluctuations in core temperature and even moderate elevations of body temperature begin to cause nerve malfunction and metabolic malfunction. Normal human body temperature at rest is about 37 ± 1°C (21). Rises in core temperature of more than 3.0°C can be accompanied by central nervous system dysfunction, circulatory failure, and eventually irreversible tissue damage and death (32). That said, ultra-marathon runners have survived core temperatures as high as 42.0°C (19, 41). A core temperature of ~ 43.3°C is normally considered the upper limit compatible with life, although humans have survived core temperatures as high as 46°C (32). On the other hand, most of the body's tissues can withstand considerable cooling and cooled tissues need less nourishment than they do at normal body temperature because of their reduction in metabolic activity (67).

From a thermoregulatory viewpoint the body consists of a central core and surrounded by an outer shell (35). The temperature within the inner core (central nervous system, abdominal and thoracic organs, and skeletal muscles) generally remains fairly constant unless it is subjected to thermal loads such as exercise and environmental heat. It is this central core that is defined as the body core temperature and is subject to precise regulation to maintain a homeostatic environment (35). The core temperature is maintained within a narrow range; thus, the thermoregulatory system needs continuous information about core temperature (33). It is of note that there are no distinct anatomical boundaries between the core and the skin since the size of these compartments change as

a function of the degree of vasoconstriction in the peripheral tissues including the skin (65).

Core temperature may vary considerably from one site of measurement to another and depends on factors such as metabolic rate, blood supply, and the temperature of neighboring tissues (35). The tympanic temperature has been shown to be a good index of cranial temperature (59, 60), while the central blood temperature is well represented by esophageal temperature (36). The skin and subcutaneous fat constitute the outer shell of the human body and their temperature is represented by the mean surface skin temperature (18). In contrast to the high temperature of the core, the temperature of the outer shell is generally cooler and may vary substantially (35). It has been established that there are specialized nervous tissues which are responsive to temperature and/or temperature change (38, 39). Temperature sensitive free nerve endings have been found in abundance near the skin surface (40) and in the preoptic area at the hypothalamus (71). The role of these neurons is to detect the extent of the changes in the skin and hypothalamic temperature, to send this information to control centers in the CNS (mainly in the hypothalamus (18, 33)) that in turn integrate this information and subsequently elicit thermoregulatory effector responses.

To maintain a constant stable core temperature in the body there must be a balance between heat production and heat loss. This heat balance can be disturbed by exercise, which markedly increases heat production and by changes in the external

environment conditions that influences the degree of heat gain or heat loss that occurs between the body and it's surrounding. To maintain body temperature, compensatory adjustments must take place in heat loss and heat gain responses, for example, if the core temperature starts to fall, heat production is increased and heat loss is minimized so that normal temperature can be restored (21). Conversely, if the temperature starts to rise above a resting level of ~ 37°C, it can be corrected by increasing heat loss while simultaneously reducing heat production (21). The law of conservation of energy describes the avenues of heat exchange that are involved in thermoregulation. In a steady state, the rate of heat generated in the body is balanced by rate of heat loss to the environment such that rate of storage is zero (44). This relationship can be expressed and is summed up by the heat balance equation (17):

$$\dot{M} \pm \dot{W} = -\dot{E} \pm \dot{R} \pm \dot{C}_D \pm \dot{C}_V \pm \dot{S} \quad \text{.....Equation 2.1}$$

where,

$\dot{M}$ = the rate at which thermal energy is produced through *metabolic* processes

$\dot{W}$ = power or the rate at which *work* is produced by or in the body

$\dot{R}$ = the rate of heat exchange with the environment via *radiation*

$\dot{C}_D$ = the rate of heat exchange with the environment via *conduction*

$\dot{C}_V$ = the rate of heat exchange with the environment via *convection*

$\dot{E}$ = the rate of heat loss with the environment via *evaporation*

$\dot{S}$ = the rate of heat storage in the body.

2.2.1 Set-Point Model of Human Temperature Regulation

To explain the balance of heat loss and gain to human temperature regulation a set-point model has been developed (33). Satinoff (81) explained that a homeostatic regulation implies a regulated level of some variable that is sensed by the central nervous system. In control system terminology, that regulated level is called a set-point as described in thermoregulation, that implies a set, or reference, or optimal body core temperature against which actual body temperature is compared (81). If there is a discrepancy between the two, an error signal is generated which activates heat loss or heat production mechanisms to help return actual body temperature closer to the set-point temperature. The comparator, or signal mixer that compares the two, in other words, the thermostat, has been localized in the hypothalamus, specifically, in the preoptic/anterior and posterior hypothalamic area (81). The hypothalamus serves as the body's thermostat like your home thermostat, the hypothalamus has a set-point temperature that it tries to maintain (33, 81). This is the normal or thermoneutral body core temperature that is defended.

The American neurophysiologist, Stephen Ranson in 1940 (77), was one of the first to apply the technique of stereotactically placed electrolytic lesions to the study of homeostatic mechanisms. Ranson localized the "heat-loss center" to the preoptic/anterior hypothalamic area and the "heat production center" to the posterior hypothalamus. He showed cats and monkeys with preoptic lesions were unable to keep their body

temperature from rising in the heat but they could maintain near normal body temperature in the cold.

Hammel (33) examined the role of the hypothalamic and skin temperatures in controlling the thermal responses in resting mammals. The results indicated the hypothalamus is strongly responsive to rise or drop of 1°C (33) and that the set-point for temperature regulation changed by several inputs. That is, it is lowered by rising or elevated skin and extrahypothalamic core temperature (33) or exercise (45), it is raised by a falling or lowering skin and extrahypothalamic core temperature, and it is lowered upon entering and during sleep. Finally it is also raised upon awakening (33).

Central receptors in the hypothalamus are sensitive to blood temperature changes as small as 0.01°C (38). Peripheral thermosensitive neurons, located in the skin, detect changes in body skin or surface temperature and relay this information, an afferent signal, to the central thermosensitive neurons. The controller or comparator in the hypothalamus then generates an effector signal that is proportional to the difference between the hypothetical reference signal of ~ 37 °C (33) and the temperature of the hypothalamus or the blood perfusing the hypothalamus. The thermoregulatory effector responses are subsequently initiated and these include shivering and vasoconstriction that act to generate or conserve heat, whereas eccrine sweating, vasodilatation, and pulmonary ventilation act to dissipate heat (11, 49, 100).

This classical view of thermoregulation was modified by Satinoff (81) to indicate that thermoregulation is composed of a series of controllers arranged in a hierarchy along the neural axis. Examples cited by Satinoff (81) amongst others, give evidence of this hierarchy or thermoregulation in cats and dogs which were shown to retain their ability to pant after body warming with spinal cord transection rostral to the midbrain (53). Also, rabbits were able to maintain their body temperature by shivering despite a cervical section of their spinal cord (89). The hierarchy described in her model of temperature regulation suggests that the hypothalamus, the midbrain, the medulla, and the spinal cord give a collective integration of afferent signal from body temperature sensitive tissues.

Cabanac (21) examined thermoregulatory responses as a function of core temperature in humans. When six men were immersed sequentially in baths maintained at a steady temperature of either 28 $\pm$ 1°C or 38.1 $\pm$ 1°C it was evident their heat production by shivering, and heat loss by both eccrine sweating and vasomotor responses increased proportionately to core temperature starting a resting level of ~ 37.3°C (21). During cooling vasoconstriction was complete before the onset of shivering, thus thresholds for heat loss and heat gain were superimposed at a esophageal temperature (T_{es}) of approximately 37.3°C (21). This indicated a set-point, about 37.3°C for humans (21).

2.2.2 Null Zone-Model of Human Temperature Regulation

As mentioned above, various thermoregulatory responses in humans that act as effectors are controlled by the integration of afferent signals from the core and peripheral

sensors. These responses help to keep the core temperature stable within fairly narrow limits. The set-point model of temperature regulation (21, 33) was challenged by Bligh (12), who indicated in several animals a range of core temperatures is evident when no thermoregulatory responses are evident other than vasomotion. Subsequently, in humans a null-zone model was demonstrated that lent further support to Bligh's model of mammalian thermoregulation (57, 64, 66).

Initially, the null-zone was referred to the thermoneutral zone; it was defined as the range of ambient temperature (T_a) within which metabolic rate is at a minimum and where temperature regulation is achieved by non-evaporative physical processes alone (44). Mekjavic et al (66) investigated whether human T_c is regulated at a set point or whether there was a thermoneutral zone between the T_c for onsets of shivering and eccrine sweating. Their study showed the existence of a thermoneutral 'null zone' between the core temperature thresholds for shivering thermogenesis and sweating in man. Its magnitude was determined to be 0.69 + 0.23°C and 0.57 + 0.20°C for T_{es} and rectal temperature (T_{re}) (66). It was reported that the T_c threshold for eccrine sweating in men was 37.40°C and the shivering threshold was 36.80°C. This gave an eccrine sweating to shivering core temperature null zone of 0.6 ± 0.2°C (66).

The null-zone was also demonstrated by Anderson (2) with no significant differences across gender for the eccrine sweating and shivering thresholds. It was concluded that except for the quantitative differences in the eccrine response, men and

women respond to deviations in T_{es} in a similar manner (2). In addition, in the elderly of about 74 years of age, Anderson et al. (1) showed the range of or the null-zone was ~ 1.12°C for T_{es} and this was significantly greater than the null zone of 0.43°C in young adults. The null-zone or 'interthreshold range' was also confirmed to exist across gender with the sweating - to - shivering range reported to be of a 0.2 to 0.3 °C magnitude (58). In passive whole body warming and cooling the null-zone was also evident in volunteers of varied body compositions (99).

The null-zone model also appears in animals, such as the camel, which has a fairly wide range of T_{re} of approximately 4°C within which no thermoregulatory function other than alternation of skin blood flow is operating (82). Bligh has described several other mammals that demonstrate a null-zone of core temperatures (12).

2.3 Human Body Temperature Regulation with Elevated Core Temperature

The stressors of physical exertion are often complicated by environmental thermal conditions. There has been numerous studies attempting to understand the body's thermoregulatory system during exercise and/or heat stress (3-5, 13, 23, 48, 49, 54, 68, 70, 100). The two main thermolytic responses in these conditions include eccrine sweating and cutaneous vasodilatation. In order to examine the mechanism of sweating, peripheral influences upon the central drive for sweating were examined during sub-maximal exercise (70). Nadel and colleagues (70) studied differences in local sweating rates as well as sweating modifications in the same area due to local temperature

differences. It was confirmed that both local and total sweating are functions of core temperatures at a fixed constant mean skin temperature (70). In most cases, an area which initiated sweating at a lower level of T_{es} also had a higher proportional control constant (70). The sweating response appears to be modified at the periphery according to the area-specific characteristics and/or by local temperature (69).

The control of sweating in humans has been described quantitatively in terms of skin and core temperature (5, 14, 64). Mekjavic et al. (64) examined the control of sweating with body warming by immersion in water at 40°C and subsequent body cooling in water at 28°C. In addition, in a second session they raised T_{es} by cycling exercise in T_a at 20°C and then lowered T_{es} by immersion in water at 28°C. Both methods were employed to determine the core temperature thresholds for eccrine sweating. The onset of eccrine sweating at a lower T_{es} during immersion (36.9 ± 0.1°C) than during exercise (37.4 ± 0.3°C) was attributed to the high skin temperature since T_{es} was then unchanged (64). Attia et al. (5) noted that during environmental heat stress the eccrine sweat threshold in man corresponds to a T_{es} of 36.75°C. However, the T_{es} threshold for eccrine sweating was not reproducible in humans when holding the skin temperature at 38°C (14). This was explained by the rate of rise in T_{es} that was invariably higher (mean 148 %) during the second period of more rapid heating (14).

In a hot environment at rest, thermal control of sweat rate and skin/cutaneous blood flow was suggested either to have a causal link or a lack of causal association

(100). It was noted that if the cutaneous vasodilatation mechanism is secondary to sweat gland activity then the link between sweat rate and the release at a vasodilatation substance is much looser than either the proponents or opponents of this theory have assumed (100). Core temperature was the dominant factor in the control of skin blood flow, heart rate, and sweat rate during heat exposure at rest (100).

Skin blood flow in humans can increase substantially in response to thermal stress (i.e. whole body heat stress) and thermoregulatory vasodilatation can increase skin blood flow to 6 to 8 l • min^{-1} during hyperthermia (23, 51). Considering that a typical individual has only 2 to 3 kg of skin this indicates that skin blood flow can exceed 250 ml • 100 g $tissue^{-1}$ • min^{-1} (51). With whole body exercise it was estimated that skeletal muscle blood flow can exceed 100 ml • 100 g $tissue^{-1}$ • min^{-1} and blood flow values up to 300 ml • 100 g $tissue^{-1}$ • min^{-1} have been reported during exercise that employed only small muscle masses (51). A number of reflex drives are important in the regulation of cutaneous blood flow such as skin and core temperature. It has been shown that skin blood flow elevation per °C rise in skin temperature during sub-maximal exercise averaged 0.20, 1.23 and 1.75 ml • 100 g $tissue^{-1}$ • min^{-1} (49). Non-thermal reflex drives of blood pressure and exercise also influence cutaneous blood flow (49). During sub-maximal exercise (49) the data strongly suggest that the reflex response of skin blood flow to rising skin temperature is dependent on the level of core temperature.

Forearm blood flow measurement has been employed as an index of skin blood flow in the assessment of thermoregulatory effector function (50, 55). As core temperature rises during exercise or heat stress, blood flow to cutaneous vasculature increases proportionately. This has been shown when males exercise on a stationary bike at 35, 50, and 65% of their VO_2 max for 30 min at a 28.3 ± 0.2°C T_a and 42 ± 2.4% Relative Humidity (RH) (56). The threshold for cutaneous vasodilatation tended to rise with exercise intensity, although the exercise intensity did not affect the sensitivity (the slope in the relationship T_{es} vs. percentage of maximum skin blood flow) of the forearm, forehead, and chest (56).

Although it appears that exercise does limit cutaneous vasculature dilation, skin blood flow levels off even as T_{es} continues to rise (13, 54). Brengelmann et al. (13) noted that the forearm blood flow response appeared to saturate at a plateau despite a steady rate of increase in T_{es} with time. Mechanisms accounting for this response have been a limitation of active vasodilator activity and not an increase in vasoconstrictor tone (54).

Boundaries of the eccrine sweating and cutaneous blood flow responses during heat stress are dependent on/or operate as a function of T_{es}. The magnitude of the response is also dependent on the severity of the exogenous (passive) and endogenous (exercise) heat stress.

Circadian Variation and Thermolytic Responses

During passive heat stress, cutaneous vasodilatation and vasoconstrictor systems are impacted by diurnal changes in the control of skin blood flow. With changing core and skin temperatures, cutaneous vasodilatation control is subjected during heat stress (passive heat or dynamic exercise) to a core temperature threshold which shows a circadian variation (3, 4, 20). Aoki noted during exercise these thresholds were shown to be shifted to higher internal temperatures in the evening compared to early morning (4). The variation in T_{es} thresholds for cutaneous vasodilatation to heat stress, of a local area as the leg below the knee, is similar to the circadian rhythm in resting T_{es}. The T_{es} at rest was significantly higher in evening than in morning and hence a higher T_{es} threshold was reported in the evening (3). The study by Aoki et al. (4) suggested the diurnal change in the sensitivity of cutaneous vasodilatation depend on vasoconstrictor system function. But overall, the diurnal variation in the reflex control of skin blood flow during heat stress involves both vasoconstrictor and active vasodilator systems. Stephenson and colleagues (84) saw the thresholds for sweating and forearm vasodilatation were significantly higher at 16h00 and 20h00 than at 24h00 and 04h00, averaging 0.57 and 0.65°C higher at 16h00 than at 04h00. Resting T_{es} and the T_{es} thresholds for cutaneous vasodilatation and sweating during exercise all showed a similar circadian rhythm. To account for these results on circadian variation (3, 4, 84), it is important to standardize the time of the day when investigations of these human thermolytic responses are investigated.

2.4 Control of Human Pulmonary Ventilation

The control of human ventilation has been of interest when attempting to understand human thermoregulatory response to heat stress. It appears different mechanisms are responsible for this control of ventilation at rest, during exercise and during passively induced hyperthermia (63, 72, 74, 75, 83, 92, 95).

2.4.1 Control Resting Human Pulmonary Ventilation

The model describing control of resting pulmonary ventilation includes three main elements (95). These three elements work together in a closed loop negative feedback control of the inspiratory activity in humans. The afferent arm of the reflexes that influence ventilation begins with peripheral chemoreceptors in the aortic and carotid bodies and central chemosensitive areas in the medulla oblongata. In addition, lung stretch receptors and other receptors provide input to the central respiratory centers in the midbrain (95). Collectively, after the integration of this afferent information, the respiratory regulation centers in the medulla oblongata provides the necessary output to the effectors, the respiratory musculature (95).

The most important factor in the control of ventilation during rest are the partial pressure of carbon dioxide (P_aCO_2) and pH in the arterial blood accompanied with low partial pressure of oxygen in the arterial blood (P_aO_2). Each of these three variables act to stimulate pulmonary ventilation (72, 95). Nielson and Smith (72) analyzed the effect of CO_2 on the pulmonary ventilation at various degrees of acute hypoxia. These results

showed that in acute hypoxia a P_aO_2 of less than ~ 60 mm Hg with small elevations in P_aCO_2 increased pulmonary ventilation and this contributed to the maintenance of ventilation (72). In addition, ventilation is maintained by the hypoxic stimulus through its action on the carotid and sino aortic chemoreceptors alone (72).

2.4.2 Control of Human Exercise Ventilation

During exercise there is an increased metabolic demand by active tissues including skeletal muscle. The body's response is to increase pulmonary ventilation so that it can match and meet this metabolic demand. Despite much work in this area, the mechanism(s) that control this increase in pulmonary ventilation remains uncertain.

It is known that between the onset of sub-maximal exercise and approximately two minutes into an exercise bout, the minute ventilation has a triphasic response (25). Phase I is characterized by an instantaneous increase in ventilation that is maintained for approximately 10 to 20 s (25). Phase II shows a slower rise in ventilation after the initial increase to a steady state that is normally completed within two to three minutes of exercise. This phase may be due to increasing rates of O_2 and CO_2 flow in the alveoli (93). Phase III is a steady state ventilation and is maintained for the duration of moderate steady state exercise (25).

If the intensity of exercise incrementally increases to a maximal level, additional changes are evident in the pattern of ventilation. The positive, linear proportional

relationship between ventilation and workload or $\dot{V}O_2$ that is evident in phase III is no longer maintained. As the exercise intensity is progressively increased to a maximum level, where there are two distinct thresholds in the relationship between ventilation and oxygen consumption (92). This rise in ventilation is disproportional to the increase in metabolic demand and is termed exercise hyperpnea (98). The two breakpoints in the pattern of ventilation are termed ventilatory threshold I (VT_1) and ventilatory threshold II (VT_2). The level of exertion where these thresholds have been shown to occur are at approximately 50 to 75% of maximum workload for VT_1 and at approximately 85 to 95% of maximum workload for VT_2 (92).

The mechanisms underlying these observed disproportionate increases in minute ventilation and metabolic rate during exercise remain unclear. Ventilatory threshold I is thought to reflect the change from aerobic and anaerobic metabolism and thereby was termed the anaerobic threshold (63, 83). The mechanism(s) accounting for ventilatory threshold II is/are also unresolved although is/are thought to be of neural origin(s) (63). Several hypotheses have been presented to explain the changes in ventilation at the levels of exercise intensity that correspond to VT_1 and VT_2. These are given below.

Blood Lactate and Exercise Ventilation

Some have suggested that VT_1 and the onset of blood lactate accumulation coincide (90). However, in patients with a phosphorylase deficiency a normal hyperventilation is evident during exercise, despite no fall in pH_a (29). This

hyperventilation is also evidenced with muscle glycogen depletion studies that demonstrated a dissociation during exercise between the ventilatory break-away and decreases in blood pH (37). Due to the unresolved nature of what stimulates and triggers the rise in ventilation or blood lactate, and thereby the shift from aerobic to anaerobic metabolism, the lactate hypothesis remains controversial. The "lactate shuttle" hypothesis (15) holds that lactate plays a key role in the distribution of carbohydrate potential energy that occurs among various tissue and cellular compartments and its role is not associated with an increase in ventilation. Studies on resting and exercising humans indicate that most lactate (75 to 80%) is disposed of through oxidation.

Tissue ECF and Exercise Ventilation

Among theses hypotheses on the control of exercise ventilation (27, 74, 75) one supports that hyperventilation associated with high intense exercise is due to acidosis in the extra-cellular fluid (ECF) surrounding the muscle (74). The pH of the ECF is thought to stimulate group IV afferent nerve fibers which, in turn, increase ventilation (27). As such increasing concentrations hydrogen (H^+) ions (27) are thought to contribute to the exercise ventilation response.

There is evidence that skeletal muscle can sense the status of the peripheral vascular network through group III and IV muscle afferent fibers (34, 52). It is proposed that this sensing mechanism in respiratory control anticipates the chemical changes that occur in arterial blood during increase metabolic load and attempts are made to minimize

these chemical changes by adjusting the level of ventilation to the level of muscle perfusion (34, 52).

Oelberg et al (74) examined whether skeletal muscle H^+ ion mediates ventilatory drive in humans during exercise. They showed ventilation and H^+ in ECF, increased proportionately (74). Wasserman et al.'s (93) study noted a decrease in ventilation despite an accumulation of metabolites of H^+ and K^+ ions around group IV afferent during a chemically induced increase in cardiac output. Therefore, it appears, something other than ECF acidity plays a key role in the control of ventilation during exercise.

Potassium and Exercise Ventilation

An additional hypothesis attempted to explain control of ventilation and suggested that increased arterial potassium accounts for exercise hyperpnea. In anaesthetized cats an increase in arterial plasma K^+ was correlated to an increase in ventilation (16). With an intravenous KCl infusion of 0.1 mmol • kg^{-1} • min^{-1} this repeatedly raised arterial K^+ and this was accompanied with an increase in carotid body chemoreceptor discharge. Paterson et al. (75) investigated the relationship between arterial plasma potassium ($[K^+]$arterial) and ventilation in man during sub-maximal and maximal exercise. It was shown that $[K^+]$arterial was elevated by a modest level of exercise and that this might be sufficient to stimulate chemoreceptors that contribute to the control of breathing in exercise (75).

Overall findings indicate that the stimulation of the peripheral chemoreceptors by potassium likely has a minor role in the control of ventilation during exercise (62). Nevertheless, it is possible that increases in $[K^+]$arterial during exercise increase the sensitivity of the peripheral chemoreceptors to other respiratory stimuli such as oscillations in the PCO_2 values or increases in the arterial $[H^+]$ (62).

CO_2 flow and Exercise Ventilation

It has been also suggested that increased CO_2 flow to the lungs is the sole ventilatory stimulus during exercise (93) and this acts and to maintain the arterial isocapnia that is evident during mild to moderate exercise (93). This view was strengthened with studies that showed that elevation or lowering in cardiac output modified CO_2 flow across the lungs and subsequently this gave proportional changes in ventilation (93, 94). Also an extracorporeal gas exchanger was used to raise venous carbon dioxide in dogs, when cardiac output and P_aCO_2 were at resting values (94), and this increased ventilation. These studies (26, 93) supported the hypothesis that the CO_2 flow across the lungs controls the ventilation response during exercise.

Despite these views, the CO_2 flow hypothesis appears to fall short for a number of reasons. First there is no evidence identifying the location and mechanism of these CO_2 "sensors" thought to exist in the pulmonary circulation as sensors in CO_2 flow across the lungs. Also both venous CO_2 loading protocols or increased CO_2 flow induced by increasing cardiac output give an elevation of P_aCO_2. Presumably the consequent

increase of arterial CO_2/H^+ explains the increases in ventilation observed after CO_2/H^+ is sensed at the peripheral chemoreceptors and/or central chemosensitive areas. Overall the results illustrate the CO_2 flow hypothesis cannot fully account for the changes in exercise ventilation.

In addition, Ward and Whipp (91) noted that increased external dead space results in an increase in ventilation during rest or moderate exercise, apparently as a consequence of the increased airway CO_2 load. However, the ability of the control mechanism of the exercise hyperpnea to regulate PCO_2 in response to progressively increased metabolic rate was not impaired by the anatomical dead space. The reasons for these response patterns remain obscure.

Norepinephrine Hypothesis

Another possible modulator of exercise ventilation is norepinephrine. An intravenous infusion of norepinephrine can increase ventilation (96) either during hypocapnia (96) or during normocapnia (10). Cunningham et al. (24) showed that norepinephrine was able to increase hypoxic sensitivity but stated with an absence of hypoxia the effect of norepinephrine would disappear. Thus, norepinephrine also cannot fully account for exercise hyperpnea in normoxic exercising subjects.

Of the hypotheses on the control of ventilation as reviewed above, there does not appear to be a single hypothesis that can fully explain changes in ventilation during

exercise. The next section discusses the possible role of body temperatures in the control of ventilation during exercise.

2.4.3 Human Exercise Ventilation and Hyperthermia

A novel hypothesis in the study of human thermoregulation in heat stress is the relationships between ventilation with its associated respiratory heat loss from the upper airways and core temperature. Resting hyperthermia in humans is often accompanied by an increase in ventilation (7, 22, 28, 30). The increased ventilation in hyperthermia might be thought of as a vestigial panting response (22, 73). During passive hyperthermia, when core body temperature thresholds for ventilation are reached, thermal hyperpnea was evident and this is seen as a thermoregulatory response that may participate in selective brain cooling (22). This suggests that a defense of brain temperature in hyperthermic humans is in part due to respiratory evaporative heat loss following increases in pulmonary ventilation. Selective brain cooling in humans is reasoned to occur when cranial temperature (tympanic) falls below core temperature (esophageal) during rises in core temperature (7).

During sub-maximal exercise, at approximately 70% of maximum work capacity, core temperature thresholds for ventilation were also evident and subsequently tympanic dropped below esophageal temperature (98). This therma hyperpnea in humans was also suggested as supportive evidence for selective brain cooling in humans (98) and the exercise-induced increase in core body temperature was suggested to be a stimulus to

ventilation during this active hyperthermia. The relationship between tidal volume and frequency of respiration with esophageal temperature during maximum exercise support that initially tidal volume increases proportionately to esophageal temperature (80). Subsequently, the frequency of respiration increases proportionately to esophageal temperature.

During incremental exercise from rest to maximal attainable work-rates, Sancheti and White et al. (80) noted esophageal temperature thresholds for ventilatory equivalents for O_2 and CO_2 are reproducible during the body warming of this progressive exercise. This further supports the important role of ventilation in cranial temperature regulation.

2.5 Panting in Mammals

In several mammals, the purpose of ventilation is two-fold. Firstly it provides oxygen and removes carbon dioxide to allow normal metabolic function at the cellular level. Secondly, some mammals have a panting pattern of breathing and this raised ventilation provides a primary avenue for heat dissipation through respiratory evaporative heat loss (31). Heat energy supplied by the body is used to change liquid water to vapor thereby cooling it, this process is referred to evaporative heat loss from the respiratory tract (31). Non-thermal panting can also occur in some mammals, as in dogs, and is usually ascribed to stress (46).

Stages of Panting

For thermal panting, Hales (31) separated the integration of thermoregulatory and respiratory requirements of the respiratory system into five stages *(i to v)*. There is an *(i) Initiation Stage of a Raised Body Shell* (skin or naso-buccal muscosa) where temperature is sensed by superficial thermoreceptors, directly by the hypothalamus (31) or by extra-hypothalamic core thermoreceptors. Next, the control of *(ii) Steady Rapid Shallow Panting* during mild heat stress, known as thermal tachypnea, begins as slightly raised core temperature acts via similar neural pathways as the first stage. During this second stage, alveolar ventilation is maintained with a minimal tidal volume and a maximal frequency of breathing. Respiratory heat loss influences the stimulation of thermoreceptors and there is both a steady state core temperature and ventilation. If heat stress becomes severe this produces *(iii) Maximal Rapid Shallow Panting* (31, 61). There are further increases in both the frequency of breathing and reductions in the tidal volume or depth of breathing. The next stage is *(iv) Slower, Deeper 'Second Phase Panting'* also know as thermal hyperpnea (61). This pattern of breathing gives a severe respiratory alkalosis as a result of significant elevations in pulmonary and alveolar ventilation and the mechanisms underlying this response are unresolved. The final stage after removal of external heat load is *(v) Reversion to a Rapid Shallow Panting* that permits a 'normal' hypocapnia depression of pulmonary ventilation, This restores PCO_2 and carotid body chemoreceptors prevents post-hyperventilation (hypocapnic) hypoxia during this recovery (31).

Mechanisms and Effects of Panting

It is known that thermal panting can induce a complex train of events that effects each of pulmonary gas exchange, blood gas transport, tissue gas exchange, cellular metabolic and acid-base balance (61). Maskrey (61) reports that it is not clear what may be happening at the tissue level during heat exposure and thermal panting. When environmental temperature rises above core body temperature, panting via evaporative cooling is the only means by which an animal can lose heat for those animals who cannot sweat. The respiratory portion of the nasal cavity is long in some panting mammals and its bony arrangement and the arrangement of blood vessels in the muscosa are well suited for a heat-exchange surface (8, 88). The nasal cavity is occupied by the turbinate bones that protrude into it from bony walls and the largest of these is the maxillary turbinate (9). The muscosa covering the surfaces of the respiratory tract of the nasal cavity, including the maxillary turbinate, contains immediately below its surfaces large numbers of arteriovenous anastomoses and large venous spaces, which are exposed to the respiratory airstream (9). Evaporation from the respiratory tract is the most direct and efficient route for the heat loss in creatures with an exterior surface insulated by fur or feathers (78).

During heat stress, there are two physical mechanisms available for increasing respiratory evaporation. Firstly, it is assumed that the expired air is virtually saturated with moisture at body temperature. The vapor pressure of the evaporative surfaces (i.e. nasal muscosa) can be further increased by allowing the body temperature to rise (78). By increasing the capacity of the air for water this can have a greater cooling effect.

Secondly, Richards (78) noted the mechanism for increasing evaporation is that of raising the total ventilation. For any given value of absolute humidity in the ambient air, heat loss by evaporation bears a linear relation to ventilation of the evaporative surfaces. It has been shown that non-panting respiratory frequencies in dogs at rest extend to 60 to 80 breaths • min^{-1} and are associated with pulmonary ventilation less than 12.5 l • min^{-1} whereas, panting rates for animals exposed to acute heat are generally considered to be greater than 120 to 140 breaths • min^{-1} and are associated with pulmonary ventilation which can exceed 30 l • min^{-1} (46).

During thermal homeostasis in mammals, there is a coordinated control of the upper respiratory evaporation and increase of blood flow to elicit heat loss (76). Blood flow to the tongue and the nasal muscosa in the dog is closely related to the body temperature and to the frequency of breathing (79). In anaesthetized dogs, whole body heating or heating of the hypothalamic thermosensitive region gives a high level of blood flow in the arteries supplying the tongue and nasal cavities (9). Baile et al. (6) showed tracheobronchial blood flow increases two to fivefold in response to hyperventilation with warm or cold dry air in anesthetized, tracheostomized dogs.

Studies of blood flow using radioactive microspheres demonstrated increased blood flow to the tongue, the nasal muscosa and the maxillary turbinate in unanesthetized dogs, sheep in heat, and in dogs during exercise (9). Ronert et al. (79) showed in the unanaesthetized dog at a T_a of 20°C and 30% RH that the mean lingual blood flow was

11 ml • min^{-1}. When T_a was elevated to 38°C, at a constant RH, panting ensued with frequency of breathing of 272 breaths • min^{-1}. In parallel fashion, lingual blood flow increased to a mean rate of 60. 4 ml • min^{-1} and to a peak rate of 74.7 ml • min^{-1} (79). This suggested that convective heat loss in the tongue contributes to evaporative heat loss mechanism in concert with panting.

In many hyperthermic mammals, including sheep, goats, cats, and dogs the brain temperature is maintained below the core temperature as measured by the temperature of carotid blood close to the heart (9, 47). This difference of temperature is especially marked while the animal is losing body heat by panting, either through exposure to a hot environment or during exercise. A mechanism that selectively cools the brain lower than the trunk temperature during hyperthermic conditions is well accepted for many animals (8). In sheep and cats exposed to heat, the temperatures of cerebral arterial blood and the brain fell below central blood temperature as deep body temperature rose and the rate of panting rose (9). The temperature difference between the central and cerebral arterial blood in panting cats and sheep range from 0.7 to 1.1°C. (9).

The stabilization of the brain temperature in the face of greater fluctuation of core temperatures is carried out by the *carotid rete*, a countercurrent exchange organ, which lies along the course of the carotid arteries in the cavernous sinus just below the base of the brain (8). Here the carotid arteries break up into small branches which are surrounded by venous blood in a pool or by a small network of veins (47). This cooled venous blood

returns from the facial skin, including the pterygoid plexus, or from the upper respiratory tract where it is cooled by the air-stream passing over the moist respiratory muscosa. The arterial blood on its way up towards the brain during hyperthermia is thus pre-cooled.

Brain cooling during thermal stress can occur in both rabbits, a panting mammal with no carotid *rete* and cats, a panting mammal with a carotid *rete* (9). In rabbits, it has been shown that panting assisted in brain cooling when exposed to a T_a of 39°C and when the hypothalamic temperature reached 39.1°C (43). Tabatabai's (86) study noted the mean panting T_{re} among conscious cats under heat stress was 38.9°C and the corresponding mean respiratory rate was 272.8 breaths • min^{-1} which suggested the initiation of a brain cooling mechanism at this level of hyperthermia. For animals with or without a carotid *rete* it appears after a similar elevation in core temperature that an increase in ventilation is evident. This suggests a carotid *rete* is not essential for SBC and that ventilation contributed to SBC in these hyperthermic animals.

During exercise conditions, it was found that after a high-speed run of 7 min, the brain temperature of an antelope was as much as 2.7°C below that of the carotid blood (9). Similarly, in two dogs running in T_a of 30°C their hypothalamic temperature was maintained about 1.3°C below carotid temperature (9). These studies support that panting with an elevated respiratory evaporative heat loss, coupled closely to high rates of blood flow in the nasal and oral cavities (79), appear to be responsible for the observation that panting mammals have the greatest degrees of brain cooling during exercise.

2.6 Literature Review Summary and Thesis Rationale

As Hales (31) and White (97) outlined, the mechanisms of thermal hyperpnea in humans or other animals are unresolved. The explanation of the physiological need for this hyperventilation remains elusive and for each of the mechanisms reviewed in this chapter, none was able to fully explain the cause of the exercise-induced hyperventilation. In this context, body temperature during hyperthermia remains as a potential cause for increases of pulmonary ventilation.

An important step in the resolution of the mechanisms of thermal hyperpnea in humans is to compare this thermal hyperpnea response in hyperthermia to other thermolytic responses. In humans, it is not established how core temperature thresholds for ventilation compare to the core temperature thresholds for eccrine sweating and for cutaneous blood flow. If these thresholds fall at similar core temperatures, this supports similar mechanism(s) of control for these three responses. On the contrary, if these thresholds for eccrine sweating and cutaneous blood flow fall at different core temperatures than those for ventilation, this supports different mechanism(s) of control for these three responses.

Panting mammals core temperature thresholds with passive heating for thermal tachypnea occur at ~ 39.0°C (33, 86). If a similar mechanism that controls ventilation in hyperthermic panting mammals is also evident in humans, then core temperature thresholds for ventilation will also be at core temperatures near ~ 39.0°C during passive

body warming. During exercise-induced body warming, if this mechanism for control of ventilation is similar in panting mammals and humans, the core temperature threshold for ventilation would be expected to drop. This was shown to occur during exercise when a lowered core temperature threshold for panting was evident in the dog (45) and in humans where lowered core temperature thresholds were evident for thermolytic responses (85, 87). Thus, if similar mechanism for the control of ventilation is evident during exercise for panting mammals and humans, the human core temperature thresholds for ventilation would be expected to drop during exercise relative to the thresholds during passive body warming.

2.7 Research Hypotheses

Core temperature thresholds for ventilation are hypothesized to exist at higher core temperatures than those thresholds for eccrine sweating and cutaneous blood velocity during either passively or actively induced hyperthermia. Exercise is hypothesized to lower the core temperature thresholds for ventilation.

2.8 Testable Questions

1. How do T_{es} thresholds for $\dot{V}_E$ compare to T_{es} thresholds for eccrine sweating and cutaneous blood velocity during actively induced hyperthermia in humans?

2. How do T_{es} thresholds for $\dot{V}_E$ compare to T_{es} thresholds for eccrine sweat and cutaneous blood velocity during passively induced hyperthermia in humans?

3. How do T_{es} thresholds for ventilation compare between active and passive heating protocols in humans?

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Chapter 3: Comparison of esophageal temperature thresholds for ventilation, eccrine sweating, and cutaneous blood velocity during exercised induced hyperthermia

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3.1 Abstract

This study examined the unresolved question of how core temperature thresholds for ventilation ($\dot{V}_E$), eccrine sweating, and cutaneous blood velocity compare during exercise-induced hyperthermia. Seven untrained males who were 26.6 ± 2.6 y of age (mean ± SE), weighed 73.2 ± 3.9 kg and were 1.76 ± 0.01 m tall were studied from rest until exhaustion during incremental exercise on an electrically braked, seated cycle ergometer. Expired carbon dioxide ($\dot{V}CO_2$), oxygen consumption ($\dot{V}O_2$) and ventilation ($\dot{V}_E$) were estimated by indirect calorimetry on a breath-by-breath basis. Surface forehead eccrine sweating ($\dot{E}_{SW}$) was assessed with resistance hygrometry and cutaneous blood velocity (CBV) with a laser Doppler velocimetry system. Ventilatory equivalents for carbon dioxide production ($\dot{V}_E \cdot \dot{V}CO_2^{-1}$) and oxygen consumption ($\dot{V}_E \cdot \dot{V}O_2^{-1}$), $\dot{E}_{SW}$, and CBV were each expressed as a function of esophageal temperature (T_{es}). Thresholds for T_{es} were evident at 37.37 ± 0.06°C for $\dot{V}_E \cdot \dot{V}O_2^{-1}$ and at 37.39 ± 0.06°C for $\dot{V}_E \cdot \dot{V}CO_2^{-1}$; these 2 values were not significantly different from each other but were significantly higher ($p<0.05$) than the mean of the T_{es} thresholds of 37.00 ± 0.11°C for $\dot{E}_{SW}$ and of 36.99 ± 0.11°C for CBV. In conclusion, during actively induced hyperthermia esophageal temperature thresholds for ventilation occur at higher temperatures than those for eccrine sweating and for cutaneous blood velocity.

3.2 Introduction

During human work or exercise the mechanism(s) of regulation of pulmonary ventilation have not been clearly identified (34, 35). Several hypotheses address this topic (9) and a novel view is that ventilation may act as a thermoregulatory response, whereby core temperature is a stimulus for ventilation during passive or active hyperthermia (6, 36). During exercise at approximately 70% of an individual's maximal work-rate (36) or during passive body warming in hyperthermia (6), core temperature thresholds for ventilation were evident. During passive warming these responses were evident despite metabolic rate remaining at or close to resting levels (6). Together the results show that an elevated core temperature is a common influence that increases ventilation. This suggests, as it is evident in most non-human mammals, that respiratory heat loss from ventilation may be important avenue in cranial thermoregulation in humans (22, 36).

In panting mammals, ventilation is a two-phase thermoregulatory response (15). At the onset of heavy exercise in dogs, a first phase of panting occurs prior to changes to core temperature and includes rapid increases in respiratory rate and reductions in tidal volume (2). This elevates respiratory evaporative heat loss that is coupled closely to high rates of blood flow in the nasal and oral cavities (1). These studies support the observation that panting mammals show the greatest selective brain cooling during exercise (2). Although humans do not adopt a first phase panting of breathing, their nasal mucosal blood flow (37) and ventilation (6) both increase during hyperthermia, thus suggesting that a similar avenue of cranial cooling exists in humans. During exercise in

both panting mammals and humans, once there are significant elevations in core temperature, a thermal hyperpnea or second phase pattern of ventilation is evident. This is a slower rate and deeper pattern of breathing that brings on a hypocapnia (27, 28).

In hyperthermic humans eccrine sweating provides the main avenue of heat loss, although elevated cutaneous blood flow through vasodilatation also contributes significantly to whole body heat loss (19, 39). During hyperthermia core temperature is the dominant variable in the regulation of both eccrine sweat rate and cutaneous blood flow (19, 39) and core temperature thresholds characterize these two heat loss responses (5). What is not yet evident is how core temperature thresholds for ventilation (36) compare to core temperature thresholds for eccrine sweating and cutaneous blood flow during exercise-induced hyperthermia.

We hypothesized that if ventilation includes a similar neural control mechanism as that in panting animals, then human core temperature thresholds for ventilation would exist only after significant elevations in core temperature. As well, it was reasoned these ventilation thresholds would be greater at higher core temperatures than those for the onset of sweating and vasodilatation that can be initiated with only marginal increases in core temperature. The main testable question we asked in this study was how do esophageal temperature thresholds for ventilation compare to those for sweat and cutaneous blood flow during exercise-induced hyperthermia?

3.3 Methods

3.3.1 Participants

Seven men college aged men between the ages of 22 and 42 with a mean age of 26.6 $\pm$ 2.6 y, who were 1.76 $\pm$ 0.01 m tall, who weighed 73.2 $\pm$ 3.9 kg and had a mean BMI of 23.5 $\pm$ 1.0 kg • m^{-2} volunteered for the study. The participants were considered healthy and absent from disease or illness. All participants were nonsmokers. Their ages and physical characteristics appear in Table 3-1. All participants were made aware of any risks associated with the protocol used in this experiment. After a laboratory orientation and reading a detailed outline of the study, all participants voluntarily signed an informed consent form. The ambient temperature during exercise sessions was 24 $\pm$ 1°C and relative humidity was 45% $\pm$ 5%. During the experiment the participants wore athletic shorts and a short sleeve shirt. The experiments were approved by the Human Investigations Committee (HIC) for human experimentation at Memorial University of Newfoundland.

3.3.2 Instrumentation

Esophageal and Skin temperature

Both esophageal (T_{es}) and skin temperatures were recorded. Esophageal temperatures were estimated using a nasopharyngeal esophageal thermocouple (Size 9Fr; Mallinkroft Medical Inc., St. Louis, MO, USA). The depth of insertion was determined using the formula of Mekjavic and Rempel (24) and this places the tip of the

thermocouple at the level of the left ventricle. Mean un-weighted skin temperatures ($\bar{T}_{sk}$) were measured from thermocouples placed on the forehead (T_{fs}), chest, and lower back. All data were sampled at a rate of 333 kS/s by a SCXI 1102-32-channel input module (National Instruments, Austin, USA). The high sampling rate of the A/D input module allowed greater fidelity of the signal conversion and expression of the thermocouple values to 0.01°C. The data acquisition system was controlled by a personal computer with a National Instrument software package (version 5.1, National Instruments, Austin, USA). During experiments, values were continually displayed on a computer monitor.

Eccrine Sweating Rate

Eccrine sweating rate ($\dot{E}_{SW}$, $mg \cdot m^{-2} \cdot min^{-1}$) was estimated using resistance hygrometry (3). This instrument detected relative humidity changes under a capsule placed on the participant's forehead. With a constant airflow of anhydrous air to the capsule changes of humidity are detected before and after the capsule with humidity sensors (Omega Model RH201, USA). This technique has been repeatedly used to determine sweating thresholds and is a valid as well as reliable method (23, 38).

Cutaneous Blood Velocity

Cutaneous Blood Velocity (CBV) was also estimated during the exercise. A temperature controlled, multi-head laser-Doppler probe (Model MP1/7-V2 Skin Probe, Moor Moor Instruments Ltd., England) was positioned on the participant's temple and CBV was estimated with a laser Doppler blood velocity monitor (Model DRT4, Moor

Instruments Ltd., England). This method depends on the Doppler shift of laser light reflected from the tissue (20). This frequency shift is due to the velocity of moving particles (red blood cells) within the tissue and, therefore, is directly related to the tissue blood flow assuming no changes in capillary diameter (20). This gives a valid measure of cutaneous blood flow as demonstrated by Johnson et al. (20).

Ventilation and Metabolic Rate

The participant breathed from a low resistance mouthpiece and both ventilation as well as expired oxygen and carbon partial pressures were measured on a breath-by-breath basis with a Vmax229 series metabolic cart (Sensormedics, Yorba Linda, CA, USA). Prior to all trials the gas analyzers were calibrated against three primary standard gases; (1) 26% O_2, balance N_2, (2) 4% CO_2, 16% O_2, balance N_2 and (3) room air. The cart's flow sensor was calibrated prior to each experiment using a syringe of known volume.

Heart Rate

The heart rate was measured both with telemetry using a Polar heart monitor (Polar, USA) and a 4-channel ECG monitor integral to the Vmax229 metabolic cart (Sensormedics, Yorba Linda, CA, USA).

Exercise

An electrically braked seated cycle ergometer (LODE, Excalibur, Groningen-Netherlands) was employed for exercise trials to provide a workload that was

independent of pedaling cadence. The participant pedaled at a prescribed cadence of 70 revolutions per minute.

3.3.3 Protocol

Each participant's weight and height was taken just prior to sitting on cycle ergometer and prior to instrumentation. The test protocol used was an adapted form of the Thoden protocol (32). It involved one session of an incremental exercise test on the cycle ergometer. Following a 5 min rest period, each participant had a 5 min warm-up period pedaling at 60 to 70 rpm. The intensity was subsequently raised by 40 Watts every two minutes thereafter until the participant could no longer maintain the prescribed pedaling cadence, until he reached two values maximal values for oxygen consumption that were within 5% or until he reached his age-predicted maximum heart rate. Age-predicted maximal heart rate was determined by subtracting the participant's age from 220. By these criteria each participant reached his maximal oxygen consumption. The exercise test times durations were between 18 and 25 min. Prior to the exercise test the participant was asked to refrain from strenuous or prolonged activity in the preceding 24 h and from ingesting coffee in the preceding 12 h.

3.3.4 Statistics and Data Analysis

One-way ANOVA models were used to compare the T_{es} thresholds for eccrine sweating, CBV, and ventilation as well as the time course (Levels: min 1, 6, 10, 15 and 20) of the ventilatory, metabolic and temperature outcome variables. Ventilation, as in

previous work (36), was expressed as ventilatory equivalents for oxygen ($\dot{V}_E \cdot \dot{V}O_2^{-1}$) and carbon dioxide ($\dot{V}_E \cdot \dot{V}CO_2^{-1}$). The T_{es} thresholds for the ventilatory equivalents were determined with a program written in a Labview programming environment that employed Vieth's piece-wise linear regression model (33). The T_{es} threshold was analyzed by piece-wise linear regression and the thresholds were identified by the lowest residual sum of squares for these two measures of ventilation. This automated method of threshold detection removed any user bias or need for blinding the analyzer to the condition as would be evident for hand-picked thresholds. Vieth's method (33) has been employed across in several areas of physiology (18, 21, 29) which attests to the validity of this assessment method. Post-hoc tests were made with a paired Student's t-test with control for the level of Type I error using the Bonferonni correction so as to keep level of significance at $p < 0.05$.

3.4 Results

Mean responses for $\dot{V}_E$ and its component tidal volume (V_T) and frequency of respiration (f) during the incremental exercise are given in Figure 3-1. Following resting rate of approximately 15 l • min^{-1}, $\dot{V}_E$ significantly increased to ~ 20 l • min^{-1} by min 6 and the progressively to ~100 l • min^{-1} by min 20 (Fig. 3-1A). Frequency of respiration was approximately 15 to 20 breaths • min^{-1} until ~ 15 min of exercise when it had significantly increased ($p<0.01$) to ~ 25 breaths • min $^{-1}$; thereafter it significantly increased to ~ 40 breaths • min^{-1} by 20 min (Fig. 3-1B). Tidal volume increased steadily from the onset of exercise, when it was approximately 1.0 l • breath^{-1}, after which it significantly increased to ~ 1.25 l • breath^{-1} by min 10 and to ~ 2.5 l • breath^{-1} by min 20 (Fig. 3-1C).

Figure 3-2 gives the participants' oxygen consumption and respiratory exchange ratio (RER) during the incremental exercise. Oxygen consumption significantly increased from the resting rate of ~ 0.3 l • min^{-1} to ~ 0.6 l • min^{-1} by min 6 and subsequently at each comparison point until reaching a mean maximal rate of ~ 2.75 l • min^{-1} at min 20. The RER remained at ~ 0.85 until min 10 after which it increased in a linear manner to a significantly elevated level of ~ 1.1 at min 20.

Mean T_{es} was ~ 36.7°C until 10 min and then increased in an approximately linear manner until a significantly higher maximal value of approximately 37.6°C (Fig 3-3A).

Mean skin temperature was constant at ~ 33.7°C for the first two-thirds of the exercise after which it increased significantly to approximately 35.0°C at the end of the exercise (Fig 3-3B).

A typical participant's ventilatory equivalents are given as a function of T_{es} in Fig. 3-4. There was a three phase response for these ventilatory equivalents. Initially in Phase I the steady state T_{es} was at ~ 36.5°C when the participant was at rest. In Phase II exercise was initiated and the ventilatory equivalents remained at levels of approximately 25 to 30 until distinct core temperature thresholds were reached. These, T_{es} thresholds were evident for both $\dot{V}_E \cdot \dot{V}O_2^{-1}$(Fig. 3-4A) and $\dot{V}_E \cdot \dot{V}CO_2^{-1}$ (Fig. 3-4B). For this sample participant the values were the same at T_{es} of ~ 37.35°C. Phase III was the post threshold phase at higher T_{es} levels when ventilatory equivalents increased in proportion to T_{es}. The mean T_{es} thresholds for ventilatory equivalents for the group are given in Table 3-2 and Figure 3-5. The mean T_{es} threshold for $\dot{V}_E \cdot \dot{V}O_2^{-1}$ was 37.37 ± 0.06°C and this was not significantly different from the T_{es} threshold of 37.39 ± 0.06°C for $\dot{V}_E \cdot \dot{V}CO_2^{-1}$.

For a sample participant $\dot{E}_{SW}$ and CBV were expressed as function of T_{es} in Figure 3.6. The variables remained constant at rates of ~ 6 mg $\cdot m^{-2} \cdot min^{-1}$ for $\dot{E}_{SW}$ and at ~ 1.5 AU for CBV of until T_{es} thresholds of 36.98°C for $\dot{E}_{SW}$ (Fig. 3-6A) and 37.05°C for CBV (Fig. 3-6B), respectively. Mean T_{es} threshold for $\dot{E}_{SW}$ for the group was 37.00 ±

0.11°C and this was not significantly different than the T_{es} threshold of 36.99 ± 0.11°C for CBV (Table 3-2, Fig. 3-7).

In Figure 3-8, the pooled T_{es} threshold for $\dot{V}_E \cdot \dot{V}O_2^{-1}$ and $\dot{V}_E \cdot \dot{V}CO_2^{-1}$ of 37.38 ± 0.06°C was significantly greater than the pooled T_{es} thresholds of 37.00 ± 0.11°C for $\dot{E}_{SW}$ and CBV ($p<0.05$).

3.5 Discussion

The main result of the current investigation was esophageal temperature thresholds for cutaneous blood velocity and eccrine sweating occurred at significantly lower T_{es} than those for the ventilatory equivalents for carbon dioxide and oxygen. The results suggest that increases in human respiratory heat loss, that are concurrent with the hyperpnea of intense exercise, are initiated at higher core temperatures than is evident for thermoregulatory heat loss responses. This supports that humans have two groups of thermoregulatory heat loss responses. Eccrine sweating and cutaneous blood flow are responses initiated after small rises in skin and/or core temperature and pulmonary ventilation is a thermoregulatory response initiated only after significant increase in core temperature. Human esophageal temperature thresholds for ventilation were previously demonstrated both in passively (6) and actively (36) induced hyperthermia and more recently shown to be reproducible for actively exercising participants (30).

The observed increase in ventilation appears linked to the rise in esophageal temperature at intense levels of exercise. Nybo and Nielsen (25) demonstrated that when a hyperthermia was superimposed on a exercising individual there was an additional hyperventilation of ~ 42% over and above a normal steady state exercise ventilation of ~ 60 l • min^{-1}. This agreed with our previous suggestion (36) that an elevated core temperature can act to stimulate exercise ventilation in an apparent vestigial panting response (25). In addition, Dempsey and colleagues illustrated that suppression of core

temperature during exercise gives a relative hypoventilation and removes the associated hypocapnia (10). Without exercise, a passive hyperthermia also causes a hyperventilation (13, 14, 17) and together the evidence supports that ventilation in hyperthermic humans contributes to an elevated respiratory heat loss from the body.

White and colleagues (36) demonstrated core temperature thresholds for ventilation during exercise with progressively increasing intensity from rest to maximum level. Once core temperature thresholds were reached there was a divergence in cranial and thoracic temperature, which supports an existence of selective brain cooling in humans (4). In mammals, second phase panting or a thermal hyperpnea is initiated when the core temperature is in the range of 38.0 to 38.9°C (2, 7, 31). In comparison to panting mammals, participants presently and previously in a similar exercise protocol (36), had core temperature thresholds for ventilation at a ~ 37.4 to 37.6°C (Table 3-2). Although these core temperature thresholds for ventilation in exercising humans were at substantially lower levels than those for the onset of second phase panting, these core thresholds T_{es} thresholds were significantly higher than the T_{es} thresholds for the onset of eccrine sweating and vasodilatation (Table 3-2, Fig. 3-7). This suggests that the thermolytic responses for surface sweating and vasodilatation may have a different underlying mechanism than that for the temperature induced hyperpnea of intense exercise (10, 25).

In panting mammals the pattern of ventilation is divided into a first and second phase. During the first phase response, rises in surface or skin temperature bring on a decrease in tidal volume as well as elevations in both the frequency of breathing and the functional residual capacity. This gives a preferential ventilation of the upper airways and it acts as an effective thermolytic heat loss response. During this first phase panting blood gases and pH are maintained, but after a significant rise in core temperature, a second phase panting is evident that is characterized by deeper breaths and a moderate but elevated increase in the frequency of breathing. A main distinction is second phase panting is coupled with a respiratory alkalosis. It is second phase panting that most closely describes the human ventilation response to hyperthermia.

One proposed mechanism of the increase in ventilation or "ventilatory breakaway" during intense exercise is thought to be an increased carbon dioxide sensitivity, that is known to occur during hyperthermia in humans (8, 30). An increased sensitivity of chemoreceptors peripherally to carbon dioxide is shown to occur when their temperature increases (11, 12). This suggests that a similar or reduced partial pressure of arterial carbon dioxide relative to that measured at rest may still contribute to the ~ 15 fold increase in ventilation during intense exercise.

An increased respiratory heat loss is evident in hyperthermic humans during intense exercise (26). A nasal mucosal vasodilatation is also evident during hyperthermia (37) suggesting that heat loss can occur in the nasal passage and a similar avenue of heat

loss exists in humans as it does panting mammals. The magnitude of the respiratory heat loss is considerably smaller (16) than total surface heat loss possible in a hyperthermic sweating human, however, ~ 46% of the total cephalic heat loss is respiratory heat loss in differing environmental conditions during exercise with an intensity of only 150 W (26). This supports at elevated core temperatures during exercise, that respiratory heat loss contributes directly to cranial heat loss and thermoregulation.

A direct demonstration of heat loss from the upper airways influencing intracranial heat loss in humans is strong support for the view that human respiratory heat loss contributes significantly to cranial thermoregulation (22). Mariak and colleagues showed with small increases in breathing by resting, mildly hyperthermic patients, that substantial decreases in cribriform plate temperature were observed. Since the hypothalamus, that acts as a primary site of temperature regulation in humans (5, 15), is only a fraction of a millimeter away from the cribriform plate, it suggests an important role of the heat loss from the upper airways in human temperature. This respiratory heat loss in the upper airways may become especially important during exercise when ventilation can exceed 150 $l \cdot min^{-1}$.

3.6 Conclusion

This study demonstrated that esophageal temperature thresholds for ventilation during incremental exercise from rest to maximal attainable work rates were at higher esophageal temperatures than those for eccrine sweating and for cutaneous

vasodilatation. This suggests the ventilation response to the hyperthermia of exercise is brought about by a differing mechanism than those for eccrine sweating and for cutaneous vasodilatation.

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3.7 References

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Table 3.1. Participants' physical characteristics.

Subject #	Age (y)	Weight (kg)	Height (m)	BMI ($kg \cdot m^{-2}$)
1.	24.0	65.9	1.78	20.8
2.	25.0	87.3	1.80	26.9
3.	22.0	88.2	1.79	27.6
4.	22.0	63.2	1.75	20.7
5.	26.0	70.9	1.73	23.7
6.	25.0	68.6	1.76	22.1
7.	42.0	68.5	1.73	22.9
Mean	26.6	73.2	1.76	23.5
SE	2.6	3.9	0.01	1.0

Table 3.2. Esophageal temperature (T_{es}) thresholds for cutaneous blood velocity (CBV), eccrine sweating ($\dot{E}_{SW}$) and ventilatory equivalents for oxygen ($\dot{V}_E \bullet \dot{V}O_2^{-1}$) and carbon dioxide ($\dot{V}_E \bullet \dot{V}CO_2^{-1}$) during exercise-induced esophageal temperature warming in college aged males (NS = Non Significant, † $p<0.01$).

Participant #	$\dot{E}_{SW}$ Threshold (°C)	CBV Threshold (°C)	$\dot{V}_E \bullet \dot{V}O_2^{-1}$ Threshold (°C)	$\dot{V}_E \bullet \dot{V}CO_2^{-1}$ Threshold (°C)
1.	36.86	36.58	37.54	37.45
2.	37.04	37.07	37.22	37.25
3.	37.09	37.25	37.52	37.52
4.	36.92	37.01	37.55	37.49
5.	37.59	37.38	37.22	37.22
6.	36.90	36.63	37.19	37.19
7.	36.62	36.99	37.35	37.59
Mean	37.00	36.99	37.37	37.39
SE	0.11	0.11	0.06	0.06
	•---------NS-------•		•---------NS-------•	
	37.00 ± 0.11		37.38 ± 0.06	
	•----------†----------•			

Figure 3-1. Mean responses (n=7) for (A) ventilation ($\dot{V}_E$), (B) frequency of respiration (f), and (C) tidal volume (V_T) given as a function of time during exercise on a seated, cycle ergometer from rest until exhaustion (NS=Non-Significantly different; significantly different from resting values at *p< 0.05, †p< 0.01; ‡p< 0.001; Error bars are ±SE).

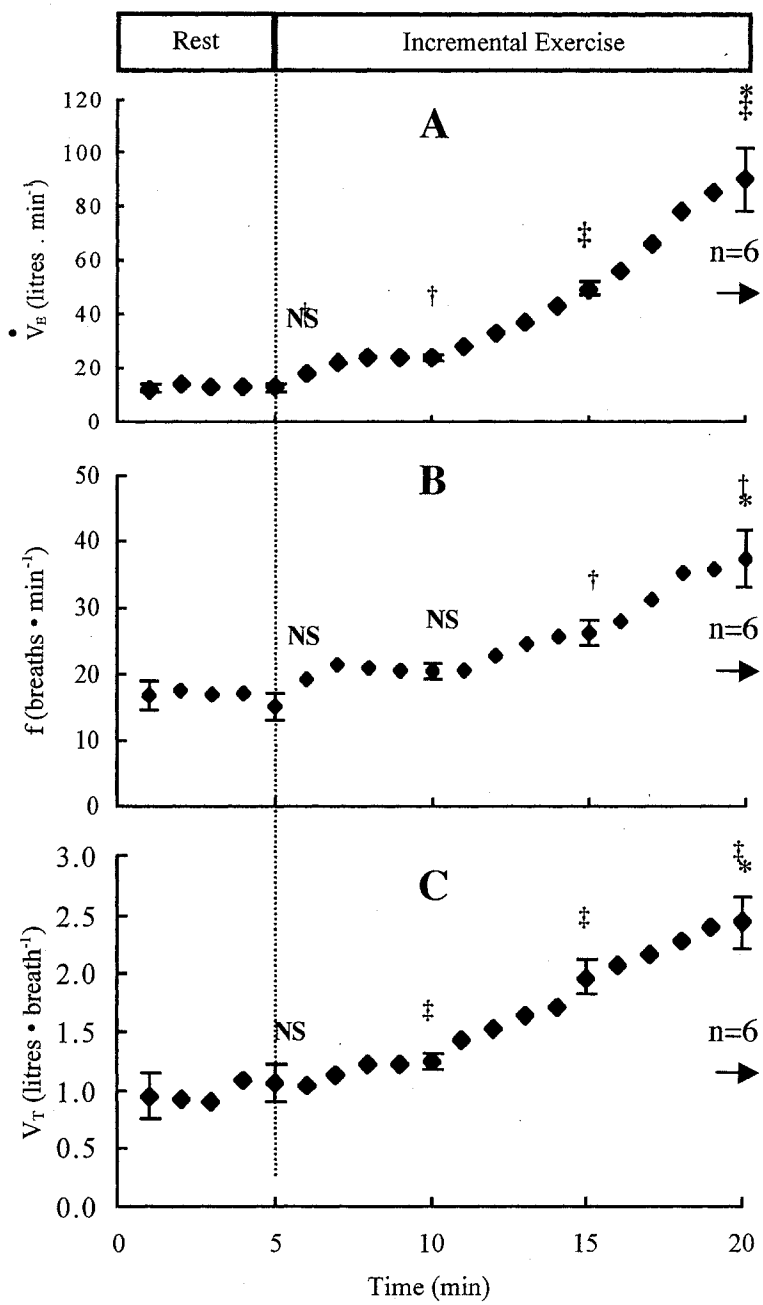


Figure 3-2. Participants mean responses (n=7) for (A) oxygen consumption ($\dot{V}O_2$) and (B) respiratory exchange ratio (RER) each expressed as a function of time during exercise on a seated, cycle ergometer from rest until exhaustion (NS=Non-Significantly different; significantly different from resting values at *p< 0.05, †p< 0.01; ‡p< 0.001; Error bars are ±SE).

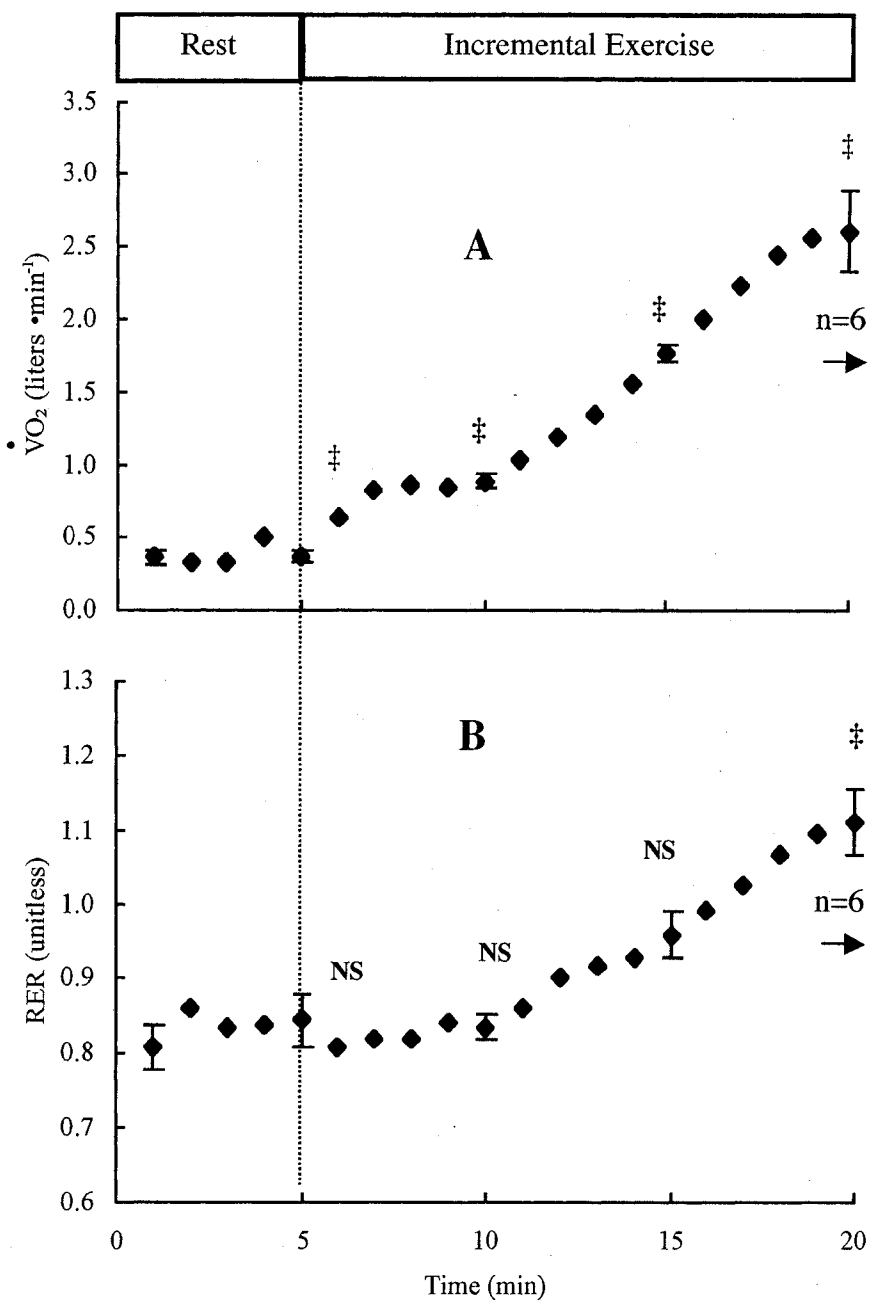


Figure 3-3. Means (n=7) of (A) esophageal temperature (T_{es}) and (B) mean skin temperature ($\bar{T}_{sk}$), each expressed as a function of time during exercise on a seated, cycle ergometer from rest until exhaustion (NS=Non-Significantly different; significantly different from resting values at *p< 0.05, †p< 0.01; Error bars are ±SE).

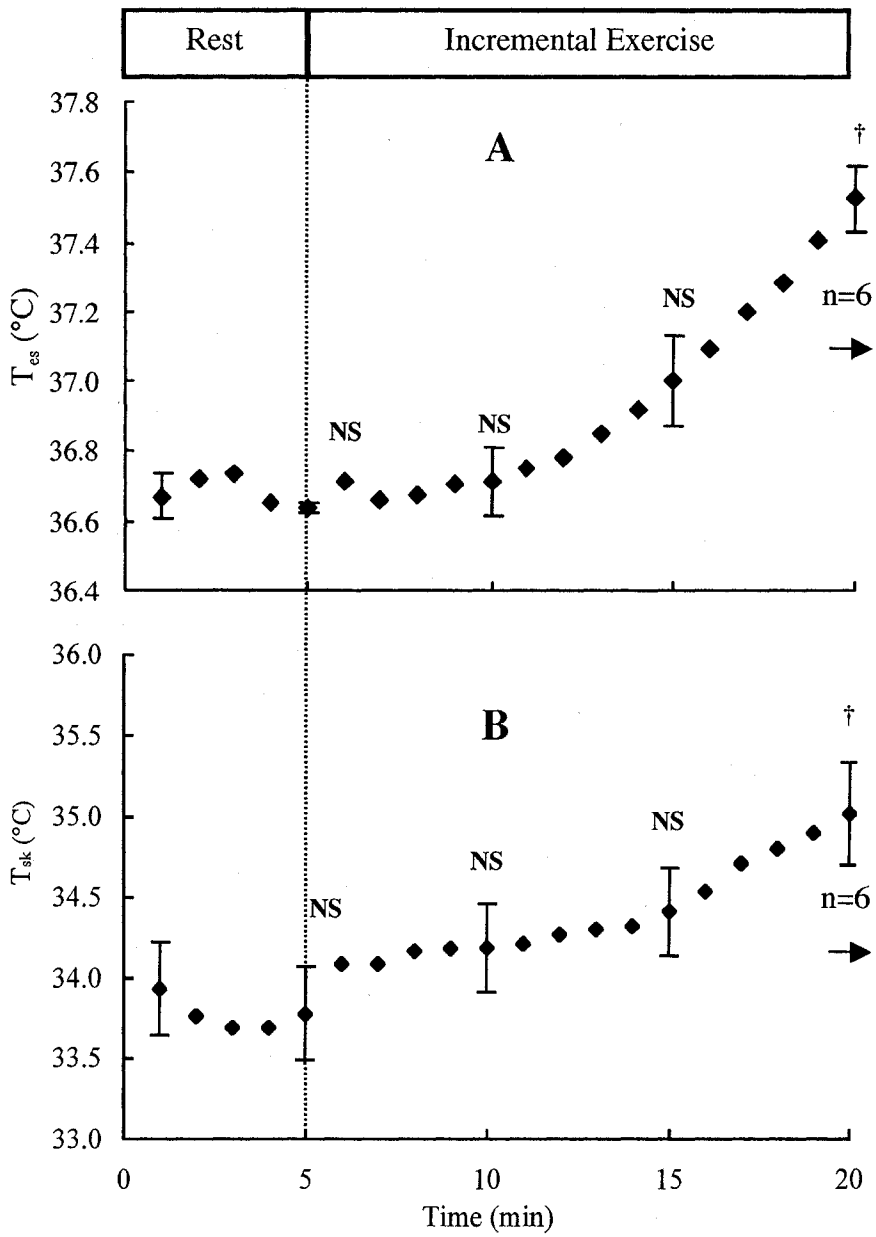


Figure 3-4. A sample participant's esophageal temperature (T_{es}) thresholds for (A) ventilatory equivalents for oxygen ($\dot{V}_E \bullet \dot{V}O_2^{-1}$) and (B) for carbon dioxide ($\dot{V}_E \bullet \dot{V}CO_2^{-1}$) during exercise on a seated, cycle ergometer from rest until exhaustion. Arrows indicate the T_{es} thresholds for $\dot{V}_E \bullet \dot{V}O_2^{-1}$ and $\dot{V}_E \bullet \dot{V}CO_2^{-1}$ for this participant.

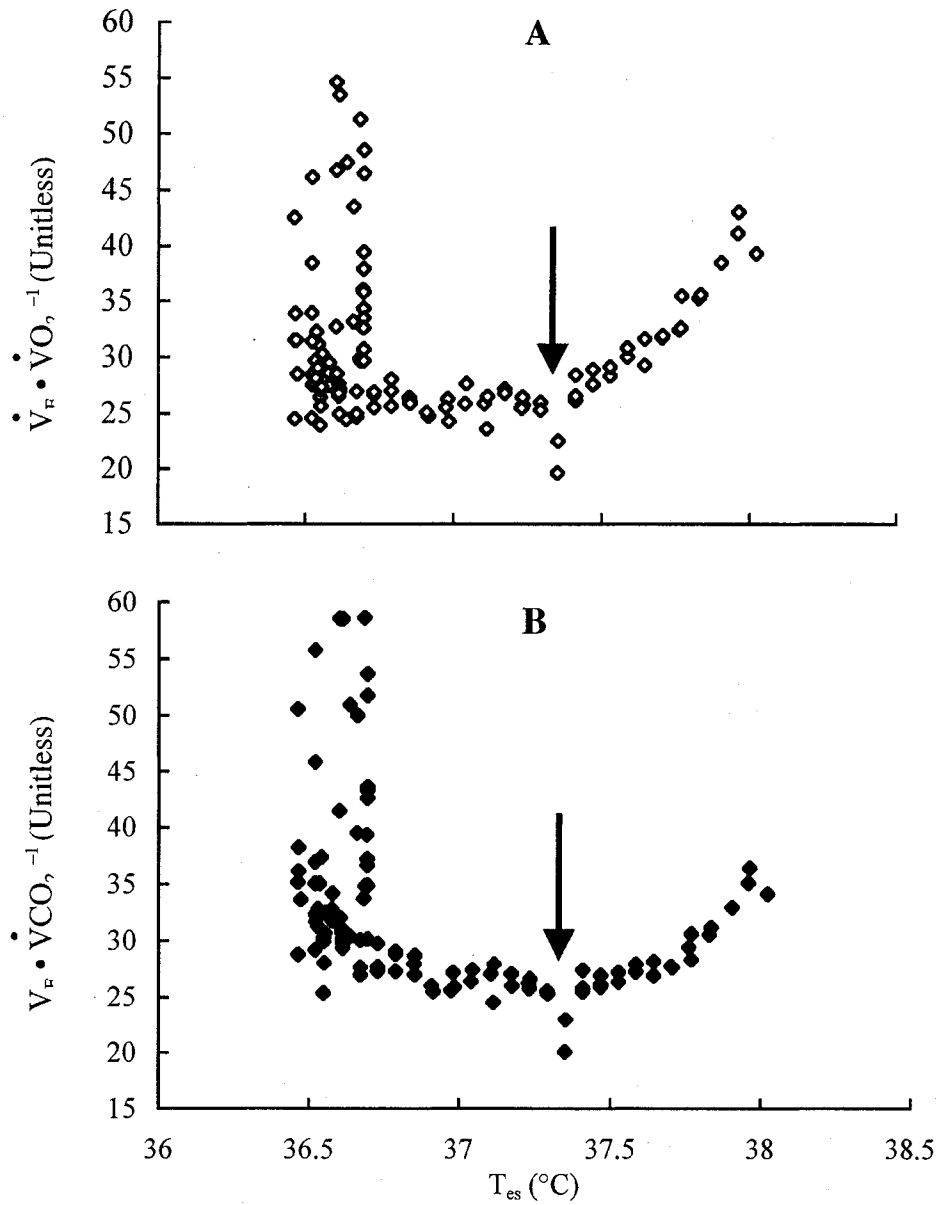


Figure 3-5. Mean (n=7) esophageal temperature (T_{es}) for ventilatory equivalents for (A) oxygen ($\dot{V}_E \bullet \dot{V}O_2^{-1}$) and for (B) carbon dioxide ($\dot{V}_E \bullet \dot{V}CO_2^{-1}$) during exercise on a seated, cycle ergometer from rest until exhaustion. Arrows indicate the mean T_{es} thresholds for $\dot{V}_E \bullet \dot{V}O_2^{-1}$ and $\dot{V}_E \bullet \dot{V}CO_2^{-1}$ for the seven participants.

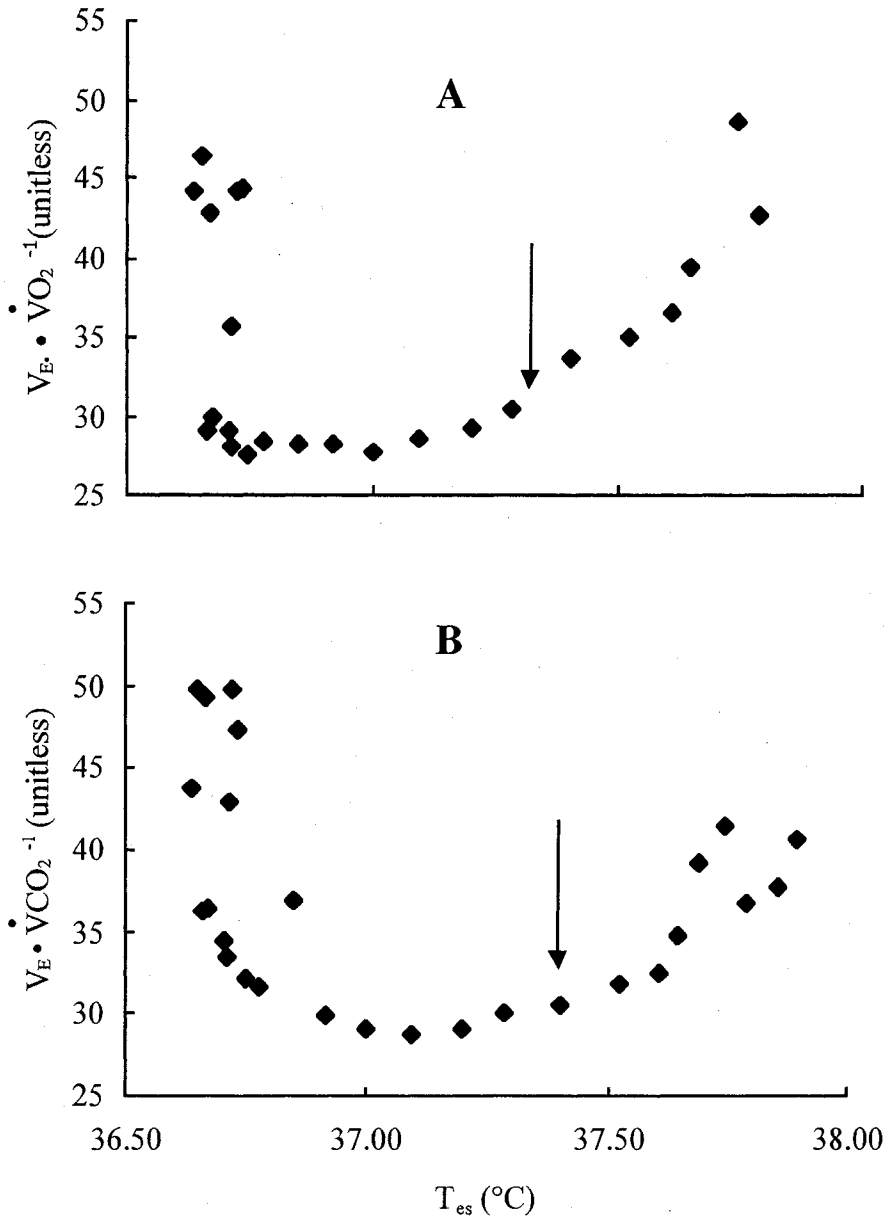


Figure 3-6. A sample participant's esophageal temperature (T_{es}) thresholds for (A) eccrine sweating ($\dot{E}_{sw}$) and (B) cutaneous blood velocity (CBV) during exercise on a seated, cycle ergometer from rest until exhaustion. Arrows indicate the T_{es} thresholds for $\dot{E}_{sw}$ and CBV for this participant.

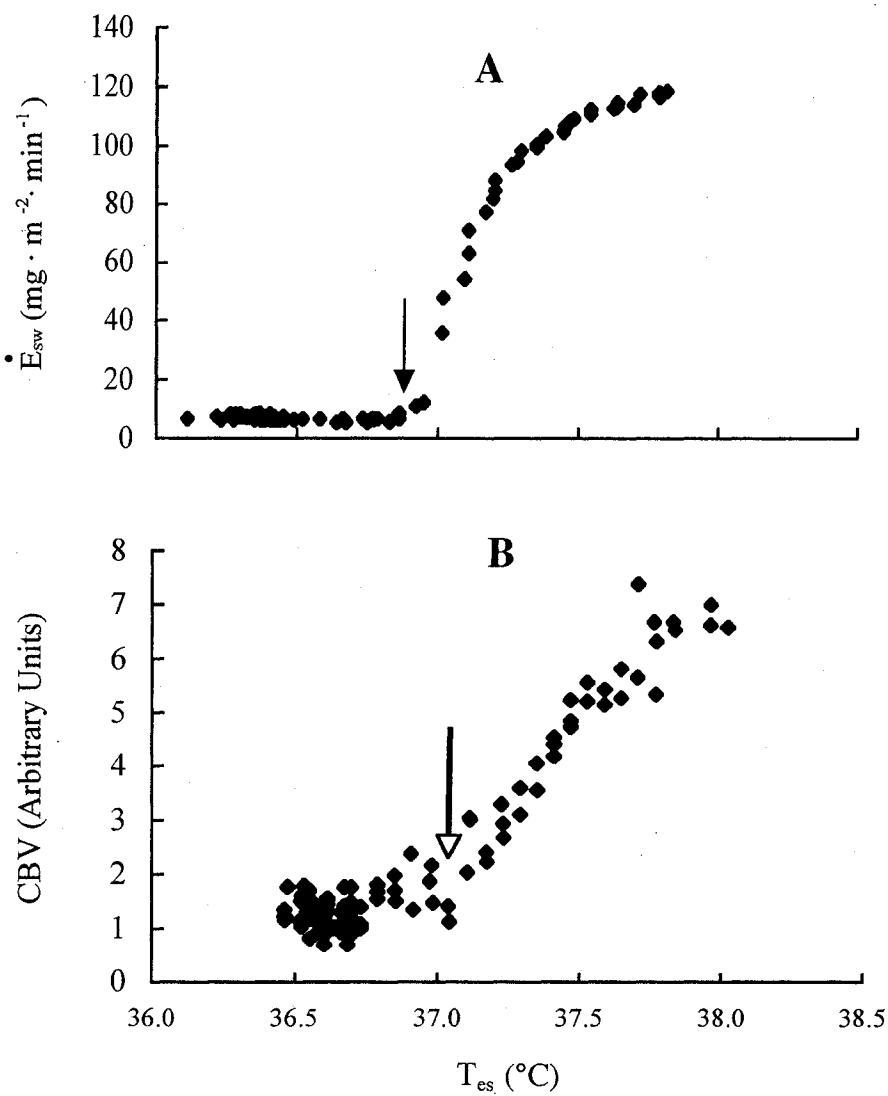


Figure 3-7. Participants' mean (n=7) esophageal temperature (T_{es}) thresholds for (A) eccrine sweating ($\dot{E}_{SW}$) and (B) cutaneous blood velocity (CBV) during exercise on a seated, cycle ergometer from rest until exhaustion. Arrows indicate the mean T_{es} thresholds for $\dot{E}_{SW}$ and CBV for the seven participants.

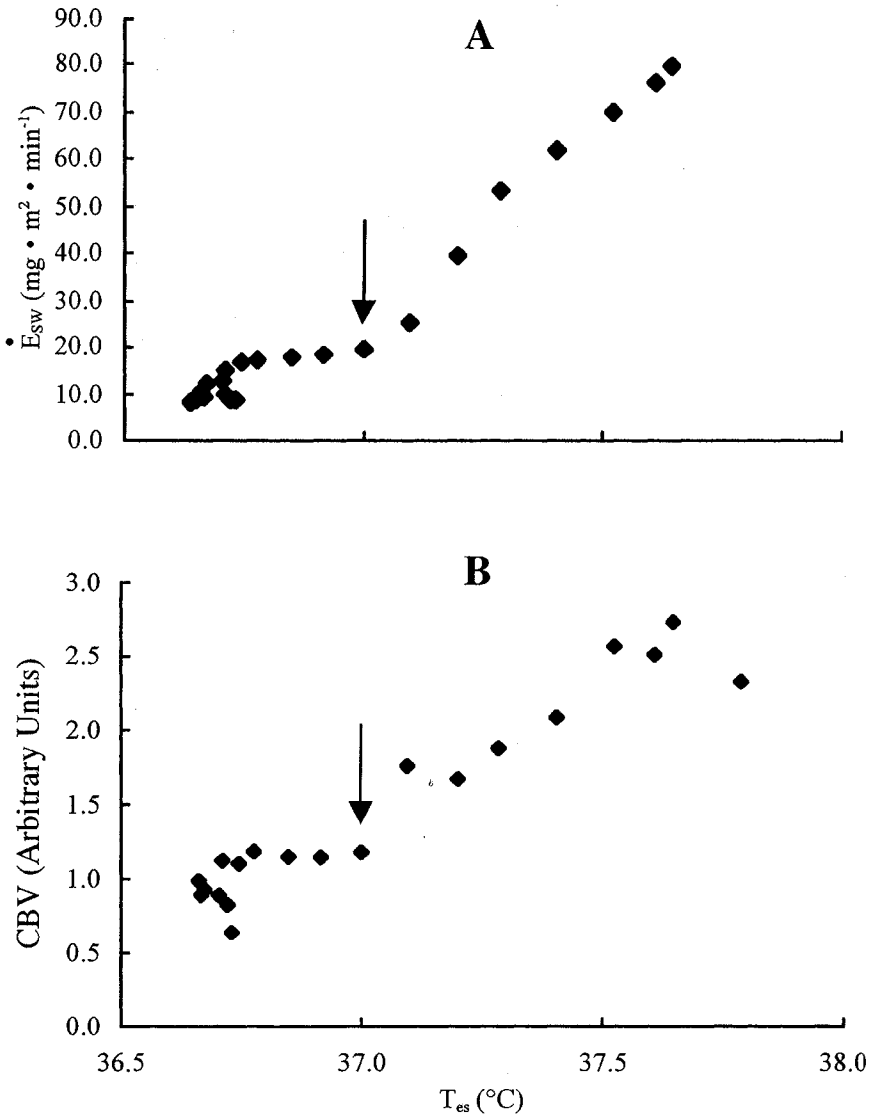
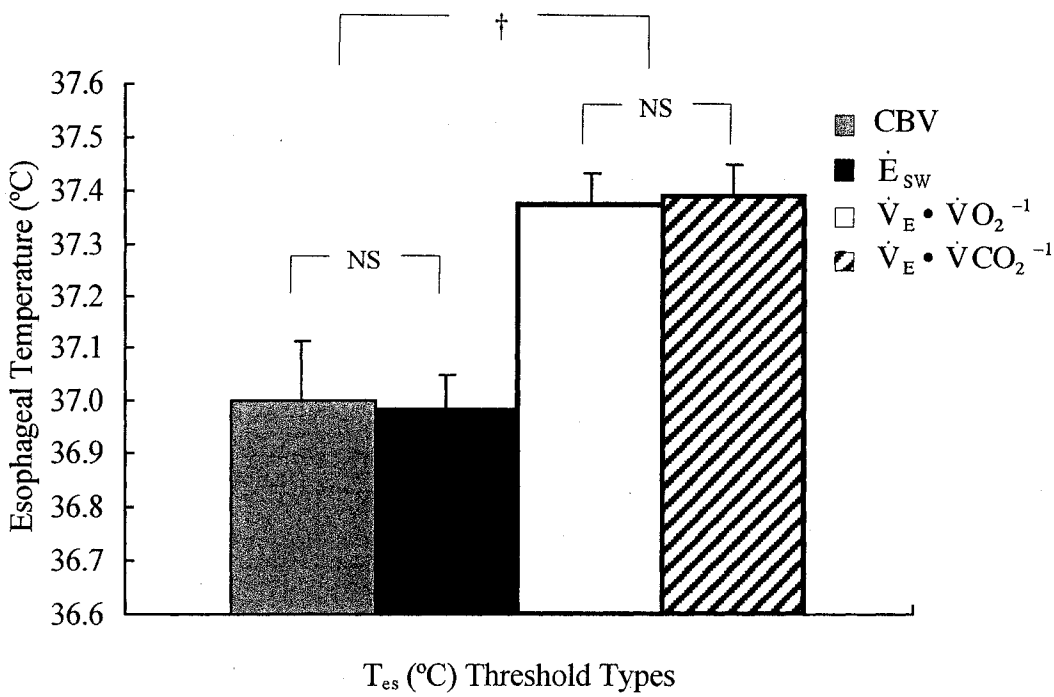


Figure 3-8. Mean esophageal temperature (n=7) thresholds (T_{es}) for cutaneous blood velocity (CBV), eccrine sweating ($\dot{E}_{SW}$) and ventilatory equivalents during exercise on a seated, cycle ergometer from rest until exhaustion (NS = Non Significant, *p < 0.05; †p<0.01; Error bars = + SE).



Chapter 4: Comparison of core temperature thresholds for ventilation, eccrine sweating, and cutaneous blood velocity during passive hyperthermia

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Keywords: core temperature, eccrine sweating, end-tidal carbon dioxide tension, exercise ventilation, hyperthermia, skin blood flow

4.1 Abstract

This study compared core temperature thresholds for pulmonary ventilation, eccrine sweating, and cutaneous blood velocity plus examined the pattern and nature of ventilation during passively induced hyperthermia. Seven untrained males sat in a hot bath at 40°C until their esophageal temperature (T_{es}) reached ~ 38.5°C. They were instrumented for breath-by-breath measurement of ventilation ($\dot{V}_E$), oxygen consumption ($\dot{V}O_2$) and end-tidal carbon dioxide partial pressure ($P_{ET}CO_2$). They were assessed for mean skin temperatures ($\bar{T}_{sk}$), cutaneous blood velocity (CBV), and forehead eccrine sweating ($\dot{E}_{SW}$). Passive heating gave significant increases of each of $\dot{V}_E$, $\dot{E}_{SW}$, and CBV and small but significant increases in the hyperthermic participants' $\dot{V}O_2$. The hyperpnea was brought about by significant elevations in tidal volume ($p<0.05$) while the frequency of breathing remained at pre-immersion levels. When $\dot{V}_E$, $\dot{E}_{SW}$, and CBV were each expressed as a function of esophageal temperature (T_{es}), the mean T_{es} threshold of 37.91 ± 0.13°C (mean ± SE) for $\dot{V}_E$ was significantly higher ($p < 0.001$) than those of 36.96 ± 0.04°C for $\dot{E}_{SW}$ and of 36.90 ± 0.07°C for CBV. At higher T_{es} the increases in $\dot{V}_E$ gave a hypocapnia indicated by a significant reduction in $P_{ET}CO_2$ ($p<0.05$) and a significant increases in the respiratory exchange ratio ($p<0.05$). In conclusion, the T_{es} thresholds evident for $\dot{V}_E$ were higher than those for $\dot{E}_{SW}$ and CBV and subsequent to these $\dot{V}_E$ thresholds the participants became hypocapnic, indicative of a thermally induced hyperpnea.

4.2 Introduction

Saxton (30), Cunningham and O'Riordian (9), House and Holmes (14) and Haldane (13) have all shown that passive hyperthermia induces an increase in ventilation when core temperature had risen by approximately 1°C. Cabanac and White (6) demonstrated core temperature thresholds for ventilation during passive body warming and at core temperatures higher than these thresholds, a hyperpnea was evident despite metabolic rate remaining at a resting values. It was concluded (6) that this hyperpnea could be a thermoregulatory response likely to participate in cranial heat exchange.

Panting mammals such as cats, dogs, and sheep (1) demonstrate selective brain cooling, a condition where the temperature of the whole brain is below the temperature of the rest of the body in hyperthermia (19). Humans do not appear to have specialized anatomical features for this response but they do appear to demonstrate selective brain cooling (4). This view was supported with directly measured intracranial temperatures in humans, that decreased at a rate of up to $6°C \cdot h^{-1}$ (20).

In hyperthermia, nasal mucosal blood flow increases (34) and an increased nasal patency reduces thermal strain in humans (35). This suggests that humans have a group of physiological responses to promote cranial hat loss similar to panting animals in hyperthermia. Unlike humans, several mammals pant instead of sweating for heat loss during hyperthermia. The cat is an example and has a resting body temperature of

38.3°C. These felines have a mean panting rectal core temperature threshold of ~ 38.9°C (31). Globally in panting mammals, their second phase panting response or thermal hyperpnea is typically initiated when the core temperature is in the range of 38.0 to 38.9 °C (1, 7, 31).

Eccrine sweating in humans is the most effective means of heat loss during hyperthermia, assuming an adequate vapor pressure gradient from the skin to the ambient air and that the sweat evaporates. Both eccrine sweating and cutaneous vasodilatation are thermolytic responses that together dependent upon skin and core temperatures (24). As the body core temperature is passively increased, for a fixed levels of core temperature, thresholds for these responses are evident (2, 5). Typically these two thresholds are initiated with rise of T_c less than 0.1°C, with a skin temperature of ~ 38 to 40°C (5).

In humans core temperature thresholds for ventilation have been demonstrated during passively induced hyperthermia (6) but they have not been compared to core temperature thresholds for eccrine sweating and cutaneous blood flow during passive warming conditions. This study asked how core temperature thresholds ventilation of hyperthermic humans compare to those for eccrine sweating and cutaneous blood velocity. It was hypothesized that the core temperature thresholds for ventilation would be at higher core temperatures than the thresholds for eccrine sweating and cutaneous blood velocity.

4.3 Methods

4.3.1 Participants

Seven men between the ages of 22 and 42, with a mean age of 26.6 $\pm$ 2.6 y, who were 1.76 $\pm$ 0.01 m tall, who weighed 73.2 $\pm$ 3.9 kg, and had a mean BMI of 23.5 $\pm$ 1.0 kg $\cdot$ m^{-2} volunteered for the study. The participants were healthy, absent from disease/illness and were all nonsmokers. Their ages and physical characteristics appear in Table 4-1. They were made aware of any risks associated with the protocol used in this experiment. After a laboratory orientation, a 24-h reflection period and reading a detailed outline of the study all participants voluntarily signed a consent form. The experiments were approved by the Human Investigations Committee (HIC) for human experimentation at Memorial University of Newfoundland.

4.3.2 Instrumentation

Esophageal and Skin temperature

Core temperatures were estimated using a nasopharyngeal esophageal thermocouple (T_{es}) probe (size 9Fr; Mallinkroft Medical Inc., St. Louis, MO, USA) inserted to the level of left ventricle (23). Skin temperature was recorded from a thermocouple taped on the forehead (T_{fs}). All data was sampled at a rate of 333 kS/s by a SCXI 1102-32-channel input module (National Instruments, Austin, USA). The high sampling rate of the A/D input module allowed greater fidelity of the signal conversion

and expression of the thermocouple values to 0.01°C. All thermocouples were connected to a 32-channel data acquisition system (National Instruments, San Antonio, Tx, USA) and controlled by a National Instrument software package (Labview v. 5-1). During experiments values were continually displayed on a computer monitor.

Eccrine Sweating Rate

Eccrine sweating rate ($\dot{E}_{SW}$, mg • m^{-2} • min^{-1}) was estimated using resistance hygrometry (3). This instrument detects relative humidity changes under a capsule placed on the participant's forehead. With a constant flow of 1 l • min^{-1} of anhydrous air to the capsule changes of humidity are detected before and after the capsule with humidity sensors (Omega, Model RH201, USA). This technique has been repeatedly used to determine sweating thresholds and is a valid as well as reliable method (21, 36).

Cutaneous Blood Velocity

Cutaneous Blood Velocity (CBV) was also estimated during the hot water immersion. A temperature controlled, multi-head probe (Model MP1/7-V2 Skin Probe, Moor Moor Instruments Ltd., England) was placed on the participant's temple using a laser Doppler blood velocity monitor (Model DRT4, Moor Instruments Ltd., England). This method depends on the Doppler shift of laser light reflected from the tissue (17). This frequency shift is due to the velocity of moving particles (red blood cells) within the tissue and, therefore, is directly related to the tissue blood velocity assuming no changes in capillary diameter (17). This frequency shift is due to the velocity of moving particles

(red blood cells) within the tissue and, therefore, is directly related to the tissue blood flow assuming no changes in capillary diameter (17). This gives a valid measure of cutaneous blood flow as demonstrated by Johnson et al. (17).

Ventilation and Metabolic Rate

The participant breathed from a low resistance mouthpiece and both ventilation as well as expired oxygen and carbon partial pressures were measured on a breath-by-breath basis with a Vmax229 series metabolic cart (Sensormedics, Yorba Linda, CA, USA). Prior to all trials the gas analyzers were calibrated against three primary standard gases; (1) 26% O_2, balance N_2, (2) 4% CO_2, 16% O_2, balance N_2 and (3) room air. The cart's flow sensor was calibrated prior to each experiment using a syringe of known volume.

Heart Rate

The heart rate was measured both with telemetry using a Polar heart monitor (Polar, USA) and a 4-channel ECG monitor integral to the Vmax229 metabolic cart (Sensormedics, Yorba Linda, CA, USA).

Hyperthermia

Each participant was rendered hyperthermic by immersion to the level of the shoulders in a 40°C water bath.

4.3.3 Protocol

Prior to the passive warming session each participant was asked to refrain from strenuous or prolonged activity for a 24-h period and from ingesting coffee for 12 h. Each participant's weight and height were taken just prior to 5-min resting period when pre-immersion data was collected. Then the participant was seated within 5 s in a 40°C tub to the level of the shoulders and was asked to relax during immersion. The session ended when one of the following conditions was met: T_{es} reached ~ 38.5°C or the participant expressed a desire to leave the tub. All 7 subjects had a 40°C immersion of 20 min and 6 subjects where still immersed at 25 min. The ambient temperature during passive warming sessions was 23 to 24°C and relative humidity was 45% $\pm$ 5%. The participant wore athletic shorts/trunks and breathed room air during the passive warming sessions that took place between 16h30 and 18h30.

4.3.4 Statistics and Data Analysis

One-way ANOVA models were used to compare the T_{es} thresholds for eccrine sweating, CBV and ventilation as well as the time course (Levels: min 1, 6, 10, 15 and 20, 25) of the ventilatory, metabolic and temperature outcome variables. The T_{es} thresholds for the ventilation were determined with a program written in a Labview programming environment that employed Vieth's piece-wise linear regression model (32). The T_{es} threshold was analyzed by piece-wise linear regression and the thresholds were identified by the lowest residual sum of squares for these two measure of ventilation. This automated method of threshold detection removed any user bias or need

for blinding the analyzer to the condition as would be evident for hand-picked thresholds. Vieth's method (32) has been employed across in several areas of physiology (15, 18, 28) which attests to the validity of this assessment method. Post-hoc tests were made with a paired Student's t-test with control for the level of Type I error using the Bonferonni correction so as to keep level of significance at $p < 0.05$.

4.4 Results

Mean T_{es} prior to the passive warming session was ~36.7°C and it rose significantly ($p<0.001$) to values between ~ 37.9°C at 15 min and ~38.8°C at the end of the immersion (Fig. 4-1A). Likewise mean skin temperature rose from a resting level of ~35.1°C prior to immersion to significantly greater ($p<0.001$) values between min 15 and 25 (Fig. 4-1B).

Ventilation ($\dot{V}_E$) and its components at rest and during the immersion are given in Figure 4-2. Ventilation was ~ 11 l • min^{-1} at rest, it significantly ($p<0.01$) increased to ~ 18 l • min^{-1} on immersion and then returned to pre-immersion levels until min 15. Subsequently $\dot{V}_E$ increased to significantly greater values ($p<0.05$) between min 20 and 25 of immersion. Ventilation reached a significantly greater ($p<0.05$) final maximal value of ~ 19 l • min^{-1} at min 25 (Fig. 4-2A). Frequency of breathing (*f*) before immersion was ~ 17 breaths • min^{-1} and it transiently and significantly ($p<0.05$) increased after immersion to 24 breaths • min^{-1}. Subsequently *f* returned to pre-immersion values for the remainder of the immersion (Fig. 4-2B). In the pre-immersion period tidal volume (V_T) was ~ 0.7 l • $breath^{-1}$ and after immersion it remained constant until min 10. Following this V_T significantly ($p<0.05$) increased by min 20 and reached a maximal value of ~ 1.3 l • $breath^{-1}$ at min 25 of immersion (Fig. 4-2C)

Esophageal temperature thresholds for a sample participant's $\dot{E}_{SW}$, CBV and ventilation are given in Figure 4.3. The participant's $\dot{E}_{SW}$ remained at a resting level of

~ 14 mg $\cdot m^{-2} \cdot min^{-1}$ until reaching a T_{es} of 36.87°C when sweating was initiated. His CBV remained at a resting level of ~ 2 AU until a T_{es} of 36.73°C. Likewise his $\dot{V}_E$ after an initial gasp-like response of ~ 26 l • min^{-1} on immersion, at T_{es} ~ 36.5°C, increased to a maximum value of ~ 30 l • min^{-1} following a T_{es} threshold of 37.80°C.

The mean T_{es} threshold for CBV was 36.90 ± 0.07°C, and it was not significantly different from the mean T_{es} threshold for $\dot{E}_{SW}$ that was 36.96 ± 0.04°C (Table 4.2, Fig.4. 4). The mean T_{es} threshold for $\dot{V}_E$ of 37.91 ± 0.13°C was significantly ($p<0.001$) higher than both the thresholds for $\dot{E}_{SW}$ and CBV (Table 4.2, Fig. 4.4).

Oxygen consumption ($\dot{V}_{O2}$) remained constant at ~ 0.25 l • min^{-1} until the point of immersion when it transiently and significantly increased ($p<0.01$) to ~ 0.5 l • min^{-1}. Then $\dot{V}_{O2}$ returned to pre-immersion levels until min 25 when it significantly increased ($p<0.05$) to 0.36 l • min^{-1} (Fig. 4.5A). $P_{ET}CO_2$ remained at a pre-immersion of ~ 5.0 kPa and then it significantly ($p<0.05$) decreased to ~ 4.0 kPa by the end of immersion (Fig. 4.5B). The respiratory exchange ratio was ~ 0.80 until the point of immersion when it subsequently significantly ($p<0.05$) increased to ~1.05 (Fig. 4.5C).

In Figure 4.6 the mean frequency of breathing and tidal volume are given as a function of T_{es}. A T_{es} threshold was evident for V_T at 37.27°C (Fig. 4.6A) but there was little evidence of a threshold for the frequency of breathing (Fig. 4.6B). The mean T_{es} thresholds CBV, $\dot{E}_{SW}$, and $\dot{V}_E$ are summarized in Figure 4.7 and Table 4.2.

4.5 Discussion

Previously during passive warming of humans, core temperature thresholds for ventilation were demonstrated (6). The result of the present study was to reproduce these ventilatory core thresholds and compare them to core temperature thresholds for eccrine sweating and cutaneous blood flow during passive warming in a 40°C water bath. Core temperature thresholds for cutaneous blood velocity occurred at a significant lower core temperature than the ventilatory thresholds (Fig. 4.7). This indicated that vasodilatation caused an increase of cutaneous blood velocity prior to when there was a significant increase in ventilation during immersion. In addition, the core temperature threshold for eccrine sweating occurred at a significant lower core temperature than the ventilatory threshold (Fig. 4.7). This added that the onset eccrine sweating also occurs prior to when there was an increase in ventilation during immersion. The esophageal temperature threshold for cutaneous blood velocity and eccrine sweating were at close to normothermic esophageal temperatures and this can be attributed to the high skin temperature during the passive warming (21).

In this study, as in others, a hyperventilation is reported to occur in resting hyperthermic humans (13, 14). This increase in ventilation or thermal hyperpnea, has been suggested to act as a thermolytic response rather than one needed only to meet metabolic needs (6). Immediately upon immersion there was a significant increase in ventilation, as reported previously to be due to a hydrostatic pressure (22). This was

followed by a stable ventilation period and subsequently there was a significant increase in ventilation towards the end of immersion (Fig. 4.1). The initial increase in ventilation was due to an increase in frequency of breathing (Fig. 4.1B), but following this initial significant increase in ventilation the frequency of breathing returned towards pre-immersion levels. The large increases in ventilation towards the end of immersion were due to increases in tidal volume rather than increases in frequency of breathing (Fig. 4.1C). This was also evident when V_T and f were expressed as a function of esophageal temperature (Fig. 4.6AB); a distinct T_{es} threshold at ~ 37.3°C was evident for V_T whereas no T_{es} threshold was evident for f. This agrees with previous findings (6, 12) that showed following the transient increases in ventilation on immersion, that for hyperthermic humans increases in their ventilation was from increases breath depth or V_T rather by increases in breathing frequency or f. This response appears to be similar to second phase panting that is also seen in panting animals (16) since the increases in ventilation were evident after significant increases in T_{es} (26).

One physiological rationale for an increase of ventilation observed in passive warming is to increase respiratory heat loss and contribute to selective brain cooling (25, 34, 36). For hyperthermic humans White and Cabanac (34) showed that nasal mucosal blood flow increases by approximately three times relative to normothermic values. An increase in ventilation and respiratory mucosal vasodilatation are well documented responses in panting mammals and these responses act together to increase heat loss from the body (1). In dogs, panting was initiated at a core temperature of ~ 38 °C and in a

parallel fashion lingual blood flow increased (27). This suggested that the tongue contributed to respiratory evaporative heat loss mechanism and that panting was associated with increased lingual blood flow (27). Hence, the core temperature threshold indicates an increase in ventilation during passive warming was at a similar (Figs. 4.4 and 4.7) level to that of panting animals. This suggests a vestigial panting response involved in the control of ventilation could be evident in humans

During the 40°C immersion oxygen consumption transiently increased on immersion, but then remained relatively constant at ~ 0.3 l • min^{-1} and finally increased marginally to 0.36 l • min^{-1} at the end of the immersion (Fig. 4.5A). These increases were substantially less than the increase in ventilation (Fig. 4.1) and supports this hyperventilation was temperature induced. Evidence for a hyperventilation came from both $P_{ET}CO_2$ that dropped from ~ 5.0 kPa to 4.0 kPa (Fig. 4.5B) and from RER that rose from a pre-immersion level of 0.8 to a maximal value of ~1.05 at the end of immersion (Fig. 4.5C). An elevated ventilation by ~ 50% (Fig. 4.1A) together with lowered $P_{ET}CO_2$ and raised RER, despite marginal changes in oxygen consumption, support the conclusion that the ventilation response was thermally rather than metabolically induced.

Eccrine sweating and cutaneous blood flow are human thermolytic responses that act to help dissipate heat. During the passive warming both these responses were initiated at slightly above normothermic esophageal temperatures (Fig. 4.4A,B) to help dissipate heat from the body. Subsequently, when esophageal temperature reached ~ 38

°C, a hyperventilation began and this appeared to further contribute to heat loss from the body in its hyperthermic state. Thus, at lower core temperatures eccrine sweating and cutaneous blood flow act to dissipate heat as a consequence of elevated body temperatures. These responses are followed at higher core temperatures by increases in ventilation and the associated increases in respiratory evaporative heat loss.

The potential mechanism for this temperature-induced increase in ventilation has been recently reviewed (33) and is discussed briefly here. Evidence suggests elevated temperatures of each of the carotid and aortic bodies as well as the central chemoreceptive areas of the medulla oblongata increases the firing rates of these chemosensitive tissues (10, 11). This suggests at given partial pressures of the arterial blood gases and hydrogen ion concentration, that a greater ventilation is expected during hyperthermia. Hyperventilation or a thermal hyperpnea (33) has been reported in hyperthermic humans (6, 13, 29) as well as in hyperthermic animals (8, 11) in support of this mechanism of control of ventilation during heat stress.

4.6 Conclusion

This study demonstrated that core temperature thresholds for human ventilation were significantly higher than those for cutaneous blood velocity and eccrine sweating during passively-induced hyperthermia. This suggests that core temperature thresholds for hyperventilation in humans are similar to those for the onset of panting (i.e. at ~

38.0°C) in other mammals. This would support similar mechanism(s) of control of ventilation during passive hyperthermia in humans and non-human panting mammals. This type of ventilation pattern is best described as a second phase panting response that gives a hyperventilation relative to metabolic needs coupled with a respiratory alkalosis.

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Table 4.1. Participants' physical characteristics.

Participant #	Age (y)	Weight (kg)	Height (m)	BMI ($kg \cdot m^{-2}$)
1.	24.0	65.9	1.78	20.8
2.	25.0	87.3	1.80	26.9
3.	22.0	88.2	1.79	27.6
4.	22.0	63.2	1.75	20.7
5.	26.0	70.9	1.73	23.7
6.	25.0	68.6	1.76	22.1
7.	42.0	68.5	1.73	22.9
Mean	26.6	73.2	1.76	23.5
SE	2.6	3.9	0.01	1.0

Table 4.2. Esophageal temperature (T_{es}) thresholds for cutaneous blood velocity (CBV), eccrine sweating ($\dot{E}_{sw}$) and ventilation ($\dot{V}_E$) during passive warming of college aged males immersed to the level of the shoulders in a 40°C hot water bath. (NS=non significant; ‡ $p < 0.001$)

Participant	CBV Threshold (°C)	$\dot{E}_{SW}$ Threshold (°C)	$\dot{V}_E$ Threshold (°C)
1.	36.73	36.95	37.38
2.	36.95	37.05	37.57
3.	37.06	37.09	37.98
4.	36.69	36.71	37.96
5.	37.23	36.92	38.37
6.	36.75	37.01	37.75
7.	36.87	36.97	38.35
Mean	36.90	36.96	37.91
SE	0.07	0.04	0.13
	•--------NS--------•		
		•----------‡----------•	

Figure 4.1. Participants (n=7) mean responses for (A) esophageal temperature (T_{es}) and (B) forehead skin temperature (T_{fs}) each as a function of time during body warming in a 40°C hot water immersion (NS= Non Significant; * $p< 0.05$; ‡ $p<0.001$; Error bars = ± SE).

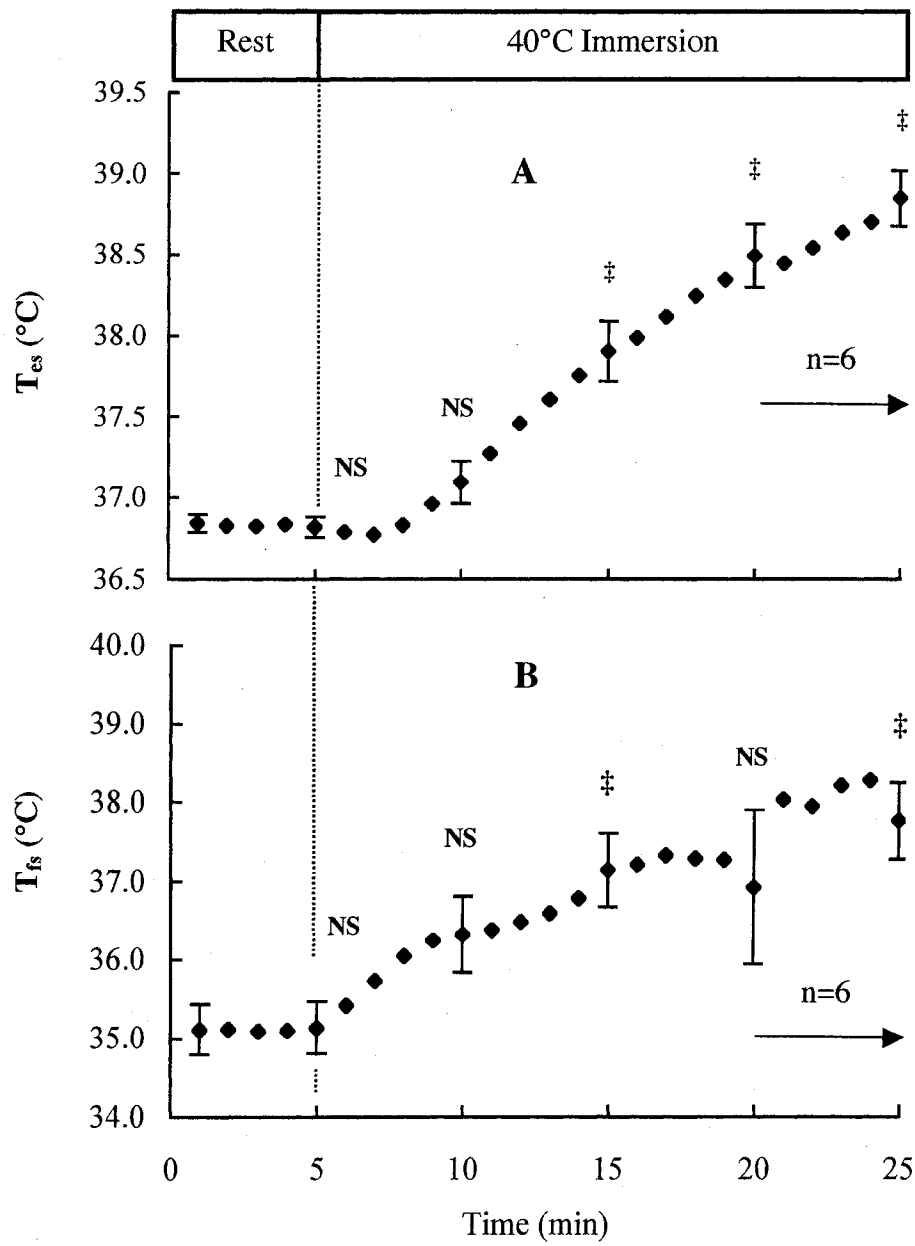


Figure 4.2. Participants (n=7) mean responses for (A) ventilation (V_E), (B) frequency of breathing (f) and (C) tidal volume (V_T) each as a function of time during body warming in a 40 °C hot water immersion (NS= Non Significant; * $p< 0.05$; $p<0.01$; Error bars = ±SE).

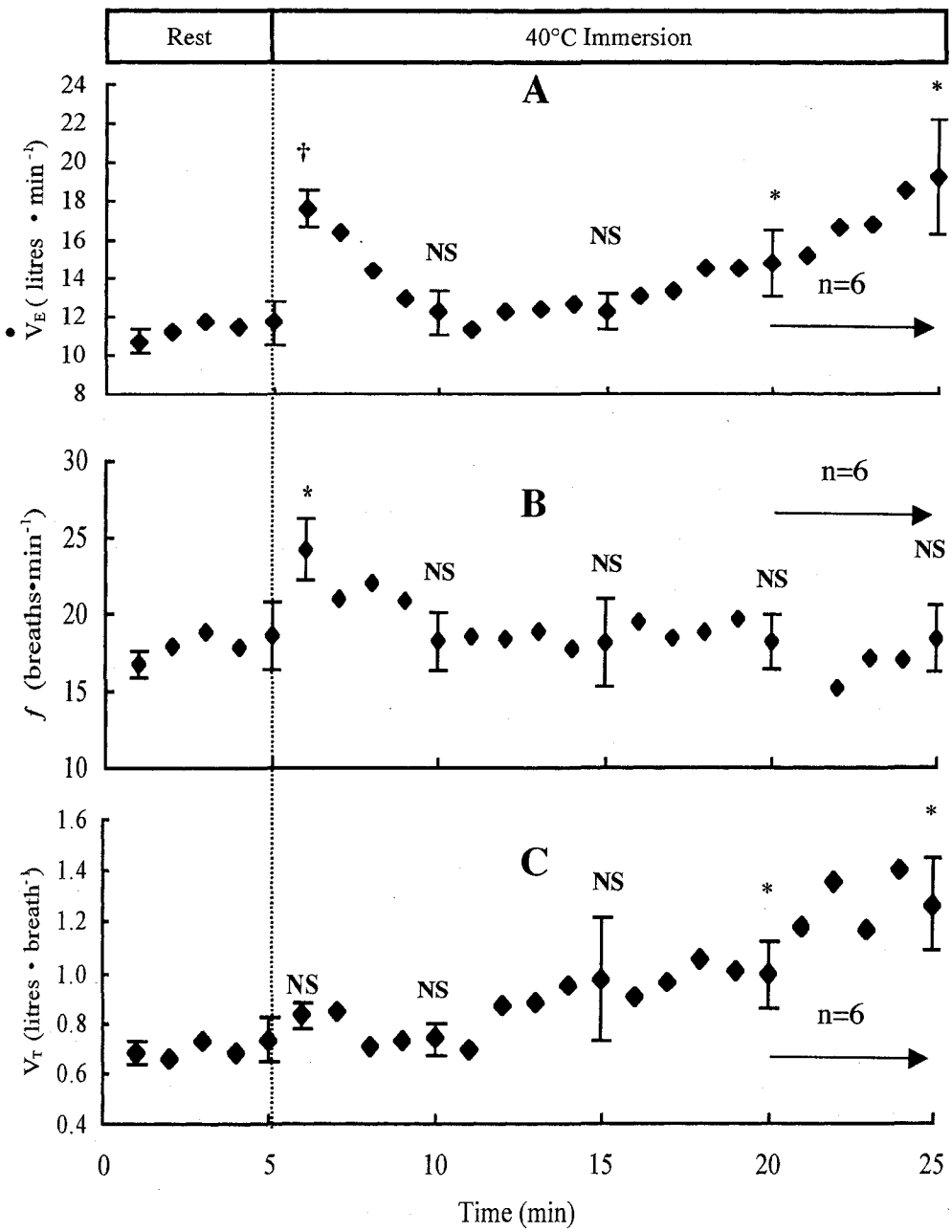


Figure 4.3. A sample participant's core temperature thresholds for (A) eccrine sweating ($\dot{E}_{SW}$), (B) cutaneous blood velocity (CBV), and (C) ventilation ($\dot{V}_E$) during body warming in a 40°C hot water bath. Arrows indicate the T_{es} thresholds for $\dot{E}_{SW}$, CBV, and $\dot{V}_E$ for this participant.

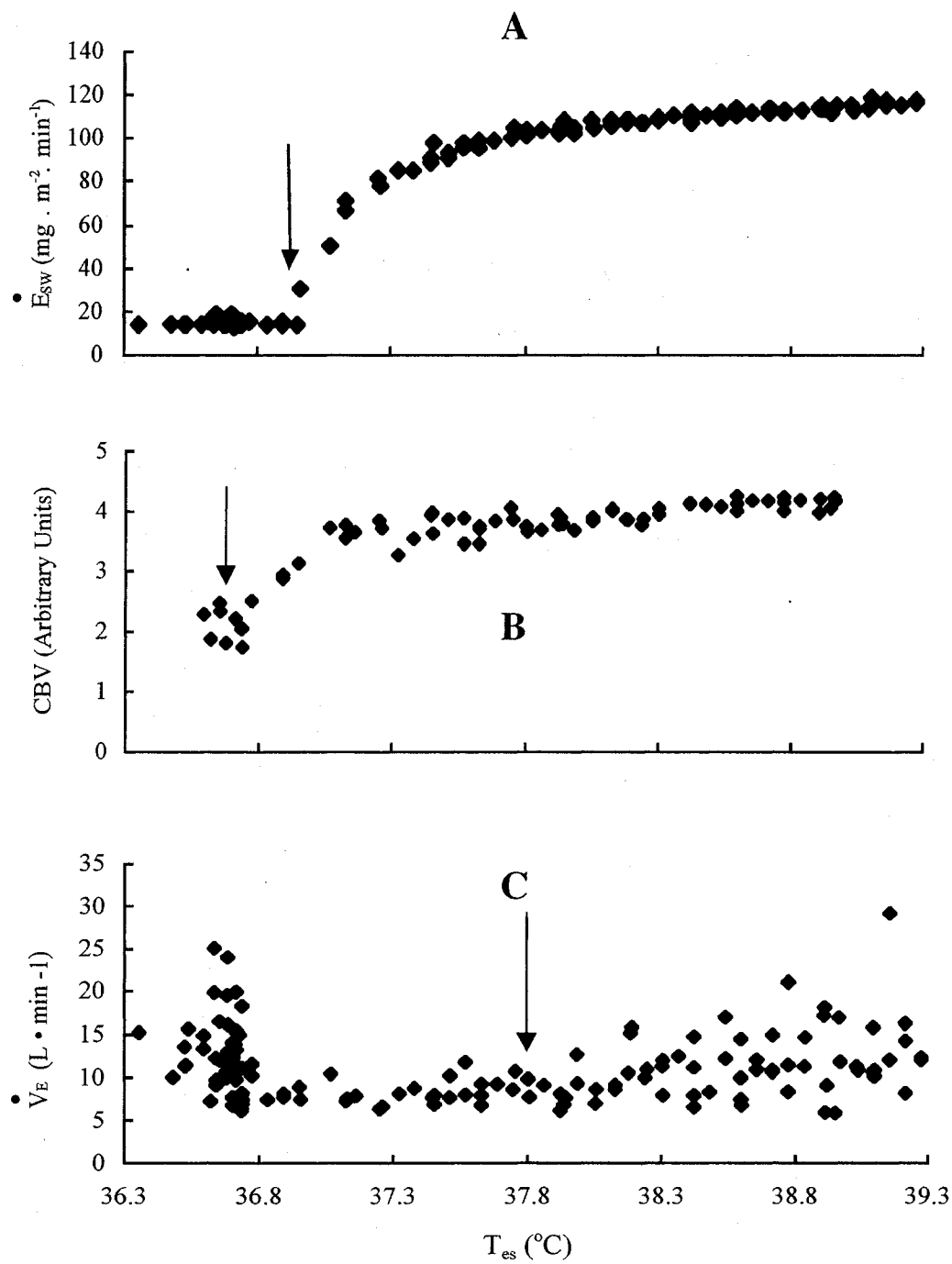


Figure 4.4. Mean (n=7) responses for (A) eccrine sweating ($\dot{E}_{SW}$), (B) cutaneous blood velocity (CBV), and (C) ventilation ($\dot{V}_E$) given as a function of mean esophageal temperature (T_{es}) during body warming in a 40°C hot water immersion. Arrows indicate the mean T_{es} thresholds for $\dot{E}_{SW}$, CBV, and $\dot{V}_E$ for the seven participants.

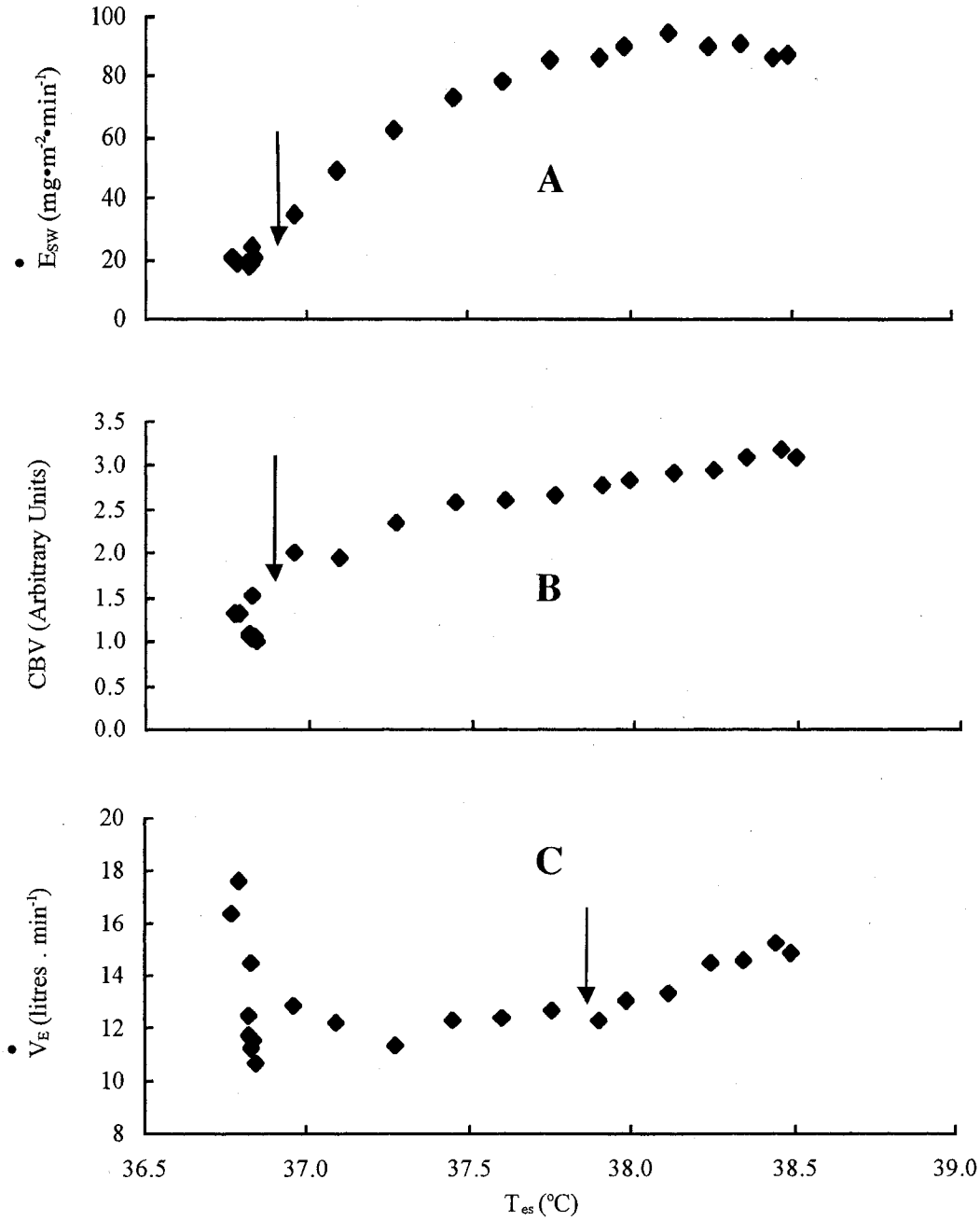


Figure 4.5. Mean (n=7) responses for (A) oxygen consumption ($\dot{V}O_2$), (B) end-tidal carbon dioxide tension ($P_{ET}CO_2$) and (C) respiratory exchange ratio (RER) each expressed as a function of time during body warming in a 40°C hot water immersion. Pre-immersion data was collected in the first 5 min and immersion data 5 to 25 min, (NS=Non-significant; † p< 0.01; ‡ p<0.001; Error bars = ± SE).

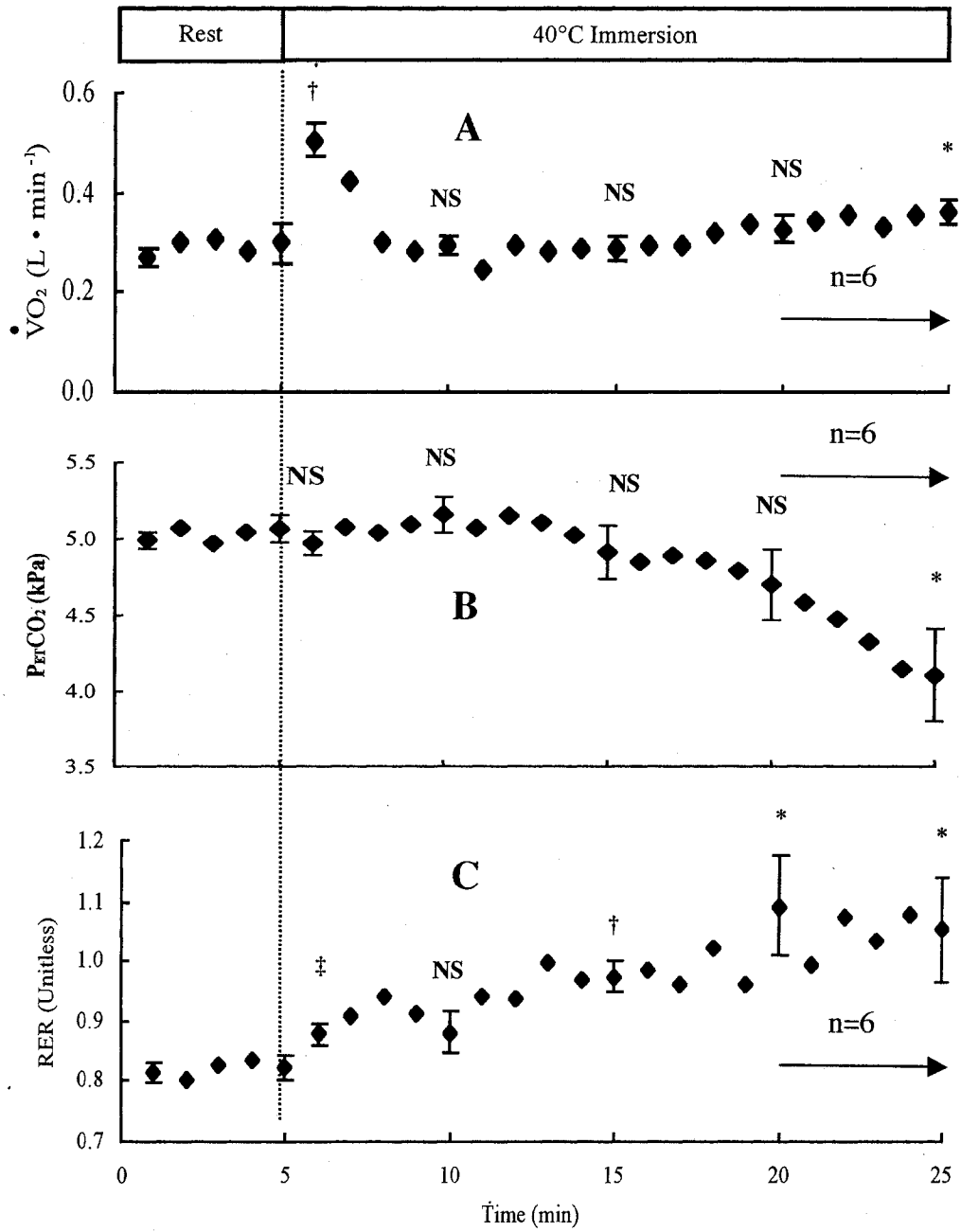


Figure 4.6. Participants (n=7) mean responses for (A) frequency of breathing (*f*) and (B) tidal volume (V_T) as a function of esophageal temperature (T_{es}) during body warming in a 40°C hot water immersion. Arrow indicates the mean T_{es} threshold for V_T for the seven participants.

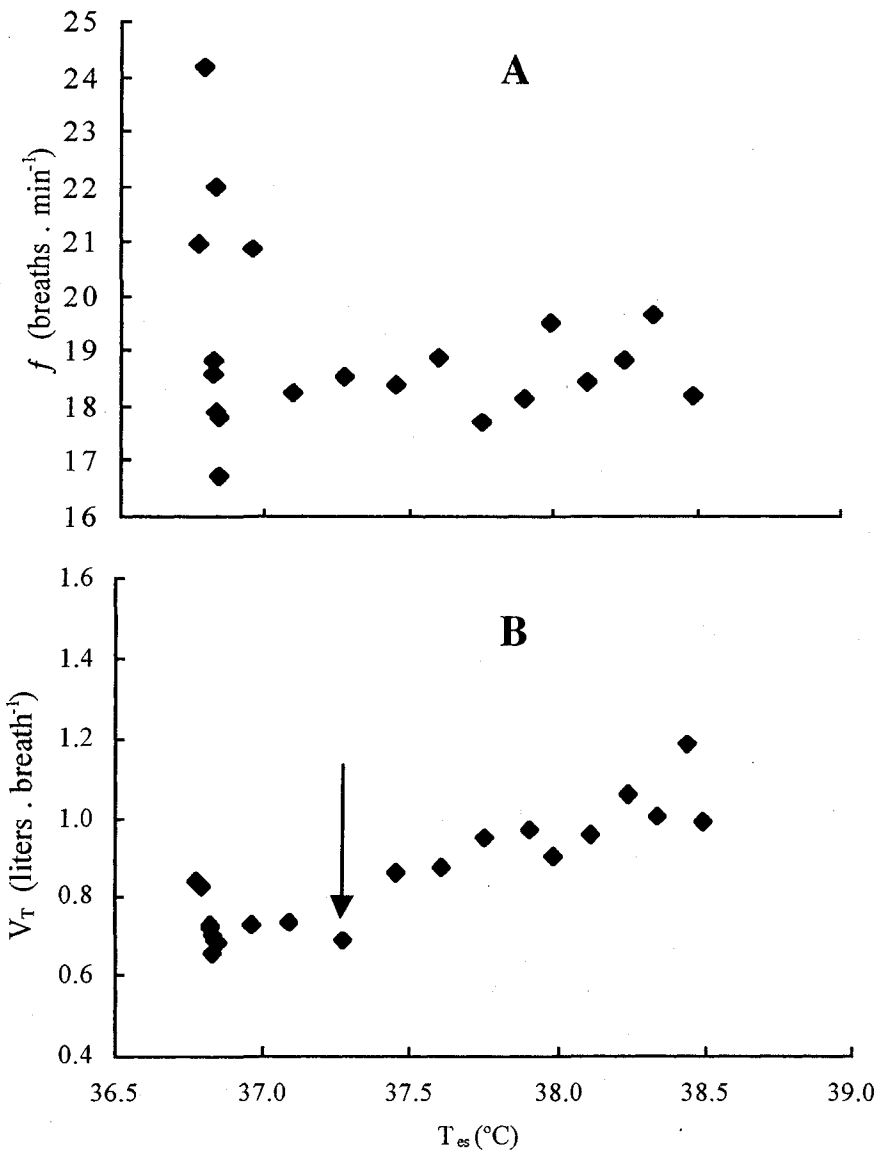
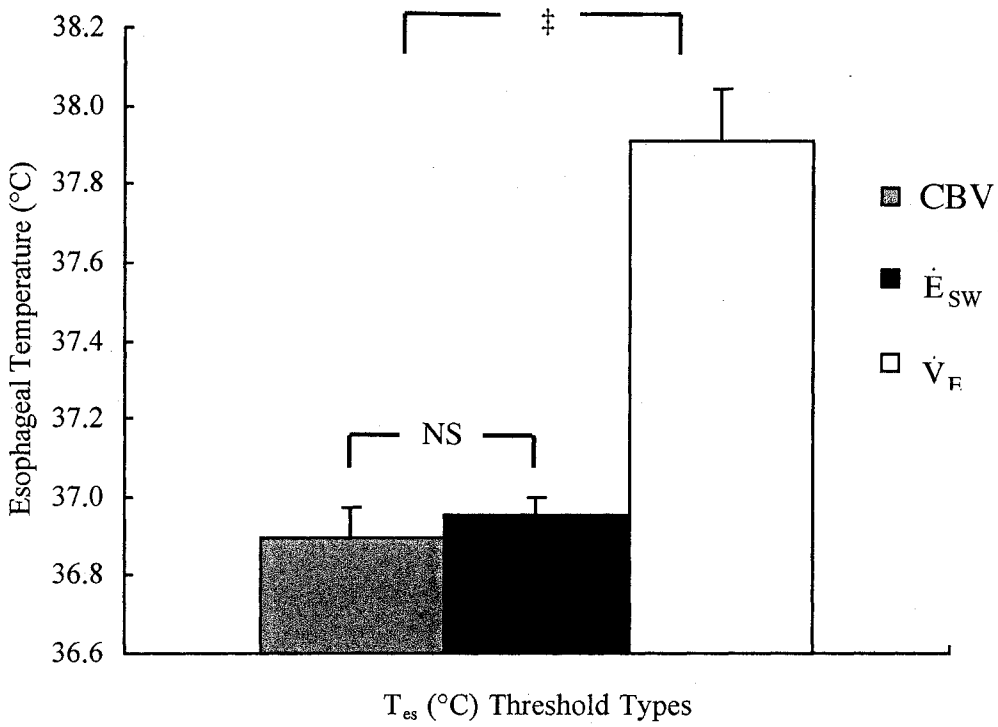


Figure 4.7. Mean esophageal temperature (T_{es}) thresholds (n=7) for cutaneous blood velocity (CBV), eccrine sweating ($\dot{E}_{SW}$), and ventilation ($\dot{V}_E$) during immersion in a 40°C bath (NS, Non Significant, ‡ $p < 0.001$; Error bars = +SE).



Chapter 5 Summary and Conclusions

5.1 Summary

The literature supported that T_{es} thresholds for ventilation, eccrine sweating and cutaneous blood flow were evident during hyperthermia in humans. However, a gap existed in the understanding of the T_{es} thresholds for cutaneous blood flow and eccrine sweating, and their relationship with T_{es} thresholds for ventilation. This thesis bridges a this gap and demonstrates how eccrine sweating and cutaneous blood veleocity T_{es} thresholds differ from ventilation thresholds during both exercise- and passively-induced hyperthermia.

The two studies showed that T_{es} thresholds for eccrine sweating and cutaneous blood velocity were significantly lower than those for ventilation. In addition, the exercise study showed ventilation thresholds were at lower core temperatures than during passive body heating. Both studies show that human ventilation appears to act as a thermoregulatory response when the body is actively or passively heated.

The mechanisms accounting for the different levels of core temperature at the thresholds for ventilation during passive versus active heating was not the focus of this thesis but is an area of future investigation. This raises the possibility that blood borne metabolites such as carbon dioxide or oxygen interact with temperature at both peripheral chemoreceptors and central chemosensitive areas to influence the level of ventilation in humans. Another possibility is non thermal factors during exercise lower the core

temperature thresholds for ventilaton. Future studies will be directed towards examining interactions between hypercapnia and hypoxia each with core temperature during hyperthermic rest or during exercise. Non-thermal factors can be examined also for their influences on these core temperature thresholds for ventilaton.

When human T_c is raised either during exercise or work, or when humans are exposed to high ambient temperatures, core temperature thresholds show that ventilation increases in proportion to core temperature. This is similar to eccrine sweating or cutaneous blood flow responses in hyperthermia. This supports that ventilation provides an additional thermolytic effector response that contributes to the thermoregulation of hyperthermic humans. This may be especially important for cranial thermoregulation in humans. In an applied context these ventilation responses and the associated respiratory heat loss can also be considered in heat stress scenarios to help prevent hyperthermia and heat exhaustion.

5.2 Limitation of Methods

(i) Indirect calorimetry

Indirect calorimetry measures respiratory gas exchange and can be employed to estimate energy production. Limitations explained by Ferrannini (4) stated that in situations where there is a post exercise oxygen consumption, a shift in acid-base balance such as acidosis or alkalosis, or hyperventilation/hypoventilation, gas movements reflect

other, non-metabolic processes, an indirect calorimetry for energy production estimation will be substantially invalidated. This thesis focused on gas exchange measurements and not energy expenditure and as such these limitations were not relevant. Another potential sources of error is CO_2 losses through the skin or non respiratory routes (4).

The technical requirements of indirect calorimetry can cause limitations of the procedure. Sensitive stable O_2 and CO_2 analyzers are needed for continuous sampling of expired air. To address this concern high precison O_2 and CO_2 analyzers were employed and in addition, a calibration routine was routinely employed using known gas mixtures. Some systems tend to trap or condense out the moisture of the expire air line feeding into the sensors (4) but this was addressed by using the proper desiccant procedure.

(ii) Resistance hygrometry

Resistance Hygrometry is influenced by changes in ambient conditions such as relative humidity, surface temperature, and convection currents which are each potential sources of measurement error (1). In the thesis all factors (i.e. air flow and ambient temperature) were keep constant for each subject. A limitation of this method is that it is useful for threshold detection, but not valid for expressing maximum or absolute levels of sweating. This problem is not relevant to this study since only thresholds were analyzed; a future solution to this problem, if quantification of sweating is needed, is to employ a heated humidity sensor that does not saturate with water vapour.

(iii) Laser Doppler estimation of cutaneous blood velocity

This technique measures blood velocity rather than blood flow. The flow term can only be employed if cutaneous capillaries do not dilate. Since how patent the cutaneous capillary were could not be assessed with the present methods, the term cutaneous blood velocity rather than cutaneous blood flow is employed throughout the thesis. Thus the units employed for CBV are arbitrary units. Normal values in resting conditions are difficult to express. Laser Doppler measures small areas of skin and this makes extrapolation of the measure to larger areas of skin somewhat dubious. In the study, a small region of the temples on the head was measured in both conditions for consistency and since with the full body immersion a limited number of measurement sites were available for this assessment.

(iv) Thermocouple temperature recordings and precision

During an analog to digital conversion the fidelity of the signal transduction is dependent on the precision of the recording device and on the sampling rate. The T-Type copper constantan thermocouples employed were limited to resolution of 0.1°C unless sampled at high frequency. In these studies temperatures were sampled at high frequencies of 333 kiloSamples/sec with a National Instruments SCXI 1102 32 Channel Thermocouple Input module. This allowed the expression of these temperatures to a resolution of 0.01°C.

(v) Heart rate monitoring

Averages of 3 beats were employed rather than beat-by-beat values. This limitation gave a lower resolution of the cardiac rate signal but did not influence the main outcome variables in the thesis.

(vi) Core threshold assessment method

As previously noted, the Vieth method assumes that the variables are best described by two rectilinear functions. A given function may be best described by one or more than two rectilinear functions. Also one needs to assume a slope of zero for the first regression line. Previous demonstration of these 3 types of thresholds, with a zero slope line prior to the threshold and a linear relationship for suprathreshold values confirm these assumptions were justified (2, 3).

5.3 Responses to the Research Hypotheses

The research hypotheses from Chapter 2, Section 2.7 state:

(i) Core temperature thresholds for ventilation are hypothesized to exist at higher core temperature thresholds than core temperature thresholds for sweating and cutaneous blood velocity during either passively or actively induced hyperthermia.

(ii) Exercise is hypothesized to reduce the core temperature thresholds for ventilation.

The first hypothesis was accepted because the core temperature thresholds for ventilation were at significantly higher core temperatures that those for eccrine sweating or cutaneous blood velocity both during passively or actively induced hyperthermia. The second hypothesis was also accepted because exercise lowered the core temperature threshold for ventilation relative that observed during passively induced hyperthermia.

5.4 Response to Testable Questions

Response to the testable questions from Chapter 2:

1. *How do T_{es} thresholds for $\dot{V}_E$ compare to T_{es} thresholds for eccrine sweat and cutaneous blood velocity during actively induced hyperthermia in humans?*

The first study supported that T_{es} thresholds for ventilation were significantly higher than T_{es} thresholds for eccrine sweating and cutaneous blood velocity with actively or exercise induced hyperthermia.

2. *How do T_{es} thresholds for $\dot{V}_E$ compare to T_{es} thresholds for eccrine sweating and cutaneous blood velocity during passively induced hyperthermia in humans?*

The second study also supported that T_{es} thresholds for ventilation were significantly higher than T_{es} thresholds for eccrine sweating and cutaneous blood velocity with passively induced hyperthermia.

3. How do T_{es} thresholds for ventilation compare between active and passive heating protocols in humans?

The esophageal temperature thresholds for ventilation were ~ 37.4°C (Table 3-2) in actively induced and ~ 38.0°C (Table 4-2) in passively induced hyperthermia. The difference of thresholds between protocols suggests when core temperature acts alone it has a less pronounced influence on ventilation than it does during actively induced hyperthermia.

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Chapter 6 Overall Thesis References (Alphabetical)

Overall Thesis References (Alphabetical)

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