THE EFFECTS OF HYPOXIA AND CORE TEMPERATURE ON VENTILATION DURING LOW INTENSITY EXERCISE

by

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ABSTRACT

The independent and combined effects of hypoxia and elevated esophageal temperature (T_{es}) were investigated for their effects on the level and kinetics of exercise ventilation ($\dot{V}_E$). In either a 'hyperthermic' T_{es} or a 'normothermic' T_{es} session, 11 college-aged, healthy males were immersed to the shoulders and pedalled on an underwater cycle ergometer at a steady-state oxygen consumption ($\dot{V}O_2$) of 0.87 $L \cdot min^{-1}$ (SD 0.07). Following a 30-min rest and 20-min warm-up, a 30-min steady-state cycling period was divided into three 10 min gas phases when participants inhaled: air (Euoxia 1 (E1)), hypoxic gas (12 % O_2 and 88 % N_2 (H1)), and air (Euoxia 2 (E2)). End-tidal CO_2 ($P_{ET}CO_2$) was maintained at an isocapnic level of 5.19 kPa (SD 0.71) throughout the exercise. Venous blood samples were drawn at rest and 5 min into all gas phases. Results showed a significant increase in $\dot{V}_E$ during all hyperthermia conditions ($0.01 < P < 0.048$), however, during hyperthermic hypoxia there was a disproportionate and significant ($P = 0.017$) increase in $\dot{V}_E$ relative to normothermic hypoxia. This was the main explanation for a significant core temperature and gas type interaction ($P = 0.012$) for $\dot{V}_E$. A main effect of core temperature ($P = 0.007$) was evident on ventilation frequency (f_v) with an increased rate of breathing in hyperthermic relative to the normothermic exercise. This gave evidence of a thermally-induced tachypnea which corresponded to significant decreases in inspiratory time (T_I) ($P = 0.035$) and expiratory

time ($P = 0.014$) and was independent of any changes in tidal volume (V_T) ($P = 0.801$). As such inspiratory flow ($V_T \cdot T_I^{-1}$) was significantly increased in hyperthermic- relative to normothermic ($P = 0.003$) exercise, an increase that was pronounced ($P = 0.013$) during hyperthermic hypoxia. A significant reduction of the time constants (τ) for $\dot{V}_E$ was evident ($P = 0.032$) during the onset of exercise under the hyperthermic as compared to the normothermic condition. This reduction in τ was associated with an increase in T_{es} ($R^2 = 0.829$, $P = 0.011$) but not in skin temperature. Between core temperature levels there were no significant changes in τ for the $\dot{V}_E$ response from euoxic to hypoxic steady-state exercise. From normothermic to hyperthermic exercise increases of $\dot{V}_E$ in E1 were 9.4 % (SD 9.7) and not significantly different than the 6.9 % (SD 10.7) increase in $\dot{V}O_2$. However in H1, $\dot{V}_E$ and $\dot{V}O_2$ increased by 29.2 % (SD 25.5) and 13.5 % (SD 10.1), respectively, which bordered a significant difference ($P = 0.056$). No changes in lactate or potassium (K^+) levels were evident across all gas type and core temperature conditions. In conclusion, these results suggest the following: 1) During low intensity, steady-state exercise an elevated T_{es} caused an increased $\dot{V}_E$, which was mediated by an increased f_v. 2) The addition of hypoxia during hyperthermic exercise caused a multiplicative increase in $\dot{V}_E$ which corresponded with a multiplicative increase in $V_T \cdot T_I^{-1}$. This would suggest the possibility of a core temperature mediated stimulation of the peripheral chemoreceptors. 3) An increased T_{es} during the onset of exercise but not during the transition from low intensity euoxic to hypoxic exercise shortened the time course of the $\dot{V}_E$ response. 4) Oxygen consumption, K^+ and lactate did not appear to be significant mediators of the augmented hyperthermic hypoxic $\dot{V}_E$ response. Overall the results

support the hypothesis that temperature plays a significant role in the control of ventilation, particularly during hypoxic exercise.

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ABBREVIATIONS AND ACRONYMS

The following abbreviations, definitions and units have been used throughout this thesis, in addition to those abbreviations commonly accepted.

ANOVA ..... analysis of variance
BSA ..... body surface area
CA ..... carbonic anhydrase
CI ..... 95 % confidence interval
cm ..... centimeter
CNS ..... central nervous system
CO_2 ..... carbon dioxide
D ..... Cook's distance values
E1 ..... euoxic exercise period
E2 ..... euoxic recovery exercise period
f_v ..... ventilation frequency
h ..... hour
H^+ ..... hydrogen ion
H1 ..... hypoxic exercise period
H_2O ..... water
$H_2CO_3^-$ ..... carbonic acid
HCO_3^- ..... bicarbonate ions
HR ..... heart rate
HVR ..... hypoxic ventilatory response
I_{max} ..... overall resting body insulation
I_{ex} ..... 40 % of I_{max}
K^+ ..... potassium ions
kcal ..... kilocalorie
kg ..... kilogram
kPa ..... kiloPascal
L ..... litre
LM ..... low-moderate intensity exercise
m ..... metre
$\dot{M}$ ..... metabolic heat production
MFT .... mean subcutabeous fat thickness
MH ..... moderate-high intensity exercise
min ..... minute
mm ..... millimetre
mM ..... milliMolar
mV ..... milliVolt
ml ..... millilitre
NE ..... norepinephrine
N_2 ..... nitrogen
O_2 ..... oxygen
P value ..... alpha value
P_aCO_2 ..... arterial CO_2 pressure
P_aO_2 ..... arterial O_2 pressure
$P_{ET}CO_2$ ..... end-tidal CO_2 pressure
$P_{ET}O_2$ ..... end-tidal oxygen pressure
pH_a ..... arterial pH
pH_e ..... extracellular pH
pH_i ..... intracellular pH
RER ..... respiratory exchange ratio
rpm ..... revolutions per minute
s ..... second
$\dot{S}$ ..... rate of heat storage
S_aO_2 ..... arterial oxygen content
SBC ..... selective brain cooling
SNS ..... sympathetic nervous system
SD ..... standard deviation
SS ..... sum of skinfolds
τ ..... time constant
t ..... time
T_{es} ..... esophageal temperature
T_E ..... expiratory time
T_I ..... inspiratory time
T_{sk} ..... skin temperature
T_w ..... water temperature
$\dot{V}CO_2$ ..... CO_2 production
$\dot{V}_E$ ..... ventilation

$\dot{V}_E(t)$ ..... the change in $\dot{V}_E$ at any given time

$\dot{V}_E(ss)$ ..... difference between the 1st and 2nd steady-state $\dot{V}_E$ exercise level

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

$\dot{V}O_{2peak}$ ..... peak oxygen consumption

V_T ..... tidal volume

VT_1 ..... first ventilation threshold

VT_2 ..... second ventilation threshold

V_T/T_I^{-1} ..... inspiratiry drive

W ..... watts

yr ..... year

μL ..... microlitre

°C ..... degrees Celcius

ϕ_1 ..... phase 1 of exercise ventilation

ϕ_2 ..... phase 2 of exercise ventilation

ϕ_3 ..... phase 3 of exercise ventilation

% ..... percent

~ ..... approximately

TERMS AND DEFINITIONS

Active hyperthermia: An exercise-induced hyperthermia

Aortic body: Group of chemoreceptor cells between the aorta and pulmonary artery sensing the arterial oxygen pressure, arterial carbon dioxide pressure and pH of arterial blood.

Arterial baroreceptors: Stretch receptors in wall of carotid sinus and arch of aorta, sensing arterial blood pressure continuously.

Arterial oxygen saturation: Concentration of oxygen in the arterial blood, mostly in red cells, dependent on hemoglobin concentration and partial pressure of oxygen.

Blood brain barrier: Capillaries of cerebral circulation have a uniquely restricted permeability to larger non-lipid molecules. Not present in specific areas. Structurally made up of glial cells.

Body temperature: The combined core and skin temperature

Carotid body: Group of cells containing chemoreceptors close to internal carotid artery that constantly sense the levels of arterial oxygen pressure, arterial carbon dioxide pressure and pH of arterial blood.

Central chemosensitive areas: The primary chemical control areas of regular breathing. They are located in the ventro-lateral medulla in close contact to cerebrospinal fluid and responds to increases in arterial carbon dioxide pressure

Central respiratory control centre: The control centre is located in the brain stem and consist of the medullary respiratory centre, the apneustic centre and the pneumotaxic centre.

Core temperature threshold for ventilation: A core temperature level past which ventilation increases with increasing core temperature.

Core temperature: Mean temperature of the thermal core of the body

Dorsal respiratory group: This group controls the basic rhythm of breathing and regulates inspiration

Eccrine Sweating: A response of the eccrine sweat glands to a thermal stimulus.

End-tidal carbon dioxide pressure: Alveolar carbon dioxide gas tension at the end of a normal expiration.

Evaporative heat loss: Evaporative heat transfer from the body to the ambient air by evaporation of water from the skin and the surfaces of the respiratory tract.

Expiratory time: The length of single expiration measured in seconds.

Heart rate: The rate at which the heart beats in beats per min.

Heat storage: The rate of gain or loss of heat associated with change in body temperature or body mass.

Hyperpnea: Rapid and deep breathing associated with metabolic changes.

Hyperthermia, induced: The state of hyperthermia produced purposefully by an increase in heat load and/or inactivation of heat dissipation by physical and/or pharmacological means.

Hyperthermia: The condition of a temperature regulator when core temperature is 1°C above its set-range specified for the normal active state of the species.

Hyperventilation: Excessive breathing; greater rate and/or depth than required for metabolic needs.

Hypoxia: A condition of low arterial oxygen pressure within the body

Hypoxic ventilatory response: The hyperventilation response associated with decreasing levels of arterial oxygen pressure.

Inspiratory flow: A measure of the total amount of air (tidal volume) inspired as a function of the time to inspire.

Inspiratory time: The length of a single inspiration measured in seconds.

Low intensity exercise: Exercise at ~ 20-40 % of an individuals VO_{2peak}

Metabolic heat production: Rate of transformation of chemical energy into heat in an organism, usually expressed in terms of unit area of the total body surface

Metabolic rate: The total energy production in an organism per unit surface area

Metabolism: The transformation of chemical energy into work and heat.

Oxygen consumption: Volume of oxygen used by body in each minute expressed in STPD. Varies directly with the level of activity in which one is engaged.

Passive hyperthermia: Rendering of the body to a hyperthermic state by passive means (i.e. heating in elevated water or air temperature)

Peripheral chemoreceptors: Chemical receptors located at the bifurcation of the common carotid arteries. They respond to decreased arterial oxygen pressure, increased arterial carbon dioxide pressure, and decreased pH.

Pneumotaxic centre: This centre is located in the upper pons and appears to be responsible for the cessation of inspiration thereby contributing to the control of ventilation frequency.

Q_{10} effect: The ratio of the rate of a physiological process at a particular temperature to the rate at a temperature 10°C lower, when the logarithm of the rate is an approximate linear function of temperature.

Respiratory alkalosis: Increase in plasma pH above 7.4 caused by reduced levels of carbon dioxide; usually induced by excessive ventilation of pulmonary alveoli, i.e. hyperventilation.

Respiratory evaporative heat loss: Heat dissipated by exhalation of air saturated with water vapour.

Respiratory exchange ratio: Defined as ratio of volume of CO_2 exhaled to volume of O_2 consumed.

Selective brain cooling: Lowering of brain temperature, either locally or as a whole, below aortic temperature.

Set-point: The value of a regulated variable which a healthy organism tends to stabilize by the process of regulation.

Skin temperature: The temperature at the surface of the skin at a specific site

Steady-state: Condition when variables are not changing with time.

Temperature sensitive: Descriptive of thermoresponsive neural structures with the implication that the neural elements involved provide specific temperature signals.

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. Deep breathing is also named second phase panting since it is usually preceded by a phase of typical panting (rapid shallow breathing).

Thermal panting: Open-mouthed thermal tachypnea.

Thermal tachypnea: A rapid ventilation frequency accompanied by an increase in ventilation minute volume and, sometimes, a decrease in tidal volume, in response to a thermoregulatory need to dissipate heat. Also known as a thermal polypnea.

Thermoeffectors: An organ and its function, respectively, which affects heat balance in a controlled manner as part of the process of temperature regulation.

Tidal volume: Volume of air entering and leaving the lungs with each breath.

Time constant: The time in which an exponential process is 63% complete, represented by (τ).

Ventilation: A common measurement of pulmonary ventilation, it is the amount of air inspired or expired each minute, calculated as a product of tidal volume and frequency of respiration.

Ventilation frequency: The number of breathes per minute.

Ventilation/perfusion ratio: Relationship between alveolar ventilation and blood flow through alveolar capillaries.

Ventilatory kinetics: Time dependent behaviour of ventilation responses to different stimuli.

Ventral respiratory group: This area regulates expiration, but is inactive during normal breathing.

$VO2_{PEAK}$: A measurement of peak oxygen uptake during physical activity which will fall between 66% and 86% of an individual's maximal value for oxygen uptake.

CHAPTER 1 THESIS OVERVIEW

An anomaly in human physiology that has existed for over a century is how ventilation is controlled during exercise (1, 3). Both metabolic (4, 6, 7) and non-metabolic neural modulators (2, 5) have been implicated in the regulation of exercise ventilation. It is also apparent that there is no single hypothesis that can explain each of the phases (2) of exercise ventilation. Furthermore, there are many confounding factors that can influence ventilation during exercise and rest. Two of the known modulators influencing human ventilation are elevated body temperature and hypoxia. The independent and combined effects of hypoxia and hyperthermia on human exercise ventilation are the focus of this thesis.

The content of this thesis is as follows. Initially a review of the mechanisms of the regulation of body temperature is given for homeotherms and how these relate to hyperthermia. Next, the phases of exercise ventilation are described, followed by a review of several hypotheses on the control of human exercise ventilation. A review of the control of ventilation during hyperthermia and hypoxia are subsequently given in addition to the effects of hypocapnia on ventilation. The literature review concludes with a section that illustrates that there are independent and combined effects of hypoxia and exercise on ventilation. The objectives of the thesis studies are then stated as an

examination of the independent and combined effects of hypoxia and hyperthermia on human exercise ventilation. At the conclusion of the literature review, research hypotheses based on the evidence available in the current literature are given together with testable questions that are specifically addressed in studies presented in Chapter 3, 4 and 5.

Chapter 3 investigated the independent and combined effects of hypoxia and elevated core temperature on the level of exercise ventilation and its components. In addition Chapter 3 examined the effects of hypoxia and core temperature for their influence on the timing of ventilation and the inspiratory flow. Chapter 4 investigated the effects of core temperature on the kinetics of the ventilatory response from rest to low intensity exercise and from euoxic to hypoxic low intensity exercise. Finally, Chapter 5 investigated the potential effects of changes in metabolic rate and blood borne metabolites on low intensity steady-state exercise ventilation during hypoxia and hyperthermia.

The thesis is concluded with a final Chapter 6, which responds to the research hypotheses and testable questions, as stated in Chapter 2.

Reference lists are given at the end of each chapter and an overall reference list is given in Chapter 7.

1.1 References

1. **Dejours P.** Control of respiration in muscular exercise. In: *Handbook of Physiology*, edited by Society AP. Washington, DC: Williams & Wilkins, 1964, p. 631-648.

2. **Dejours P.** The regulation of breathing during muscular exercise in man: A neurohumoral theory. In: *The regulation of human respiration*, edited by Cunningham DJC and Lloyd BB. Oxford, England: Blackwell Scientific Publications, 1963, p. 535.

3. **Dempsey JA, Vidruk EH, and Mitchell GS.** Pulmonary control systems in exercise: update. *Fed Proc* 44: 2260-2270, 1985.

4. **Evans AB, Tsai LW, Oelberg DA, Kazemi H, and Systrom DM.** Skeletal muscle ECF pH error signal for exercise ventilatory control. *J Appl Physiol* 84: 90-96, 1998.

5. **Strange S, Secher NH, Pawelczyk JA, Karpakka J, Christensen NJ, Mitchell JH, and Saltin B.** Neural control of cardiovascular responses and of ventilation during dynamic exercise in man. *J Physiol* 470: 693-704, 1993.

6. **Wasserman K, Van Kessel AL, and Burton GG.** Interaction of physiological mechanisms during exercise. *J Appl Physiol* 22: 71-85, 1967.

7. **Wasserman K, Whipp BJ, Casaburi R, and Beaver WL.** Carbon dioxide flow and exercise hyperpnea. Cause and effect. *Am Rev Respir Dis* 115: 225-237, 1977.

CHAPTER 2 LITERATURE REVIEW

2.1 Temperature Regulation

2.1.1 Thermoregulation in homeotherms

Temperature regulation is largely an autoregulatory system in the human body that functions to help maintain thermal homeostasis. Despite regional internal and external heat loss or heat gain, homeotherms maintain their body temperature within narrow limits. DuBois (33) in his early work proposed the human body functioned optimally in an oral or rectal temperature range of 36.2°C to 37.8°C. Subsequently, under adverse environmental or experimental conditions, the human body was shown to function in a greater range of internal core temperatures from ~31°C to ~41°C (93). Ted Hammel (45) at the John B. Pierce Foundation at Yale described the first set-point model of the thermoregulation by which a homeotherm's body temperature is regulated.

2.1.2 The set-point model of thermoregulation

In Hammel's (45) set-point model of thermoregulation the regulated variable is core temperature and the model includes three main components in a negative feedback loop. These components are temperature sensitive neurons, a proportional controller in

the central nervous system (CNS), and a group of thermoregulatory effectors (45). On the afferent side of this reflex loop the temperature sensitive neurons feed information about peripheral (skin) temperature and the temperature in the CNS to the hypothalamus. In the model (45), the hypothalamus acts as a proportional controller that compares the signals from these temperature sensitive neurons to a set-point or a hypothetical reference signal. If there is a difference between these incoming signals and the hypothesized set-point, or reference temperature, efferent signals are sent to the appropriate thermo-effectors that help bring the body temperature back towards the set-point. The efferent signals are sent in proportion to the difference between the incoming afferent signals and the reference signal. In this negative feedback system, homeotherms are able to maintain a fairly consistent core temperature despite significant changes in ambient temperature. The primary autonomic thermoregulatory effectors that enable this temperature regulation include variations in peripheral vascular tone and consequent variations in skin blood flow, eccrine sweating, and shivering plus non-shivering thermogenesis (60).

2.1.3 Relative influences of skin and core temperature on thermoregulatory responses

Initially there were two general classes of temperature sensitive neurons described in humans and other mammals (49). One class of temperature sensitive neurons were thought to function as cold sensitive receptors which elicit maximal responses near ~25°C, while the other class were thought to function as warm sensitive receptors which elicit maximal responses near ~40°C (49). Later work suggests there is one group of temperature sensitive neurons with increased activities at low and high temperatures (12).

To be consistent with the past literature these are described as cold and warm temperature sensitive neurons.

Temperature sensitive neurons are practically grouped into peripheral and central temperature sensitive neurons. The peripheral temperature sensitive neuron activity is represented by skin temperature and central temperature sensitive neuron activity is represented by core temperature. As such, these groupings allow a study of the relative influences of these temperature sensitive neurons' activities on the magnitude of thermoregulatory responses. In this context, both dynamic and static activities of these temperature sensitive neurons are quantified to assess their proportion of the afferent input to the integrative centres in the CNS. Within the CNS, the hypothalamus and other lower level centres, integrate the afferent information about central and peripheral temperature levels. Subsequently efferent signals are sent to the thermoeffectors that are proportional to the deviation or offset from a hypothetical reference temperature level that is at ~37°C. This reference core temperature level varies slightly in accordance with the bodies circadian rhythms with the lowest levels in the morning and the highest in the late afternoon (121). Within the framework of this temperature regulation model, core temperature thresholds exist where thermoregulatory responses are evident as the core temperature is increased or decreased from the reference level of ~37°C.

Core temperature thresholds for thermoregulatory responses can be influenced by both changes in skin and hypothalamic temperature (7, 10, 45). Specifically, Benzinger et al. (7, 10) demonstrated that the thresholds for the onset of thermoregulatory effector

responses such as eccrine sweating and metabolic heat production (i.e. shivering) were sensitive to the skin temperature level. For thermolytic heat loss responses a lower skin temperature delayed their onset and for thermogenic heat production responses a higher skin temperature delayed their onset (7, 10). The rationale for these observations was that reciprocal inhibition of warm and cold temperature sensitive neurons was evident (11). As core temperature increased warm sensitive central neurons were activated that promoted thermolytic responses, however, the onset of the thermolytic response or core threshold, was delayed to a higher core temperature if the skin temperature was held at a lower temperature level. This was reasoned to be due to higher activity of peripheral temperature sensitive neurons that acted to inhibit the thermolytic pathway with elevated body temperature. A full description of this model is given by Bligh (11).

Benzinger (8) proposed that the skin and central (core) thermoreceptors both contributed to thermoregulation, but that core temperature had a more predominant role. One experiment Benzinger (8) employed was to have his subjects sit in a heated chamber at 45°C, and swallow ice continuously so the core temperature sensors would signal a drop in temperature. He observed an attenuation of the sweating rate despite the external air and skin temperature remaining constantly elevated. He concluded from this that the central thermosensors appeared to have dominance over the peripheral (skin) thermosensors in body temperature regulation for thermolytic responses.

As Benzinger showed above (7, 10) skin temperature and core temperature in a case study on a single subject (7), indicated that when skin temperature was below 33°C,

the onset and rate of sweating was delayed and diminished with increasing core temperature. This suggested a fall in skin temperature below 33°C shifted the core temperature threshold for sweating to a higher value. In this case, it appeared that skin temperature and core temperature had a dual role in controlling evaporative heat loss or sweating but it was not clear what their relative importance was in the control of this thermolytic response. Conversely, Benzinger (7) showed that skin temperatures in the warm-reception range of 33°C to 38°C had no direct influence on evaporative heat loss through eccrine sweating. Wyss et al. (140) performed a similar experiment in which they looked at the effect of skin temperature on sweating rates by increasing the skin temperature of their subjects at different rates from a thermoneutral skin temperature of ~35°C to a maximum of ~40°C. Similar to Benzinger (7), they found the sweating rate to be virtually independent of skin temperature, however they did not look at the effects of skin cooling below 33°C. It appeared that there is a critical skin temperature threshold for the modulation of eccrine sweating is 33°C. Skin temperatures above this threshold appear to have no direct influence on evaporative heat loss, however, when core temperature rises if skin temperature is lower than 33°C there seems to be a blunting of the onset of eccrine sweating (139). In addition to his finding in humans for eccrine sweating, Benzinger (7, 9) found that increasing skin while cooling core temperature delayed the onset of cold-induced shivering thermogenesis. A problem with this initial finding arose in that humans cannot maintain a constant high skin and low core temperature for even a short period of time, so the phenomena being observed here was probably a transient response.

With the availability of new research techniques Jessen et al. (59) and Nagel et al. (88) were able to maintain changes in core temperature independently of changes in skin temperature. They did this by employing a large mechanical arteriole-venous shunt equipped with an extracorporeal heat exchanger that was connected to the aorta of a goat allowing for independent control of core and skin temperature. When core temperature was decreased there was a concomitant increase in shivering thermogenesis by more than 300 % despite very high skin temperature exceeding 43°C. A similar study by Kuhnen and Jensen (69) looked at the relative effects of decreasing skin temperature on shivering thermogenesis while maintaining a constant core temperature. Core temperature was kept constant at 38.8°C* in the goat while skin temperature was clamped at different temperatures ranging from 13 to 41°C. As skin temperature fell, heat production increased, although at a much lower rate than in the first series of experiments when core temperature was changed. It appears that at least in goats, core temperature seems to play a larger contribution to the control of heat production than skin temperature does. Jessen (59) quantified this relationship in terms of a ratio and found it to be 3:1 in favour of core temperature over skin temperature in the control of shivering thermogenesis in goats in the cold. The role of skin temperature on overall temperature regulation in the body for heat exchange therefore appears not to be a primary one in initiating the thermoregulatory effectors, more so it appears to play a secondary role once changes in core temperature occur. As mentioned previously, when core temperature deviates in either direction, opposing changes in skin temperature can blunt the thermo-effector responses decreasing

* ~39°C is a resting core temperature for a goat (69).

heat loss or gain. In summary, significant changes in skin temperature can cause a change in the core temperature threshold for thermoregulation responses.

2.1.4 Resetting of the thermoregulation set-point

There are several examples which illustrate the core temperature set-point from this model of temperature regulation can be reset (45). These include sustained thermal stress (45), sleep (7, 10), fever (64), circadian rhythms (41, 117) and the ovarian cycle (50, 51).

As illustrated during simple manipulations of skin temperature by Benzinger (7) and Hammel et al (45) the set-point of temperature regulation was suggested to be adjustable. In a study on the effects of manipulations in hypothalamic and skin temperatures in the rhesus monkey and resting dog, results indicated that increases or decreases in skin temperature as a result of changing environmental temperatures elicited thermoregulatory effector responses despite core temperature remaining fairly constant throughout these changes (45). It was also shown these effector responses were in proportion to the changes in skin temperature (45). Hammel et al. (45) proposed these mechanisms occurred as a result of changes in the steady state and phasic firing of cold and warm skin receptors located in the hypothalamus. This would cause the set-point of temperature regulation to shift (elevates in a cold environment and lowers in a warm environment) thereby driving the thermoregulatory effector responses while maintaining a fairly steady-state core temperature (45).

Further evidence has been found to support Hammel et al.'s (45) adjustable set-point model in studies looking at the effects of fever. The onset of fever is marked by a pyrogen mediated elevation of the set-point above the core temperature. In mammals and birds a drop of core temperature below the elevated set-point during a fever results in a load error and a stimulation of the cold sensors, which causes paradoxical skin vasoconstriction and shivering (65). During normal thermoregulation, core temperature eventually rises in fever as a result of the shivering induced thermogenesis and eventually becomes equal to the elevated set-point. At this phase of fever the body ceases the paradoxical skin vasoconstriction and shivering but continues to protect the elevated set-point and core temperature (64).

Another example of the adjustable set point is evident during the luteal phase of the ovarian cycle in human females. Hessemer and Bruck (50, 51) found that body temperature is regulated about 0.5°C higher in the luteal phase than in the follicular phase of the menstrual cycle. The cause of this increase in threshold temperature was not fully elucidated but they have suggested a possible role of progesterone in the CNS as a mediator in this mechanism, as it has a concomitant increase during the luteal phase (50, 51). Progesterone has been found to cause an increase in body temperature in both females (58) and males (104).

A final example of the adjustable set-point is evident during the circadian rhythms of a standard 24 hour day. Stephenson et al. (7, 10) showed that the threshold for sweating and forearm vasodilatation decreased upon entering and during sleep and increased on awakening. From this finding they proposed that the set-point for temperature regulation varies throughout the 24 hour day in humans, with a significant fall during the sleeping hours (7, 10). The cause of these circadian fluctuations in core temperature thresholds have been unclear, some researchers have proposed that this is caused by variations in activity throughout the day (66), however other studies (39, 121, 133) have clearly shown that activity levels only play a minor role in these observed changes. It has been shown (54) that there appears to be a circadian rhythm in the sympathetic nervous system (SNS), which regulates sympathetic tone. Coincidentally the circadian rhythm of the SNS mirrors that of the core temperature thresholds for temperature regulation (i.e. sympathetic tone was lowest during sleep). This observation made by Stephenson et al. (117) was the basis for their proposal that the mechanism responsible for these observed differences may be the result of the relative inhibition of the sympathetic mediated noradrenergic outflow during sleep as compared with the waking hours. While there are several plausible explanations for the observed decrease in core temperature thresholds for temperature regulation during sleep there is still no finite explanation, it is clear however that the set-point for temperature regulation is adjustable.

While the set-point theory still remains to be a widely accepted model in humans describing temperature regulation, there are other hypotheses that have been proposed

that have modified some of the original postulates of this theory. The most notable alternate hypothesis is the null zone model of thermoregulation proposed by Mekjavic et al. (84), which is widely accepted as the temperature regulation model for other mammals (108).

2.1.5 Null zone for thermoregulation

Mekjavic et al. (84) presented evidence for the existence of a null zone of core temperatures in humans in which there is no eccrine sweating or shivering. Their findings are contrary to the traditional set-point model of temperature control that was developed almost half a century earlier (8, 45). The null zone of core temperature can be demonstrated by expressing thermoregulatory effector responses of heat production and heat loss as function of core temperature with a clamped skin temperature of ~28°C (84). More recently Lopez et al. (75) illustrated a range of core temperatures within which there is neither shivering nor eccrine sweating. It was suggested that within this null zone, temperature regulation depends only on variations in skin blood flow as function of variations in vasomotor tone (84).

The null zone hypothesis has been well established for many species other than humans. For example, camels have a null zone of almost 4°C in which their core temperature can deviate without significant thermoregulatory responses other than skin blood flow (110). In humans this hypothesis is controversial as previous studies (45, 60) have found that a set point exists in which rises or drops below this point will elicit a

shivering or sweating response. Cabanac and Massonnet (16) found this set point to exist in humans at a core temperature of ~37.3°C. Mekjavic et al. (84), however, replicating a similar experiment to that of Cabanac and Massonnet (16) observed a thermoneutrality zone of core temperature of about 0.6°C. They attributed this difference in their findings to the change in experiment protocol. Their subjects exercised to increase core temperature and then were cooled both in a constant temperature 28°C bath that allowed maintenance of a constant skin temperature. In Cabanac and Massonnet's (16) protocol the subjects were exposed to large changes in water temperature, which inevitably effected skin temperature and was suggested to confound their expression of thermoregulatory thresholds. Whether a core temperature null zone or point exists still remains an actively researched topic. In humans however, there does appear to be a significant range in which core temperature is regulated independent of increased shivering or eccrine sweating.

2.1.6 Behavioural control of thermoregulation

Behaviour is an important aspect that is often undervalued as a significant means of thermoregulation (108). Humans like other homeotherms prefer thermal conditions that allow for the maintenance of body temperature. Hensel (49) described this as the "thermal comfort zone" (49). The "thermal comfort zone" for humans would appear to exist at the thermoregulatory set-point or null zone (49). When humans are subjected to conditions which cause the body's temperature to deviate from this comfort region, temperature sensitive neural signals are relayed to the cerebral cortex causing conscious

measures by the body to bring core temperature back toward resting levels (15, 60, 107). Behavioural responses vary greatly depending on the type and severity of thermal stress, but the primary ones in both humans and animals include changes in locomotion (60), orientation (116), posture (42, 81) and social behaviour (107). In animals wallowing and saliva spreading are also common active behavioural measures in heat stress environments (57). The body also uses behaviour as a means of reducing the costs of autonomic thermoregulation such as shivering and sweating thereby reducing strain on the body (60).

Both autonomic and non-autonomic pathways can elicit behavioural responses to temperature changes in the body, although the majority of thermoregulation is under autonomic control by the hypothalamus and the CNS. It is evident that central temperature sensitive neurons have dominance over body temperature regulation (8, 59, 69), however, there appears to be other avenues of temperature regulation that involve the skin temperature sensitive neurons. Benzinger (8) also proposed that the nerve endings in the skin could act as sensory organs for the conscious centres of the cerebral cortex, bypassing the autonomic (unconscious) control centres of the hypothalamus. The conscious centres of the CNS can act as a defence mechanism to prevent any deviations in core temperature by sensing initial changes in the temperature of the external environment (via the skin thermoreceptors) and guide behavioural patterns to counteract the change.

Satinoff (108) reviewed the neuronal organization of complex thermoregulatory-guided behaviours. She has proposed that complex behavioural responses to thermal stresses are continually evolving. She presents that there are several competing patterns for homeostatic thermoregulation, not just a single-integrator model such as suggested by Hammel et al. (45) and Benzinger (9). Examples cited by Satinoff (108) amongst others, give evidence of this hierarchy of thermoregulation in cats and dogs which were shown to retain their ability to pant after body warming with spinal transection rostral to the midbrain (62). Also rabbits were able to maintain their body temperature by shivering despite a cervical section of their spinal cord (120). The hierarchy described in her model of behavioural temperature regulation suggests that the hypothalamus, the midbrain, the medulla and the spinal cord give a collective integration of afferent signals from body temperature sensitive tissues.

2.2 Control of Exercise Ventilation

2.2.1 Control of ventilation during exercise

During high intensity exercise it has been shown that ventilation increases approximately 15 fold from resting ventilation (124). This exercise-induced hyperpnea is a result of an increase in the rate of ventilation to match the increase in metabolic rate during exercise. Modulators responsible for this hyperpnea appear to be different from those for resting ventilation, as the normal modulators of resting ventilation such as arterial carbon dioxide arterial pressure (P_aCO_2), oxygen arterial pressure (P_aO_2) and arterial pH (pH_a) remain virtually unchanged during moderate intensity exercise (124). The cause of this hyperpnea associated with exercise has been examined in great detail, but to date, the mechanisms underlying human exercise ventilation remains to be clearly identified (32, 72, 124). Several hypotheses however have been suggested for this important form of respiratory stimulation, which possibly involve metabolic modulators and/or neurogenic inputs. The severity of the exercise-induced hyperpnea is also dependent on the intensity and duration of exercise (135).

Dejours (31) proposed that the magnitude of the exercise-induced hyperpnea could be apportioned into two general intensity levels. Low-Moderate (LM) intensity exercise at ~30-50 % of maximal work capacity described the first classification of exercise intensity. At this intensity the metabolic demand is mainly from skeletal muscle

(135). The body compensates by increasing ventilation to reach this metabolic demand. Increases in ventilation during LM intensity exercise are in linear proportion to increases in $\dot{V}O_2$ (124). Moderate-High (MH) intensity exercise at ~ 60-75 % of the subjects maximal work capacity is the second of Dejours' (31) exercise intensity classifications. Similar to LM intensity exercise, MH intensity exercise is marked by an initial increase in ventilation. However, during MH intensity exercise, once the anaerobic or lactate threshold is reached (also known as the first ventilation threshold (VT_1)) there is a subsequent isocapnic buffering period in which there is no discernable decrease in $P_{ET}CO_2$ and P_aCO_2 (125). A compensatory hyperventilation thus develops during this period causing ventilation to increase at a steeper rate than $\dot{V}O_2$ (125). This is subsequent to the isocapnic buffering period there is an even greater disproportionate increase in ventilation, which has been suggested to be the second ventilation threshold (VT_2), and is described in further detail below (82, 125).

Dejours (31) further divided the steady-state exercise session, at a given static exercise intensity, into three temporal ventilatory phases. "Phase 1"(ϕ_1) represents the initial, usually rapid ventilatory increase with the onset of exercise. This initial increase is evident for approximately 10 to 20 s (31, 127) and is suggested to be neurally mediated with little influence from the peripheral chemoreceptors (135). This was inferred by studies showing that hypoxia, a known stimulator of the peripheral chemoreceptors and consequently ventilation (27, 31, 87), and surgical resection of the carotid bodies (129) did not influence the magnitude or onset of this initial ventilatory response. "Phase II"(ϕ_2) represents the slower, exponential increase in ventilation after approximately 20

seconds of the onset of exercise and lasts about 2 to 3 minutes (137). It has been suggested to occur immediately following the change in mixed venous gas tensions due to the increased muscle metabolic rate after ϕ_1 (18). The carotid bodies are suggested to serve an important role in modulating ϕ_2 dynamics of the ventilatory response (129). A new steady state level of ventilation characterizes the final "phase III" (ϕ_3) as exercise continues at the same LM intensity level. At this stage there is a linear relationship between ventilation and $\dot{V}O_2$ (31, 135). This occurs with P_aCO_2 being maintained at, or fairly close to resting levels (35, 126).

There are only minor changes in ventilation during these temporal phases for LM intensity exercise (31, 136). However, for MH intensity exercise there is a gradual increase in ventilation during a prolonged ϕ_2 as compared to LM intensity exercise. This phenomenon is known as a "ventilatory drift", which was initially postulated by Martin et al. (80) to be a result of the increase in core temperature evident during MH intensity exercise. This was based on the finding that the exercise-induced hyperthermia was in-part responsible for the elevated ventilation during MH intensity exercise (95). However, Martin et al.'s (80) study showed that despite the influence of core temperature on exercise hyperpnea, it appears to have no role in mediating the ventilatory drift evident in a prolonged bout of MH intensity exercise. The exact mechanism of this ventilatory drift still remains to be elucidated.

Unlike steady-state LM exercise, if the exercise loads are progressively increased, during ϕ_3 of MH exercise there is a break in the linear relationship of $\dot{V}_E$ vs. $\dot{V}O_2$. As described above this is where VT_1 occurs and is generally at ~ 40-70 % of a persons maximal work capacity (82). A second ventilation threshold also exists, but unlike the first one is suggested to be mediated by neurogenic mechanisms (82, 111). The second ventilation threshold is characterized by an even steeper rise in the $\dot{V}_E$ vs. $\dot{V}O_2$ relationship and usually occurs at exercise intensities of approximately 70 % to 90 % of a persons maximal work capacity (82). Similar to VT_1 there are also several hypotheses that exist for VT_2.

2.2.1.1 Hypotheses for VT_1

There are several hypotheses for VT_1, but the mechanism for the disproportionate increase in ventilation and either $\dot{V}O_2$ or carbon dioxide production ($\dot{V}CO_2$) at VT_1 has not yet been identified. Four of the most prominent hypotheses are the lactate hypothesis, the hydrogen ion hypothesis, the CO_2 flow hypothesis, and the carotid body stimulation hypothesis. Potassium (K^+) and norepinephrine (NE) have also been implicated as possible modulators of the VT_1.

Briefly the lactate hypothesis is based on the accumulation of lactic acid in the extra cellular fluid of the body during heavy exercise (76). This is the point where lactate production by active tissues exceeds lactate removal in the plasma. Lactic acid at a physiological pH readily disassociates into lactate and hydrogen ions (H^+). According to

the Henderson-Hasselbach equation (1) where the hydration of CO_2 is catalyzed by carbonic anhydrase (CA),

$$CO_2 + H_2O \overset{CA}{\leftrightarrows} H_2CO_3^- \overset{CA}{\leftrightarrows} HCO_3^- + H^+ \quad \text{(Henderson-Hasselbach equation)} \ldots\ldots\ldots\ldots (2.1)$$

when there is an increase in H^+ the equilibrium shifts to the left producing more CO_2. Carbon dioxide can then act both directly on the peripheral chemoreceptors located in the aortic and carotid bodies and indirectly on the central chemosensitive areas in the brain by diffusing through the blood brain barrier. The central effect of increased CO_2 is mediated by the resultant decrements in pH of the cerebrospinal fluid. In each of these areas an increased level of CO_2 increases $\dot{V}_E$.

Glass et al. (40) however found some inconsistencies with this hypothesis. They found that under normal levels of muscle glycogen the lactate threshold appeared to occur at a similar $\dot{V}O_2$ levels as the VT_1. In subjects that were depleted of their glycogen stores prior to exercising they found however that the lactate threshold had shifted to a higher $\dot{V}O_2$ in relation to the VT_1. From this finding they suggested that lactate accumulation was not a controlling mechanism of the VT_1 during progressive exercise in humans. Similar findings were found by Heigenhauser et al. (48) whom also suggested that lactate accumulation while being a stimulus for $\dot{V}_E$ may not be the cause of the VT_1.

Oelberg et al. (91) and Evans et al. (36) indicated declining levels of intracellular and extracellular muscular pH (pH_i and pH_e) may contribute to increases in exercise ventilation. Oelberg et al. (91) proposed that pH_i is an independent stimulator of ventilation. In this experiment a bilateral lower extremity positive pressure cuff was used to isolate the effects of pH_i from arterial pH (pH_a) and it was shown that after applying the cuff the hyperventilatory response was not due to changes in pH_a but was related to acid changes within the exercising muscle (91). Evans et al. (36) similarly looked at this concept but measured pH_e as this is where the neural afferents are situated that would be the main stimulus for the postulated metaboreflex for ventilation. Their findings were also similar, and they concluded that muscle acidosis is necessary for the ventilatory metaboreflex and can occur independent of changes in pH_a (36, 91). Wasserman et al. (126) suggested that these two changes, the increase in non-metabolic CO_2 production and the fall in muscular pH_i and pH_e as a result of the dissociation of lactate acid, are the cause for VT_1. It has been shown however that paraplegics show a ventilatory response similar to normal human subjects during electrically stimulated exercise (13), which would suggest that the exercise-induced hyperpnea is not critically dependent on spinal afferent pathways and thereby, the skeletal muscle chemoreflex.

The CO_2 flow hypothesis is based on the premise that ventilation increases in proportion to CO_2 flow across the lungs (127) irrespective of any changes in P_aCO_2 (129). This hypothesis suggested little involvement of the peripheral and central chemoreceptors in the ventilation response at VT_1 and possible involvement of a CO_2 flow receptor in the pulmonary circulation that has yet to be demonstrated (127).

Wasserman et al. (129) suggested a possible role of the chemoreceptors in the carotid body as the modulators for the increase in exercise ventilation at intensities above VT_1. In their study they found that humans with a resected carotid body (resections were done 3-9 years prior to the study) did not display the same exponential increase in ventilation as humans with intact carotid bodies when exercising at intensities above VT_1. This finding was in contrary to previous studies that showed ventilation was not mediated by the carotid bodies (53, 76, 129). The previous studies, however, all examined the control of ventilation prior to reaching VT_1 making it difficult to compare the studies.

In contrast to the findings above, Mitchell et al. (85, 86) in studies with goats showed the contrary. In their study they had 4 groups: control, carotid body intact with serotonin depletion, carotid body denervated, and carotid body denervated with serotonin depletion (86). The serotonin depletion was used to induce a hyperventilation. The results showed that the goats hyperventilated as a result of the serotonin depletion in both the carotid body intact and denervation groups (86). These results suggest a basic property of the ventilatory control system whereby enhanced ventilatory activity at rest is associated with an increased ventilatory response to exercise via a mechanism that does not require peripheral chemoreceptors (85).

Potassium and norepinephrine have also been implicated as possible modulators of the VT_1. Infusion of norepinephrine was shown to stimulate transient increases in

ventilation regardless of changes in P_aCO_2 (6, 134). Cunningham (25), however showed that the only consistent effect of norepinephrine on ventilation was during hypoxic exercise. He suggested norepinephrine played a role in increasing hypoxic sensitivity to changes in P_aO_2 during exercise but had little effect on normoxic exercising subjects (25).

Increasing (94) K^+ levels during exercise has been shown to be positively correlated with increasing ventilation (94). In further studies it has also been shown that plasma K^+ can double during muscular exercise and seems to increase in proportion to the intensity of exercise (83). Burger et al. (14) however found some confounding results when adding a hyperoxic and hypercapnic stimulus. They showed by infusing K^+ in the form of potassium chloride this caused an increase in chemoreceptor activity which was enhanced by hypoxia, but reduced or had no effect during hyperoxia and hypercapnia (14). It is apparent therefore that K^+ is a possible mediator of ventilation during exercise but to what extent and under what conditions is still unclear.

For each hypothesis presented above, there have been studies with conflicting results (14, 25, 40, 48, 85, 86). It is apparent that although there are several plausible hypotheses, there are still no clear mechanisms underlying changes in ventilation at or about VT_1.

2.2.1.2 Hypotheses for VT_2

As mentioned above, VT_2 is thought to be a result neurogenic modulation in the respiratory centres (72, 138). There are several neurological factors that have been

advocated to underlie VT_2 that may influence the excitatory nerve impulses of the respiratory centre during exercise (72). Krogh and Lindhard (67) proposed that radiating motor nerve impulses into the respiratory centres occur during the onset of exercise, which stimulate the steep rise in ventilation evident at VT_2. Since this hypothesis, there have been many attempts to link neurological factors to the exercise-induced hyperpnea, specifically in relation to stimulus reflexes from the limbs mediated by active or passive movements (21, 28). However, there has been no conclusive evidence however that this proposed mechanism can solely account for the entire hyperpnea during exercise and therefore it's overall contribution still remains to be elucidated.

The exact causes of the exercise-induced hyperpnea at VT_1 and VT_2 are thus not fully elucidated. It appears that the exercised-induced hyperpnea is a result of a combined set of influences and interactions involving chemical and neurological stimuli rather than one single cause (72). The relative contribution of these factors is also further complicated by the degree and type of exercise as well as the physiological state of the subject and the environmental state of their surroundings. Yet another prominent mediator of ventilation is body temperature (17, 79, 95, 105, 138), which is also influenced by exercise. The next section describes how body temperature may be implicated in the control of ventilation during exercise.

2.2.2 *Control of ventilation during hyperthermia*

When core temperature rises by 1°C or more, this is known as hyperthermia. Hyperthermia can arise from external environmental conditions such as excessive heat exposure and humidity, or from internal conditions such as the body warming experienced during fever and exercise (60). When the body becomes hyperthermic the change in core temperature effects many other biological processes and in turn activates the thermoregulatory centres in the hypothalamus. As discussed above, the primary goal of the thermoregulatory system during heat stress is to dissipate heat from the body bringing the core temperature back to steady-state resting levels (in most humans this is ~ 37.0°C). The most effective form of heat loss in hyperthermic humans is through eccrine sweating and subsequent surface evaporation (60, 115). Vasodilatation of the peripheral blood vessels increasing blood flow to the skin is also another prominent form of heat loss (60, 115). In mammals such as dogs however, the most effective form of heat loss is through ventilation or panting because these animals have minimal surface sweating (5, 68).

In humans respiratory heat loss accounts for 10 to 15 % of total heat loss. However, it has been shown that a passive (17) or active (138) increase in core temperature of approximately 0.5°C to 1.0°C above normothermic body temperature is coupled with a hyperpnea that directly influences cranial heat loss (79). The point where ventilation increases when expressed as a function of core temperature was proposed as the core temperature threshold for ventilation (17, 138). Furthermore both Cabanac and

White (17, 138) demonstrated that when core temperature was elevated above this threshold, ventilation increased in direct proportion to further increases in core temperature. White et al. (138) have shown this threshold to be reproducible in humans during active (exercise-induced) hyperthermia.

Although the respiratory heat loss is considerably smaller than the skin surface heat loss, it still has a significant influence on cranial heat loss (17, 100). This respiratory heat dissipation is suggested to resemble second phase panting (44) in animals that exhibit selective brain cooling (SBC). Previously panting animals were the only species believed to be able to demonstrate a SBC (38), however, recent studies with hyperthermic humans have shown a divergence of tympanic temperature and esophageal temperature (T_{es}) after they reached their core temperature threshold for ventilation. Tympanic temperature has been shown to be a reliable approximation of brain temperature (78) and T_{es} has been shown to be a reliable index of thoracic temperature (47). White et al. (138) found that tympanic temperature dropped significantly below esophageal temperature after the temperature threshold for ventilation was reached. This finding suggested an importance of ventilation in human cerebral thermoregulation and the possible existence of SBC in humans.

The hyperpnea during an exercise-induced increase in core temperature was shown by Sancheti and White (106) to be a result of an initial increase in V_T. They showed that V_T increased proportionately with T_{es} and then reached a maximal level at which it reached a plateau despite further increases in core temperature (106).

Furthermore, they showed at higher core temperatures that the frequency of respiration increased proportionately to core temperature. They suggested this was responsible for further increases in ventilation after the V_T reached its plateau (106). The plateau point for V_T and the core temperature threshold for the f_v were also found to be repeatable (106). These results suggest evidence for a possible vestigial panting response with elevated core temperatures during exercise since a polypnea is observed at higher core temperatures (138). Nybo and Nielsen (90) in a recent study supported this hypothesis as they showed a significantly elevated ventilation during a hyperthermic exercise where core temperatures reached ~40°C as opposed to non-hyperthermic exercise where core temperature reached ~37.8°C

The mechanism by which the hyperpnea occurs during exercise or hyperthermia still remains to be fully elucidated (72). A neurogenic hypothesis (72) has been proposed implicating core temperature as a central mediating stimulus in the control of ventilation during both actively and passively induced hyperthermia. It suggests that increases in core temperature could increase ventilation by several mechanisms. One potential mechanism is elevated core temperature is associated with an increase in CO_2 sensitivity (26, 109), where sensitivity is defined as an increase in ventilation for a given increase in $P_{ET}CO_2$. This increased sensitivity to CO_2 is evident during exercise (131) and post exercise hyperthermia (105).

Another hypothesis exists suggesting a direct effect of an increase in temperature causing a change in the equilibrium constants of the CO_2 buffer system resulting in a

diminished capacity to buffer CO_2 by body fluids (114). This would lead to an increased production of H^+ (Equation 2.1) and a resultant stimulation of ventilation. This decrease in pH leads to an increase in P_aCO_2, which causes CO_2 to cross the blood brain barrier. Ventilation is then increased after H^+ levels are increased in the regions of the central respiratory centres in the medulla oblongata. Cunningham et al. (26) proposed a more direct hypothesis, which suggests a physical effect of increased temperature on the cells of the respiratory centres and/or the peripheral chemoreceptors thereby enhancing the reactivity of these respiratory control mechanisms to their normal stimuli.

In summary, there are several hypotheses for the observed hyperthermic-induced hyperpnea. There is strong evidence to support each hypothesis, however, the mechanism(s) underlying this hyperpnea may be from a combination of several factors.

Two established peripheral modulators of ventilation are hypoxia and CO_2. Although the independent effects of hypoxia, CO_2 and core temperature on exercise ventilation are well established (72), the combined effects of hypoxia and core temperature on exercise ventilation in humans are not evident in the literature. The following sections describe how hypoxia and CO_2 influence ventilation independently and when combined together with exercise.

2.2.3 Control of ventilation during hypoxia

One of the main effects of hypoxia is a hyperventilation and this is known as the hypoxic ventilatory response (HVR). The carotid bodies include peripheral chemoreceptors, which help control breathing and are thought to be responsible for the HVR (30). This is evident for carotid body resected patients that did not show a normal HVR (52, 53, 76). However, there still appears to be some residual ventilatory chemosensitivity in human subjects during hypoxia even after the resection (118). Swanson et al. (118) suggested that the aortic body must mediate the HVR with a non-functioning carotid body. Honda (53) suggested this residual chemosensitivity to account for 5-10 % of the total HVR. It appears that the peripheral chemoreceptors are the most significant modulators of the HVR but there are other confounding factors involved such as CO_2, which will be discussed in the following section.

2.2.4 The effects of carbon dioxide on ventilation

One of the consequences of the HVR is a fall in P_aCO_2 or a hypocapnia. In the human body decreased CO_2 can blunt the HVR, specifically hypocapnia during hypoxia will depress the peripheral chemoreceptor response that normally increases ventilation (55, 112). In goats this effect of hypocapnia was suggested to function by blunting the carotid body chemoreceptor sensitivity to a low P_aO_2 (29). Rapanos and Duffin (99) showed using a modified Read's rebreathing test (101) that a CO_2 peripheral-chemoreflex threshold exists in humans at which below there is no acute ventilatory response to hypoxia. Above this threshold ventilation increased linearly with $P_{ET}CO_2$ but below this

threshold ventilation did not significantly increase despite increasing severity of hypoxia to a mean end-tidal oxygen partial-pressure ($P_{ET}O_2$) of 4.9 kPa (SD 0.5). Their findings both agree (1, 22, 74, 119) and disagree (102, 113, 130) with the literature. They argued that those studies in disagreement, which found a hypoxic ventilatory response during hypocapnia might not have actually reached a level of CO_2 in their subjects that was sub-threshold, thereby not eliciting a strong enough hypocapnic effect to have suppressed the response of ventilation to hypoxia. They suggested that the CO_2 peripheral-chemoreflex threshold varies between each individual, and found a mean $P_{ET}CO_2$ threshold for ventilation of 5.2 kPa (SD 0.4).

A method (70, 77) to eliminate the potential influence of hypocapnia during hypoxia is to titrate CO_2 into the inspirate so as to clamp $P_{ET}CO_2$ at steady state isocapnic values. This condition is known as isocapnic hypoxia and allows for the isolation of the hypoxic effect from the possible influences of a hyperventilation-induced hypocapnia.

2.2.5 Control of ventilation during hypoxic exercise

As discussed previously, moderate to high intensity exercise induces an increase in ventilation, however when combined with hypoxia the resultant hyperpnea is multiplicative (46, 63, 71, 98). Griffiths et al. (43) found that with hypoxia (12 % O_2) in human exercise at a steady-state sub-maximal level, over 50 % of the resultant hyperpnea was attributed to peripheral chemoreceptor control. This was confirmed by assessing peripheral chemoreceptor activity with the Dejours 100 % O_2 test (30) which is designed

to eliminate the carotid body drive to breathe. Pure oxygen inhalation was demonstrated to suppress ventilation during exercise (3, 4, 73), with the degree of suppression being proportional to the degree of increasing work load (4, 73). Weil et al. (130) had a similar finding that exercise enhanced the HVR and the effect becomes marked as the severity of exercise increases. They gave two suggestions for the cause of this phenomenon, one being the associated increased hypercapnic drive and the other being increased peripheral chemoreceptor sensitivity due to increased sympathetic activity (131). It is therefore quite probable that hypoxia combined with exercise has a significant interaction increasing the sensitivity of the peripheral chemoreceptors to oxygen that is greater than that of hypoxia alone. Exercise per se influencing hypoxic sensitivity does not however contribute to the explanation of the mechanisms underlying this interaction. This is since "exercise" denotes physiological changes at several levels from the cell to the tissue to the entire set of organ systems. It remains to be determined what changes brought on by exercise accounts for the enhanced sensitivity of ventilation during inhalation of hypoxic gas mixtures.

2.2.6 Control of ventilation during water immersion

During water immersion up to the neck, there have been several physiological responses observed that might influence gas exchange and ventilation. These responses are primarily due to the pressure exerted on the chest from the water, which can cause the diaphragm to shift upwards decreasing the functional residual capacity of the lungs and consequently changing the ventilation-to-perfusion ratio making gas exchange in the

lungs more difficult (23, 97). Conversely, other studies have shown that water immersion is marked by a global increase in cardiac output, blood volume, and pulmonary artery pressure, which could enhance gas exchange (2, 37). Prefaut et al. (97) found that age and body build had a significant effect on both these physiological responses. They found that in their subject pool, those of younger ages (~25 years) and normal body builds had more profound hemodynamic responses thereby improving gas exchange as compared to the older and heavier body builds.

Another consequence of water immersion on ventilation is an increase CO_2 storage capacity that would enhance the accumulation of metabolically produced CO_2 in the peripheral tissues (19). This mechanism was proposed to occur due to the increase in CO_2 and tissue perfusion during whole body water immersion. The increased tissue perfusion would then mean CO_2 would be redistributed throughout the body, particularly to low-perfused, low-metabolism, and high CO_2 capacity tissues (20). This would cause an increase in resting $P_{ET}CO_2$ which was shown in Chang and Lundgren's study (20) where subjects showed a significant 8.3 % higher resting $P_{ET}CO_2$ during head-out water immersion as compared to normal conditions. The effect of this water immersion mediated increase in resting $P_{ET}CO_2$ on ventilation during exercise and hypoxia has not yet been investigated.

2.2.7 Kinetics and timing of ventilation at the onset of exercise and hypoxia

In response to a step increase in work rate $\dot{V}O_2$ and $\dot{V}CO_2$ abruptly increase due to an increase in metabolic demand at the exercising muscles and this causes a change in pulmonary gas exchange. With the start of exercise at a low to moderate intensity ($\leq$ ~60 % of $\dot{V}O_{2peak}$), ventilation increases proportionately to $\dot{V}O_2$ and a new steady state of ventilation is established at these exercise intensities. (128). The kinetics of this response is characterized by a mono-exponential function (56, 122, 137). There are several factors that can influence the kinetics of ventilation from rest to exercise and euoxic to hypoxic exercise, which include varying levels of exercise intensity (135), P_aO_2 (122), and P_aCO_2 (123).

During rest the lowering of arterial oxygen content (S_aO_2) to ~80 % has been shown to stimulate a proportionate increase in ventilation (34, 61). The increase is mediated primarily by the stimulation of the peripheral chemoreceptors due to low P_aO_2 levels (31, 53). This initial increase in ventilation has been further shown to be proceeded by a gradual fall in ventilation, which is commonly evident in progressive hypoxia tests (34). However, during isocapnic hypoxia, ventilation remains consistently elevated for up to 15 min after the initial peak increase before a significant ventilatory depression is evident (34, 61, 132). The ventilatory kinetic response to this acute isocapnic hypoxia has been shown to follow a pattern similar to that of a mono-exponential model (34, 61).

An exhaustive review of the literature did not uncover any studies of the influences of body temperature on the kinetics of ventilation and its parameters in humans. The effect of an increase in body temperature on the ventilation response to exercise and hypoxia in humans therefore remains to be elucidated.

2.2.8 Manipulation of core temperature during exercise

Previous studies attempting to provide thermal clamps during exercise were not able to maintain a steady-state normothermic or hyperthermic core temperature (24, 103). Two of the possible reasons for this result was that in these studies during normothermia the water temperature was set too low at 23°C (103) and 18°C (24) and the work rate was set too high at a $\dot{V}O_2$ of ~2 $L \cdot min^{-1}$ (24). The lower water temperatures of 18 and 23°C would have induced a metabolic response from skin (i.e. shivering) and/or core cooling. In a study by Park et al. (92) it was shown that a normothermic core temperature could be achieved during low intensity exercise by shoulder level immersion in thermoneutral water between 28°C to 32°C. For each participant a critical water temperature was determined empirically. The critical water temperature was defined as a water temperature at which the participants could tolerate without shivering for 3 h (92). Based on the critical water temperature values, a predicative equation was derived to estimate overall body insulation at the prescribed exercise level. The equation is as follows:

$$I = (T_{re} - T_w) \cdot (0.92 \dot{M} \pm \dot{S})^{-1} \text{ (92)} \quad \text{.....(2.2)}$$

where I is the overall body insulation, T_{re} is the rectal temperature, T_w is the critical water temperature, $0.92\dot{M}$ is considered to be the metabolic heat production minus respiratory heat loss which is assumed to be 0.08 $W \cdot m^2$, and $\dot{S}$ is the loss or gain of body heat stores (92). The results of this study showed an effective normothermic exercise could be achieved at low intensity exercise in thermoneutral water.

2.3 Summary

1. There appears to be a combination of chemical and neurogenic stimuli mediating ventilation. The effect of the interactions these stimuli have on the overall control of ventilation is dependent on the level of exercise intensity. Individually, hypoxia and elevated body temperature have both been implicated to stimulate the peripheral chemoreceptors and/or the central respiratory centres that each increase ventilation (72).

2. In hypoxia approximately 90-95 % of the HVR is controlled by the peripheral chemoreceptors (53). The magnitude of the acute hypoxic hyperventilation is a result of the level of hypoxic stress, however, if the hypoxic stress remains constant the hypoxic-induced hyperventilation will gradually be reduced as the P_aCO_2 falls. The resulting hypocapnia inhibits the increase of ventilation (55, 112). Isocapnic hypoxia can act to prevent this fall and maintain ventilation at consistently elevated level for up to 15 min before a significant ventilatory depression is evident (34, 61, 132)

3. During exercise ventilation increases in proportion to $\dot{V}O_2$ up until VT_1 and VT_2 are reached (135). After the ventilatory thresholds, ventilation rises at a greater rate than $\dot{V}O_2$ or $\dot{V}CO_2$ (82).

4. Similarly, a ventilation threshold also exists for core temperature and it was found to be approximately 1.0°C above normothermic core temperature (17, 138). With an increase in core temperature past this threshold there is a proportional increase in ventilation and core temperature (17, 138).

5. Independently the positive influences of hypoxia and exercise intensity on ventilation are established, both causing marked increases in ventilation (72, 124, 131, 135, 136).

6. In humans the combined influence of hypoxia and exercise on ventilation causes an increase in ventilation that was greater than their combined individual influences (46, 63, 71, 98). Similarly, the effects of hypoxia and passive hyperthermia on ventilation is also suggested to be multiplicative since both have an independent influence on ventilation that gives a net increase that is less than when both stimuli are presented together (96).

7. The potential interaction of hypoxia and core temperature during exercise has not yet been established. One of the main reasons is because increased core temperature is concomitant to exercise. This makes it difficult to determine how much of the resultant hyperpnea from exercise is due to body temperature or other metabolic or non-metabolic factors.

8. From the findings of Park et al. (92) there is evidence that an effective normothermic exercise can be achieved at low intensity exercise in thermoneutral water of ~28°C to 32°C.

2.4 Objectives

1. To investigate the separate and combined influences of hypoxia and elevated body temperature during low intensity exercise on ventilation.

2. To investigate the role of body temperature on the ventilatory kinetics from rest to exercise and from euoxic to hypoxic low intensity exercise.

3. To investigate whether the changes in metabolic rate or blood borne metabolites during hyperthermia and hypoxia at low intensity exercise significantly influence ventilation.

2.5 Research Hypotheses

1. It is hypothesized that if both the combined influences of an exercise during hypoxia (46, 63, 71, 98) and passive hyperthermia during hypoxia (89, 96) would cause a multiplicative increase in ventilation ($\dot{V}_E$), then with the removal of the exercise-induced hyperthermia there will be a marked reduction in $\dot{V}_E$ during hypoxic normothermic exercise.

2. If a hyperthermia-induced hyperpnea is a vestigial panting response, then the elevations in ventilation during hyperthermic exercise would be due to increases in ventilation frequency.

3. It is hypothesized that if core temperature influences steady-state ventilation during rest (17) and exercise (138), then it may influence the ventilatory kinetics for the onset of exercise. Furthermore, if core temperature influences the HVR (89, 96) it can also be hypothesized that an enhancement of the kinetics of this response may be evident during an elevated core temperature.

2.6 Testable Questions

1. Is ventilation during low intensity exercise with an elevated hyperthermic Core Temperature different than ventilation during low intensity exercise with a normothermic Core Temperature?

2. Is there an interaction of Core Temperature and Gas Type on ventilation during low intensity exercise? Is the effect additive or multiplicative?

3. If there is an interaction between Core Temperature and Gas Type on ventilation, what components of ventilation, f_V and/or V_T, mediate this change during low intensity exercise?

4. How do Core Temperature and Gas Type influence the inspiratory flow and timing components of ventilation during low intensity exercise?

5. Is the kinetics of ventilation influenced by skin and/or core temperature during the onset of low intensity exercise and during the onset of hypoxia during steady-state low intensity exercise?

6. Do associated increases in metabolic rate and blood borne metabolites as with exercise, hyperthermia, and hypoxia significantly influence ventilation?

2.7 References

1. **Anderton JL, Harris EA, and Slawson KB.** The Repeatability of Ventilatory Responses to Excess of Carbon Dioxide and Lack of Oxygen. *Q J Exp Physiol Cogn Med Sci* 49: 43-51, 1964.

2. **Arborelius M, Jr., Ballidin UI, Lilja B, and Lundgren CE.** Hemodynamic changes in man during immersion with the head above water. *Aerosp Med* 43: 592-598, 1972.

3. **Asmussen E and Nielsen M.** Pulmonary ventilation and effect of oxygen breathing in heavy exercise. *Acta Physiol Scand* 43: 365, 1958.

4. **Asmussen E and Nielsen M.** Studies on the regulation of respiration in heavy work. *Acta Physiol Scand* 12: 171, 1946.

5. **Baker MA, Hawkins MJ, and Rader RD.** Thermoregulatory influences on common carotid blood flow in the dog. *J Appl Physiol* 52: 1138-1146, 1982.

6. **Barcroft H, Basnaykae V, Celander O, Cobbold A, Cunningham DA, Jukes M, and Young I.** The effect of carbon dioxide on the respiratory responses to noradrenalin in man. *J Physiol (Lond)* 137: 365, 1957.

7. **Benzinger TH.** The diminution of thermoregulatory sweating during cold-reception at the skin. *Proc Natl Acad Sci*, edited by Bard P, Bethesda, MD, 1961, p. 1683-1688.

8. **Benzinger TH.** The human thermostat. *Sci Am* January: 2-11, 1961.

9. **Benzinger TH.** The Thermal Homeostasis of Man. In: *Temperature, Part II: Thermal Homeostasis*. Stoudsburg: Dowden, Hutchinson & Ross, Inc., 1967, p. 289-325.

10. **Benzinger TH, Pratt AW, and Kitzinger C.** The thermostatic control of human metabolic heat production. *Proceedings of the NAS* 47: 730-738, 1961.

11. **Bligh J.** Thermal Regulation: What is regulated and how? *Proc Symp Therm Reg*, edited by Houdas Y and Guieu JD, Lille, France. Masson, 1977, p. 1-9.

12. **Boulant JA.** Thermoregulation. In: *Fever: basic Mechanisms and Management*, edited by Mackowiak P. New York: Raven Press, Ltd, 1991, p. 1-22.

13. **Brice AG, Forster HV, Pan LG, Funahashi A, Hoffman MD, Murphy CL, and Lowry TF.** Is the hyperpnea of muscular contractions critically dependent on spinal afferents? *J Appl Physiol* 64: 226-233, 1988.

14. **Burger RE, Estavillo JA, Kumar P, Nye PC, and Paterson DJ.** Effects of potassium, oxygen and carbon dioxide on the steady-state discharge of cat carotid body chemoreceptors. *J Physiol (Lond)* 401: 519-531, 1988.

15. **Cabanac M.** Heat Stress and Behaviour. In: *Handbook of Physiology, sect 4: Environmental Physiology*, edited by Fregly MJ and Blatteis CM. New York: Oxford University Press, 1996, p. 261-278.

16. **Cabanac M and Massonnet B.** Thermoregulatory responses as a function of core temperature in humans. *J Physiol (Lond)* 265: 587-596, 1977.

17. **Cabanac M and White MD.** Core temperature thresholds for hyperpnea during passive hyperthermia in humans. *Eur J Appl Physiol* 71: 71-76, 1995.

18. **Casaburi R, Daly J, Hansen JE, and Effros RM.** Abrupt changes in mixed venous blood gas composition after the onset of exercise. *J Appl Physiol* 67: 1106-1112, 1989.

19. **Chang LP and Lundgren CE.** CO2 chemosensitivity during immersion in humans. *Chin J Physiol* 38: 7-12, 1995.

20. **Chang LP and Lundgren CE.** Maximal breath-holding time and immediate tissue CO2 storage capacity during head-out immersion in humans. *Eur J Appl Physiol* 73: 210-218, 1996.

21. **Comroe JHJ and Schmidt CF.** Reflexes from the limbs as a factor in the hyperpnea of muscular exercise. *Am J Physiol* 138: 536, 1943.

22. **Cormack RS, Cunningham DJ, and Gee JB.** The effect of carbon dioxide on the respiratory response to want of oxygen in man. *Q J Exp Physiol Cogn Med Sci* 42: 303-319, 1957.

23. **Craig AB, Jr. and Dvorak M.** Expiratory reserve volume and vital capacity of the lungs during immersion in water. *J Appl Physiol* 38: 5-9, 1975.

24. **Cross MC, Radomski MW, VanHelder WP, Rhind SG, and Shephard RJ.** Endurance exercise with and without a thermal clamp: effects on leukocytes and leukocyte subsets. *J Appl Physiol* 81: 822-829, 1996.

25. **Cunningham DJC.** The effect of noradrenaline infusions on the relation between pulmonary ventilation and the alveolar PO_2 and PCO_2 in man. *Ann N Y Acad Sci*: 756-771, 1961.

26. **Cunningham DJC and O'Riordan JLH.** The effect of a rise in temperature of the body on respiratory response to carbon dioxide at rest. *QJ Exp Physiol* 42: 329-345, 1957.

27. **Cunningham DJC, Spurr D, and Lloyd BB.** Ventilatory drive in hypoxic exercise. In: *Arterial Chemoreceptors*, edited by Torrance RW. Blackwell: Oxford, 1968, p. 310-323.

28. **D'Angelo E and Torelli G.** Neural stimuli increasing respiration during different types of exercise. *J Appl Physiol* 30: 116-121, 1971.

29. **Daristotle L, Berssenbrugge AD, Engwall MJ, and Bisgard GE.** The effects of carotid body hypocapnia on ventilation in goats. *Respir Physiol* 79: 123-135, 1990.

30. **Dejours P.** Chemoreflexes in breathing. *Physiol Rev* 42: 335-358, 1962.

31. **Dejours P.** Control of respiration in muscular exercise. In: *Handbook of Physiology*, edited by Society AP. Washington, DC: Williams & Wilkins, 1964, p. 631-648.

32. **Dempsey JA, Vidruk EH, and Mitchell GS.** Pulmonary control systems in exercise: update. *Fed Proc* 44: 2260-2270, 1985.

33. **DuBois EF.** *Fever and the regulation of body temperature.* Springfield, Il.: Charles C. Thomas, 1948.

34. **Easton PA, Slykerman LJ, and Anthonisen NR.** Ventilatory response to sustained hypoxia in normal adults. *J Appl Physiol* 61: 906-911, 1986.

35. **Eisele JH, Ritchie BC, and Severinghaus JW.** Effect of stellate ganglion blockade on the hyperpnea of exercise. *J Appl Physiol* 22: 966-969, 1967.

36. **Evans AB, Tsai LW, Oelberg DA, Kazemi H, and Systrom DM.** Skeletal muscle ECF pH error signal for exercise ventilatory control. *J Appl Physiol* 84: 90-96, 1998.

37. **Farhi LE and Linnarsson D.** Cardiopulmonary readjustments during graded immersion in water at 35 degrees C. *Respir Physiol* 30: 35-50, 1977.

38. **Fuller CA and Baker MA.** Selective regulation of brain and body temperatures in the squirrel monkey. *Am J Physiol* 245: R293-297, 1983.

39. **Gale CC.** Neuroendocrine aspects of thermoregulation. *Annu Rev Physiol* 35: 391-430, 1973.

40. **Glass C, Knowlton RG, Sanjabi PB, and Sullivan JJ.** The effect of exercise induced glycogen depletion on the lactate, ventilatory and electromyographic thresholds. *J Sports Med Phys Fitness* 37: 32-40, 1997.

41. **Glotzbach SF and Heller HC.** Central nervous regulation of body temperature during sleep. *Science* 194: 537-539, 1976.

42. **Gonzalez RR, Kluger MJ, and Hardy JD.** Partitional calorimetry of the New Zealand white rabbit at temperatures 5-35 degrees C. *J Appl Physiol* 31: 728-734, 1971.

43. **Griffiths TL, Henson LC, and Whipp BJ.** Influence of inspired oxygen concentration on the dynamics of the exercise hyperpnoea in man. *J Physiol* 380: 387-403, 1986.

44. **Hales J.** Peripheral effector Mechanisms of Thermoregulation. *Regulation of Panting. Satelite of 28 Int. Congress of Physiol. Sci*, edited by Szelenyi ZaS, M., Pecs, Hungary., 1980.

45. **Hammel HT, Jackson DC, Stolwijk JAJ, Hardy JD, and Stromme SB.** Temperature regulation by hypothalamic proportional control with an adjustable set point. *J Appl Physiol* 18: 1146-1154, 1963.

46. **Hansen JE, Stelter GP, and Vogel JA.** Arterial pyruvate, lactate, pH, and PCO2 during work at sea level and high altitude. *J Appl Physiol* 23: 523-530, 1967.

47. **Hayward JS, Eckerson JD, and Kemna D.** Thermal and cardiovascular changes during three methods of resuscitation from mild hypothermia. *Resuscitation* 11: 21-33, 1984.

48. **Heigenhauser GJ, Sutton JR, and Jones NL.** Effect of glycogen depletion on the ventilatory response to exercise. *J Appl Physiol* 54: 470-474, 1983.

49. **Hensel H.** Thermoreception and temperature regulation. London: Academic Press, 1982, p. 320-321.

50. **Hessemer V and Bruck K.** Influence of menstrual cycle on shivering, skin blood flow, and sweating responses measured at night. *J Appl Physiol* 59: 1902-1910, 1985.

51. **Hessemer V and Bruck K.** Influence of menstrual cycle on thermoregulatory, metabolic, and heart rate responses to exercise at night. *J Appl Physiol* 59: 1911-1917, 1985.

52. **Holton P and Wood JB.** The effects of bilateral removal of the carotid bodies and denervation of the carotid sinuses in two human subjects. *J Physiol* 181: 365-378, 1965.

53. **Honda Y.** Role of carotid chemoreceptors in control of breathing at rest and in exercise: studies on human subjects with bilateral carotid body resection. *Jpn J Physiol* 35: 535-544, 1985.

54. **Hossman VG, Fitzgerald A, and Dollery CT.** Circadian rhythm of baroreflex activity and andrenergic vascular response. *Cardiovasc Res* 14: 125-129, 1980.

55. **Huang SY, Alexander JK, Grover RF, Maher JT, McCullough RE, McCullough RG, Moore LG, Sampson JB, Weil JV, and Reeves JT.** Hypocapnia and sustained hypoxia blunt ventilation on arrival at high altitude. *J Appl Physiol* 56: 602-606, 1984.

56. **Hughson RL and Morrissey M.** Delayed kinetics of respiratory gas exchange in the transition from prior exercise. *J Appl Physiol* 52: 921-929, 1982.

57. **Ingram DL.** Evaporative cooling in the pig. *Nature* 207: 415-416, 1965.

58. **Israel SL and Schneller O.** The thermogenic property of progesterone. *Fertil Steril* 1: 53-64, 1950.

59. **Jessen C.** Independent clamps of peripheral and central temperatures and their effects on heat production in the goat. *J Physiol (Lond)* 311: 11-22, 1981.

60. **Jessen C.** Temperature Regulation in Humans and Other Mammals. Germany: Springer-Verlag Berlin Heidelberg, 2001, p. 193-194.

61. **Kagawa S, Stafford MJ, Waggener TB, and Severinghaus JW.** No effect of naloxone on hypoxia-induced ventilatory depression in adults. *J Appl Physiol* 52: 1030-1034, 1982.

62. **Keller AD.** *Temperature: Its Measurement and Control in Science and Industry.Temperature regulation disturbances in dogs following hypothalamic ablations. In J. D. Hardy (Ed.),*. New York: Reinhold, 1963.

63. **Klausen K, Robinson S, Micahel ED, and Myhre LG.** Effect of high altitude on maximal working capacity. *J Appl Physiol* 21: 1191-1194, 1966.

64. **Kluger MJ.** Fever. New Jersey: Princeton University Press, 1975, p. 195-196.

65. **Kluger MJ.** Fever. *Pediatrics* 66: 720-724, 1980.

66. **Krieger DT.** Food and water restriction shifts corticosterone, temperature, activity and brain amine periodicity. *Endocrinology* 95: 1195-1201, 1974.

67. **Krogh A and Lindhard J.** The regulation of respiration and circulation during the initial stages of muscular work. *J Physiol (Lond)* 47: 112, 1913.

68. **Kronert H and Pleschka K.** Lingual blood flow and its hypothalamic control in the dog during panting. *Pflugers Arch* 367: 25-31, 1976.

69. **Kuhnen G and Jessen C.** The metabolic response to skin temperature. *Pflugers Arch* 412: 402-408, 1988.

70. **Lagneaux D and Lecomte J.** [Effects of the addition of carbon dioxide on manifestations of acute hypoxia in rats]. *C R Seances Soc Biol Fil* 181: 616-621, 1987.

71. **Lahiri S.** Physiological responses and adaptations to high altitude. *Int Rev Physiol* 15: 217-251, 1977.

72. **Lambertsen CJ.** Physical, chemical, and nervous interactions in respiratory control. In: *Medical Physiology* (14 ed.), edited by Mountcastle VB, 1980, p. 1873-1900.

73. **Lambertsen CJ.** Respiratory and cerebral circulatory control during exercise at 0.21 and 2.0 atmospheres of inspired PO_2. *Journal of Applied Physiology* 14: 966, 1959.

74. **Lloyd BB.** The chemical stimulus to breathing. *Br Med Bull* 19: 10-14, 1963.

75. **Lopez M, Sessler DI, Walter K, Emerick T, and Ayyalapu A.** Reduced sweating threshold during exercise-induced hyperthermia. *Pflugers Arch* 430: 606-611, 1995.

76. **Lugliani R, Whipp BJ, and Wasserman K.** A role for the carotid body in cardiovascular control in man. *Chest* 63: 744-750, 1973.

77. **Maher JT, Cymerman A, Reeves JT, Cruz JC, Denniston JC, and Grover RF.** Acute mountain sickness: increased severity in eucapnic hypoxia. *Aviat Space Environ Med* 46: 826-829, 1975.

78. **Mariak Z, Lewko J, Luczaj J, Polocki B, and White MD.** The Relationship between directly measured human cerebral and tympanic temperatures during changes in brain temperatures. *Eur J Appl Physiol* 69: 545-549, 1994.

79. **Mariak Z, White MD, Lewko J, Lyson T, and Piekarski P.** Direct cooling of the human brain by heat loss from the upper respiratory tract. *J Appl Physiol* 87: 1609-1613, 1999.

80. **Martin BJ, Morgan EJ, Zwillich CW, and Weil JV.** Control of breathing during prolonged exercise. *J Appl Physiol* 50: 27-31, 1981.

81. **McEwen GN, Jr. and Heath JE.** Resting metabolism and thermoregulation in the unrestrained rabbit. *J Appl Physiol* 35: 884-886, 1973.

82. **McLellan TM.** Ventilatory and plasma lactate response with different exercise protocols: a comparison of methods. *Int J Sports Med* 6: 30-35, 1985.

83. **Medbo JI and Sejersted OM.** Plasma K+ changes during intense exercise in endurance-trained and sprint-trained subjects. *Acta Physiol Scand* 151: 363-371, 1994.

84. **Mekjavic IB, Sunderberg CJ, and Linnarsson D.** Core temperature "null zone". *J Appl Physiol* 71: 1289-1295, 1991.

85. **Mitchell GS, Smith CA, and Dempsey JA.** Changes in the VI-VCO2 relationship during exercise in goats: role of carotid bodies. *J Appl Physiol* 57: 1894-1900, 1984.

86. **Mitchell GS, Smith CA, Vidruk EH, Jameson LC, and Dempsey JA.** Effects of p-chlorophenylalanine on ventilatory control in goats. *J Appl Physiol* 54: 277-283, 1983.

87. **Miyamura M, Ishida K, Kobayashi T, Ohkuwa T, and Itoh H.** Effects of acute hypoxia on ventilatory response at the onset of cycle exercise in man. *Jpn J Physiol* 42: 823-829, 1992.

88. **Nagel A, Herold W, Roos U, and Jessen C.** Skin and core temperatures as determinants of heat production and heat loss in the goat. *Pflugers Arch* 406: 600-607, 1986.

89. **Natalino MR, Zwillich CW, and Weil JV.** Effects of hyperthermia on hypoxic ventilatory response in normal man. *J Lab Clin Med* 89: 564-572, 1977.

90. **Nybo L, Moller K, Volianitis S, Nielsen B, and Secher NH.** Effects of hyperthermia on cerebral blood flow and metabolism during prolonged exercise in humans. *J Appl Physiol* 93: 58-64, 2002.

91. **Oelberg DA, Evans AB, Hrovat MI, Pappagianopoulos PP, Patz S, and Systrom DM.** Skeletal muscle chemoreflex and pHi in exercise ventilatory control. *J Appl Physiol* 84: 676-682, 1998.

92. **Park YS, Pendergast DR, and Rennie DW.** Decrease in body insulation with exercise in cool water. *Undersea Biomed Res* 11: 159-168, 1984.

93. **Parsons KC.** *Human thermal environments*. London: Taylor and Francis, 2003.

94. **Paterson DJ, Robbins PA, and Conway J.** Changes in arterial plasma potassium and ventilation during exercise in man. *Respir Physiol* 78: 323-330, 1989.

95. **Petersen ES and Vejby-Christensen H.** Effect of Body Temperature on Steady State Ventilation and Metabolism in Exercise. *Acta Physiol Scand* 89: 342-351, 1973.

96. **Petersen ES and Vejby-Christensen H.** Effects of body temperature on ventilatory response to hypoxia and breathing pattern in man. *J Appl Physiol* 42: 492-500, 1977.

97. **Prefaut C, Ramonatxo M, Boyer R, and Chardon G.** Human gas exchange during water immersion. *Respir Physiol* 34: 307-318, 1978.

98. **Pugh LG.** Man at high altitude: studies carried out in the Himalaya. *Sci Basis Med Annu Rev*: 32-54, 1964.

99. **Rapanos T and Duffin J.** The ventilatory response to hypoxia below the carbon dioxide threshold. *Can J Appl Physiol* 22: 23-36, 1997.

100. **Rasch W and Cabanac M.** Selective brain cooling is affected by wearing headgear during exercise. *J Appl Physiol* 74: 1229-1233, 1993.

101. **Read DJ.** A clinical method for assessing the ventilatory response to carbon dioxide. *Australas Ann Med* 16: 20-32, 1967.

102. **Rebuck AS and Woodley WE.** Ventilatory effects of hypoxia and their dependence on PCO2. *J Appl Physiol* 38: 16-19, 1975.

103. **Rhind SG, Gannon GA, Shek PN, Brenner IK, Severs Y, Zamecnik J, Buguet A, Natale VM, Shephard RJ, and Radomski MW.** Contribution of exertional hyperthermia to sympathoadrenal-mediated lymphocyte subset redistribution. *J Appl Physiol* 87: 1178-1185, 1999.

104. **Rothchild I and Barnes C.** The effects of dosage, and or estrogen, androgen or salicylate administration on the degree of body temperature elevation induced by progesterone. *Enocrinology* 50: 485-496, 1952.

105. **Sancheti A and White MD.** Human minute ventilation responses to carbon dioxide levels prior to and following an exercise induced hyperthermia. *International Union of Physiological Sciences Thermal Physiology Symposium*, Wollongong, Australia. Australian Physiological and Pharmacological Society, 2001, p. 134P.

106. **Sancheti A and White MD.** Tidal volume and frequency of respiration: Relationships to esophageal temperature during exercise induced hyperthermia. *9th Int. Conf. Environ Ergonom IX*, edited by J W and M H, Dortmund, Germany. Shaker Verlag, 2000, p. 89-92.

107. **Satinoff E.** Behavioural thermoregulation in the cold. In: *Handbook of Physiology, sect 4: Environmental Physiology*, edited by Fregly MJ and Blatteis CM. New York: Oxford University Press, 1996, p. 481-505.

108. **Satinoff E.** A reevaluation of the concept of the homeostatic organization of temperature regulation. In: *Handbook of Behavioral Neurobiology*, edited by Teitelbaum P. New York: Plenum Press, 1983, p. 443-472.

109. **Saxton C.** Effects of severe heat stress on respiration and metabolic rate in resting man. *Aviat Space Environ Med* 52: 281-286, 1981.

110. **Schmidt-Nielsen K, Schmidt-Nielsen B, Jarnum SA, and Houpt TR.** Body temperature of the camel and its relation to water economy. *Am J Physiol* 188: 103-112, 1957.

111. **Skinner JS and McLellan TH.** The transition from aerobic to anaerobic metabolism. *Res Q Exerc Sport* 51: 234-248, 1980.

112. **Somers VK, Mark AL, Zavala DC, and Abboud FM.** Influence of ventilation and hypocapnia on sympathetic nerve responses to hypoxia in normal humans. *J Appl Physiol* 67: 2095-2100, 1989.

113. **Sorensen SC and Severinghaus JW.** Respiratory sensitivity to acute hypoxia in man born at sea level living at high altitude. *J Appl Physiol* 25: 211-216, 1968.

114. **Stadie WC, Austin JH, and Robinson HW.** The effect of temperature on the acid-base protein equilibrium and its influence on the CO_2 absorption curve of whole blood, true and separated serum. *J Biol Chem* 66: 901, 1925.

115. **Stanier MW, Mount LE, and Bligh J.** Body Temperature and its regulation. In: *Energy Balance and Temperature Regulation.* Cambridge: Cambridge University Press, 1985, p. 54-72.

116. **Stelzner JK and Hausfater G.** Posture, microclimate, and thermoregulation in yellow baboons. *Primates* 27: 449-463, 1986.

117. **Stephenson LA, Wenger CB, O'Donovan BH, and Nadel ER.** Circadian rhythm in sweating and cutaneous blood flow. *Am J Physiol* 246: R321-324, 1984.

118. **Swanson GD, Whipp BJ, Kaufman RD, Aqleh KA, Winter B, and Bellville JW.** Effect of hypercapnia on hypoxic ventilatory drive in carotid body-resected man. *J Appl Physiol* 45: 871-877, 1978.

119. **Tenney SM, Remmers JE, and Mithoefer JC.** Interaction of CO2 and hypoxic stimuli on ventilation at high altitude. *Q J Exp Physiol Cogn Med Sci* 48: 192-201, 1963.

120. **Thauer R.** Warm regularization and fieberfahigkeit after operational intervened at the nervous system of homiothermic sucking animals. *Pflugers Archiv fur die Gesamte Physiologie* 236: 102-147, 1935.

121. **Timbal J, Colin J, and Boutelier C.** Circadian variations in the sweating mechanism. *J Appl Physiol* 39: 226-230, 1975.

122. **Ward SA, Blesovsky L, Russak S, Ashjian A, and Whipp BJ.** Chemoreflex modulation of ventilatory dynamics during exercise in humans. *J Appl Physiol* 63: 2001-2007, 1987.

123. **Ward SA, Whipp BJ, Koyal S, and Wasserman K.** Influence of body CO2 stores on ventilatory dynamics during exercise. *J Appl Physiol* 55: 742-749, 1983.

124. **Wasserman K.** Breathing during exercise. *N Engl J Med* 298: 780-785, 1978.

125. **Wasserman K.** Determinants and detection of anaerobic threshold and consequences of exercise above it. *Circulation* 76: VI29-39, 1987.

126. **Wasserman K, Van Kessel AL, and Burton GG.** Interaction of physiological mechanisms during exercise. *J Appl Physiol* 22: 71-85, 1967.

127. **Wasserman K, Whipp BJ, Casaburi R, and Beaver WL.** Carbon dioxide flow and exercise hyperpnea. Cause and effect. *Am Rev Respir Dis* 115: 225-237, 1977.

128. **Wasserman K, Whipp BJ, and Davis JA.** Respiratory physiology of exercise: metabolism, gas exchange, and ventilatory control. *Int Rev Physiol* 23: 149-211, 1981.

129. **Wasserman K, Whipp BJ, Koyal SN, and Cleary MG.** Effect of carotid body resection on ventilatory and acid-base control during exercise. *J Appl Physiol* 39: 354-358, 1975.

130. **Weil JV, Byrne-Quinn E, Sodal IE, Friesen WO, Underhill B, Filley GF, and Grover RF.** Hypoxic ventilatory drive in normal man. *J Clin Invest* 49: 1061-1072, 1970.

131. **Weil JV, Byrne-Quinn E, Sodal IE, Kline JS, McCullough RE, and Filley GF.** Augmentation of chemosensitivity during mild exercise in normal man. *J Appl Physiol* 33: 813-819, 1972.

132. **Weil JV and Zwillich CW.** Assessment of ventilatory response to hypoxia: methods and interpretation. *Chest* 70: 124-128, 1976.

133. **Wenger CB, Roberts MF, Stolwijk JA, and Nadel ER.** Nocturnal lowering of thresholds for sweating and vasodilation. *J Appl Physiol* 41: 15-19, 1976.

134. **Whelan RF and Young IM.** Effect of adrenaline and noradrenaline infusions on respiration in man. *Brit J Pharmacol* 8: 98-102, 1953.

135. **Whipp BJ.** Peripheral chemoreceptor control of exercise hyperpnea in humans. *Med Sci Sports Exerc* 26: 337-347, 1994.

136. **Whipp BJ.** Ventilatory control during exercise in humans. *Annu Rev Physiol* 45: 393-413, 1983.

137. **Whipp BJ, Ward SA, Lamarra N, Davis JA, and Wasserman K.** Parameters of ventilatory and gas exchange dynamics during exercise. *J Appl Physiol* 52: 1506-1513, 1982.

138. **White MD and Cabanac M.** Exercise hyperpnea and hyperthermia in humans. *J Appl Physiol* 81: 1249-1254, 1996.

139. **Wyndham CH and Atkins AR.** A physiological scheme and mathematical model of temperature regulation in man. *Pflugers Arch* 303: 14-30, 1968.

140. **Wyss CR, Brengelmann GL, Johnson JM, Rowell LB, and Niederberger M.** Control of skin blood flow, sweating, and heart rate: role of skin vs. core temperature. *J Appl Physiol* 36: 726-733, 1974.

CHAPTER 3 STUDY 1

The effects of hyperthermia and hypoxia on ventilation during low intensity steady-state exercise

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Running Head: "Core Temperature, Hypoxia and Ventilation"

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3.1 Abstract

The independent and combined effects of hypoxia and elevated esophageal temperature (T_{es}) were investigated for their effects on the level of exercise ventilation ($\dot{V}_E$). In either a 'hyperthermic' T_{es} or a 'normothermic' T_{es} session, 11 college-aged, healthy male volunteers were immersed to the shoulders and pedalled on an underwater cycle ergometer at a steady-state oxygen consumption ($\dot{V}O_2$) of 0.87 $L \cdot min^{-1}$ (SD 0.07). Following a 30-min rest and 20-min warm-up, a 30-min steady-state cycling period was divided into three 10-min gas phases when participants inhaled: air (Euoxia 1 (E1)), hypoxic gas (12 % O_2 and 88 % N_2 (H1)), and air (Euoxia 2 (E2)). End-tidal CO_2 ($P_{ET}CO_2$) was maintained at an isocapnic level of 5.19 kPa (SD 0.71) throughout the exercise. Results showed a significant increase in $\dot{V}_E$ during all hyperthermia conditions ($0.01 < P < 0.048$), however, during hyperthermic hypoxia there was a disproportionate and significant ($P = 0.017$) increase in $\dot{V}_E$ relative to normothermic hypoxia. This was the main explanation for a significant core temperature and gas type interaction ($P = 0.012$) for $\dot{V}_E$. A main effect of core temperature ($P = 0.007$) was evident on ventilation frequency (f_v) with an increased rate of breathing in hyperthermic relative to the normothermic exercise. This gave evidence of a thermally-induced tachypnea which corresponded to significant decreases in inspiratory time (T_I) ($P = 0.035$) and expiratory time ($P = 0.014$) and was independent of any changes in tidal volume (V_T) ($P = 0.801$). As such inspiratory flow ($V_T \cdot T_I^{-1}$) was significantly increased in hyperthermic- relative to

normothermic ($P = 0.003$) exercise, an increase that was pronounced ($P = 0.013$) during hyperthermic hypoxia. In conclusion, these results suggest the following: 1) During low intensity, steady-state exercise an elevated T_{es} caused an increase $\dot{V}_E$, which was mediated by an increase in f_v. 2) The addition of hypoxia during hyperthermic exercise caused a multiplicative increase in $\dot{V}_E$, which corresponds with a multiplicative increase in $V_T \cdot T_I^{-1}$. This would suggest the possibility of a core temperature mediated stimulation of the peripheral chemoreceptors.

3.2 Introduction

There have been several proposed mechanisms for the hyperpnea that occurs during exercise (12, 22, 40). A neurogenic hypothesis (12) implicates core temperature as a central mediating stimulus in the control of ventilation during both actively and passively induced hyperthermia (2, 40). It suggests that increases in core temperature could increase ventilation by several mechanisms. One proposed mechanism suggests an increase in core temperature is associated with an increase in carbon dioxide sensitivity (31), while another suggests a direct physical effect of increased temperature in the respiratory control centre and the peripheral chemoreceptors thereby enhancing the reactivity to their normal stimuli (5). This increased sensitivity to CO_2 appears to be evident during exercise (38) and during post exercise hyperthermia (28). Another hypothesis suggests a direct effect of an increase in core temperature causing a change in the equilibrium constants of the CO_2 buffer system resulting in a diminished capacity to buffer CO_2 by body fluids (33). Ventilation is then increased after hydrogen ion (H^+) levels are increased in the regions of the central respiratory centres in the medulla oblongata.

Hypoxia is another well-established mediator of ventilation. Low inspired O_2 levels are detected by the peripheral chemoreceptors stimulating ventilation (7). Exercise enhances the hypoxic ventilatory response (HVR) and the effect becomes marked as the severity of exercise increases (38). The response to hypoxia has also been shown to

depend on the level of $P_{ET}CO_2$ (25). What has not been examined is if the concomitant increase in core temperature evident with exercise has an influence on the ventilatory response to hypoxia. To this end we have implemented an underwater exercise method by Park and colleagues (21) to prevent increases in core temperature during exercise. As such, this allowed an assessment for an interaction between hyperthermia and hypoxia during exercise $\dot{V}_E$. This study also investigated changes in V_T, f_v and the timing components of $\dot{V}_E$ to determine the HVR response characteristics in these conditions. We hypothesized that the sensitivity of the peripheral chemoreceptors to hypoxia would be increased during a low intensity 'hyperthermic' exercise relative to a low intensity 'normothermic' exercise when core temperature was clamped at resting levels. That is, during the hyperthermic exercise, with an increase in core temperature, there would be a greater hypoxic sensitivity as evidenced by a greater ventilatory response to hypoxia relative to the normothermic exercise condition.

3.3 Methods

3.3.1 Participants

Eleven healthy male university participants, age 19-34 years old volunteered to participate in the study. Their individual characteristics are given in Table 3.1. Power calculation results for sample size justification are given in Appendix C. All participants were non-smokers, non-asthmatics and refrained from caffeine for 12 h prior to each test. Prior to the experimentation the participants were informed of the potential risk associated with the protocol and after a 24 h reflection period gave their written, informed consent to participate in the experiment. The participants all attended a preliminary testing period where they were familiarized with the experimental protocol and instrumentation. During the preliminary testing period the participants performed a sub-maximal exercise protocol on an underwater cycle ergometer to determine their level of fitness and ensure they would be able to undergo the experimental protocol (Appendix B). Ethics approval for the study was received from the S.F.U. Office of Research Ethics prior to experimentation.

All experimental sessions were within ± 60 min of each other and started at between 10 am or 1 pm. Participants were also required to fast, exercise and refrain from drinking any warm beverages for a minimum of 5 h prior each experimental session.

Participants were clad in shorts and kayak boots during the experiments. A medical emergency kit including a defibrillator was available at all times.

3.3.2 Instrumentation

Pulmonary function variables and ventilatory excursions were measured using a breath-by-breath Sensormedics V_{max} 229c metabolic cart (Sensormedics, Yorba Linda, CA, USA). Participants wore a nose clip and were fitted with a mouthpiece connected to a Mass Flow Sensor. The mouthpiece was connected to a two-way flow sensor housing, which was connected to a 2-way non-rebreathing valve (NRB 2700, Hans Rudolph Inc, Kansas Cit, MO, USA) that was connected with 3.8 cm diameter corrugated Collins tubing to a 350 L Tissot spirometer. Breath-by-breath gas samples were drawn from the inspired and expired air to the metabolic cart at a rate of 500 $ml \cdot min^{-1}$. Carbon dioxide partial pressure was measured using non-dispersive infrared Spectroscopy and oxygen concentration was measured using a paramagnetic sensor. A premixed hypoxic gas of 12 % O_2 and balanced nitrogen (N_2) from a compressed gas bottle was used to fill the Tissot spirometer for the hypoxic condition. A fan mounted on the Tissot spirometer was used to mixed gas within its bell during the hypoxic condition. In addition, between conditions the Tissot was flushed with room air to remove any residual gases from the hypoxic trials.

Arterial oxygen saturation (S_aO_2) was continuously measured with a pulse oximeter (Masimo Radical, Irvine, CA, USA) positioned on the participants' left ear lobe. Esophageal temperature was measured by placing a paediatric size temperature thermocouple probe of approximately 2 mm in diameter through the participants' nostril, while they were asked to sip water through a straw. The location of the tip of the probe in the oesophagus was past the nares, at the T8/T9 level, a position bounded by the left ventricle and aorta. This position is based on the equation of Mekjavic and Rempel (18) for standing height: L (cm) = 0.228 x (standing height) - 0.194. The participant was then immersed to the level of the shoulders in a water-filled tub and sat on a hydraulically braked, underwater cycle ergometer. Water temperature was maintained at a specific temperature (Table 3.1) so as to maintain T_{es} at either a normothermic or hyperthermic level. The determination of these water temperature (T_w) levels is described below in 'Water Temperature calculations'.

An analog signal for f_v from the V_{max} cart was used to trigger data collection for body temperatures, heart rate and hemoglobin saturation on acquired a National Instruments data acquisition system SCXI-1000 (Austin, USA) that was controlled by LabVIEW software program (National Instruments, Austin, USA, version 5.1).

3.3.3 Water temperature calculations

During the preliminary testing session skinfold measurements were taken at 10 different sites as described by Veicsteinas and Rennie (35) with the Harpenden skinfold calliper (British Indicators, St. Albans, UK). The skinfold values (Table 3.1) were used to determine the participant's weighted mean subcutaneous fat thickness (MFT_w) (35). The MFT_w values for each participant were used to predict their overall body insulation at rest (I_{rest}) by a regression equation derived from Park and colleagues study (21). The I_{rest} values were used to calculate the water temperature (T_w) for both the hyperthermic and normothermic sessions by using a re-arrangement of Park et al.'s (21) body insulation equation:

$$T_w = T_{es} - (I_{ex}*(0.92\ \dot{M} \pm \dot{S}))\text{.....Equation 3.1}$$

In Equation 3.1 T_w is the desired water temperature for the exercise session, T_{es} is the desired core temperature measured by an esophageal probe, I_{ex} is the overall body insulation during exercise (for healthy male participants, BSA ~ 1.9 m^2, exercising at a rate that produces a constant metabolic heat production of 145 $W \cdot m^{-2}$, I_{ex} was found to be ~40 % of I_{rest} (21)), $\dot{M}$ is the metabolic heat production, $\dot{S}$ is the rate of heat storage. For the normothermic condition $\dot{S}$ is negligible and 0.92 is a weighting factor determined by the prediction of respiratory heat loss at rest and during exercise to be ~8 % (21). For the hyperthermic condition at a core temperature of ~ 38.5°C the $\dot{S}$ was empirically determined during pilot testing to be ~140 $W \cdot m^{-2}$. This value was used as an estimated

standard for the participant pool that was of similar physique to the pilot participant. The calculated water temperatures for each participant are given in Table 3.1.

3.3.4 Protocol

All participants volunteered for 2 separate exercise-testing sessions, with each session separated by at least one week. Half of the participants were randomly chosen to start with the hyperthermic session and the other half started with the normothermic session. After instrumentation each protocol began with a 30-min rest period in room air to establish a stable resting T_{es}. The exercise began with a 5-min rest period with the participant seated on a stationary underwater bicycle ergometer in water up to their shoulder level and instrumented with a weight belt to avoid floatation. A metronome was used to maintain the pedalling cadence and the participant was monitored continuously to assure adherence.

The work rate was determined based on the equation derived from Park et al.'s (21) study as the ideal level amongst the participant population that would produce a $\dot{V}O_2$ of approximately 0.8 to 1.0 $L \cdot min^{-1}$ while cycling in a 30°C water-filled tub. A $\dot{V}O_2$ of 0.8 - 1.0 $L \cdot min^{-1}$ was shown by Park et al. (21) to correspond with a metabolic heat production of ~145 $W \cdot m^{-2}$ in a healthy male participant with a body surface area (BSA) of ~1.9 m^2 (where 1 kcal = 0.207 L of O_2). This metabolic heat production rate was chosen as the exercise intensity level to produce a steady-state normothermic core

temperature in thermoneutral water as shown in Park et al.'s (21) study. The same work rate was used for the hyperthermic condition.

Each exercise session was performed at a constant work rate and consisted of a 20-min warm-up period where a steady state $\dot{V}_E$ and T_{es} were achieved and a 30-min testing period. Both the warm-up and testing period were completed at the same work rate and cadence and there were no rest phases between each period. The 30-min testing period was divided into 3 continuous 10-min steady state exercise phases: a 10-min euoxic exercise period (E1) where the participant breathed room air, a 10-min hypoxic exercise period (H1) where the participant breath the hypoxic gas mixture (12 % O_2, balanced N_2), and a 10-min euoxic recovery exercise period (E2) when the participant again breathed room air. All participants followed this protocol in the same order for all sessions. If the $P_{ET}CO_2$ fell below resting water-immersed values, 100 % CO_2 was manually titrated into the inspirate via a non-re-breathing demand valve apparatus as described by Sommer et al. (32) to bring the $P_{ET}CO_2$ back to resting, water-immersed levels. The purpose for clamping of $P_{ET}CO_2$ was to maintain an isocapnic hypoxia, which would alleviate the possibly confounding effects of a hyperventilation-induced hypocapnia that is often associated with hypoxia and was suggested to diminish the HVR (25). The resting water-immersed $P_{ET}CO_2$ levels (3) were determined during the 5-min rest session immediately prior to commencing the exercise session.

3.3.5 Calibrations and Analysis

Calibrations of esophageal thermocouple probes were completed in regulated temperature hot water baths. Gas analyzers were calibrated against two gases of known concentrations (4 % CO_2, 16 % O_2, balanced N_2 and 26 % O_2, balanced N_2, and air) and the mass flow sensor was calibrated manually by the use of a 3 litre syringe prior to each experiment.

Ventilatory parameters, T_{es}, and S_aO_2 for the steady-state exercise phases were analyzed using a two-way ANOVA for repeated measures. The factors were Core Temperature (Levels: normothermic and hyperthermic) and Gas Type (Levels: euoxia (E1), hypoxia (H1), and euoxic recovery (E2)). Dependent *t*-tests with the Bonferroni correction for multiple comparisons of were used to compare the means so as to explain the interactions of Core Temperature and Gas Type. A paired samples t-test was used to compare ventilatory variables between the both the in and out of water rest periods. A *P* value of < 0.05 was considered significant. For comparisons values are expressed as the mean ± the Standard Deviation (SD) and 95 % Confidence Intervals [CI] of the difference between means are given in square brackets following each *P* value stated. SPSS 12.0 (SPSS Inc., Chicago, Ill., USA) was used for all the statistical analyses.

3.4 Results

All participants completed the full exercise protocol including 10 min of hypoxic exposure with only mild signs or symptoms of hypoxia including hyperventilation, lethargy, and slight nausea. The mean water temperature for the normothermic condition was 31.5°C (SD 1.3) and for the hyperthermic condition was 38.2°C (SD 0.1) (Table 3.1). Figure 3.1 indicates the Gas Type phases used for analysis and shows the typical time course responses of $\dot{V}_E$, $\dot{V}O_2$, $P_{ET}CO_2$, S_aO_2 and T_{es} for a single participant during the normothermic condition.

Upon immersion in water, resting values for $\dot{V}_E$ ($P = 0.001$, CI [1.0, 2.6]), V_T ($P = 0.386$, CI [-0.1, 0.3]), $P_{ET}CO_2$ ($P = 0.386$, CI [-0.1, 0.3]) increased significantly while f_v ($P = 0.386$, CI [-0.1, 0.3]) showed an increasing trend, which was non-significant (Table 3.2).

During the 30-min rest period prior to the commencement of the normothermic exercise sessions the mean resting T_{es} (Fig. 3.2) was 37.20°C (SD 0.37) and prior to the hyperthermic exercise sessions the mean resting T_{es} was 37.28°C (SD 0.24), a non-significant difference of 0.08°C at ($P = 0.386$, CI [-0.1, 0.3]). For the normothermic exercise condition participants' T_{es} was maintained relatively constant at 37.17°C (SD

0.34), 37.09°C (SD 0.34), and 37.02°C (SD 0.33) during E1, H1 and E2 respectively. For the hyperthermic exercise condition T_{es} increased steadily from rest and gradually approached a plateau at ~38.5°C after the completion of the warm-up exercise period. The mean T_{es} during all steady-state exercise phases of the hyperthermic condition were also significantly increased above the normothermic levels by 1.28°C (SD 0.30) (P = 0.001, CI [1.1, 1.4]) to 38.44°C (SD 0.15) at E1, by 1.52°C (SD 0.36) (P = 0.001, CI [1.3, 1.8]) to 38.6°C (SD 0.1) at H1, and by 1.71°C (SD 0.37) (P = 0.001, CI [1.5, 2.0]) to 38.7°C (SD 0.1) at E2.

The ventilatory responses (Fig. 3.3A) obtained from the three steady-state exercise phases (E1, H1, E2) during the normothermic condition indicated $\dot{V}_E$ increased from 22.8 L·min^{-1} (SD 2.7) at E1 to 34.5 L·min^{-1} (SD 4.1) at H1, a significant increase of 11.7 L·min^{-1} (SD 4.4) (P = 0.001, CI [8.7, 14.7]) and returned to steady-state levels during E2 at 22.7 L·min^{-1} (SD 2.8), a non-significant change from E1 (P = 1.000). During the hyperthermic condition $\dot{V}_E$ also increased from E1 at 24.9 L·min^{-1} (SD 2.8) to H1 at 44.6 L·min^{-1} (SD 10.6) a significant increase of 19.8 L·min^{-1} (SD 9.1) (P = 0.001, CI [13.6, 25.9]) and returned to steady-state levels at 27.9 L·min^{-1} (SD 9.3) during E2, a non-significant change from E1 (P = 0.691). For the hyperthermic condition $\dot{V}_E$ was significantly elevated in all steady-state exercise phases as compared to the normothermic condition. For E1, H1 and E2 $\dot{V}_E$ increased by 2.0 L·min^{-1} (SD 2.1) (P = 0.010, CI [0.6, 3.5]), 10.2 L·min^{-1} (SD 9.0) (P = 0.004, CI [4.1, 16.2]) and 5.2 L·min^{-1} (SD 7.7) (P = 0.048, CI [0.1, 10.4]) respectively.

Across the steady-state exercise phase during the normothermic condition V_T (Fig. 3.3B) increased from E1 at 1.11 L (SD 0.21) to H1 at 1.64 L (SD 0.20), a significant increase of 0.52 L (SD 0.21) ($P = 0.001$, CI [0.38, 0.66]) and returned to steady-state levels during E2 at 1.09 L (SD 0.18), a non-significant change from E1 ($P = 0.159$). During the hyperthermic condition V_T increased from E1 at 1.12 L (SD 0.20) to H1 at 1.70 L (SD 0.17), a significant increase of 0.58 L (SD 0.20) ($P = 0.001$, CI [0.41, 0.75]). Tidal volume also showed a trend to decrease below the previous steady-state E1 levels at 1.06 L (SD 0.19) during E2, with a reduction of 0.06 L (SD 0.06) (P = 0.026, CI [-0.11, -0.01]). There was no significant main effect of Core Temperature on V_T ($P = 0.801$).

Across the steady-state exercise phase during the normothermic condition f_v (Fig. 3.3C) showed no significant change from E1 at 21.3 breaths·min^{-1} (SD 3.2) to H1 at 21.5 breaths·min^{-1} (SD 2.6) ($P = 1.000$) and from E1 to E2 at 21.9 breaths·min^{-1} (SD 2.3) ($P = 0.979$). During the hyperthermic condition f_v also showed no significant changes from E1 at 23.5 breaths·min^{-1} (SD 3.0) to H1 at 27.3 breaths·min^{-1} (SD 7.9) ($P = 0.337$) and bordered a significant change in E2 at 27.7 breaths·min^{-1} (SD 6.0) an increase of 4.2 breaths·min^{-1} (SD 5.5) ($P = 0.089$, CI [-0.6, 8.9]). Ventilation frequency was significantly elevated in all hyperthermic steady-state exercise phases as compared to the normothermic condition. For E1, H1 and E2 f_v increased by 2.2 breaths·min^{-1} (SD 3.1) ($P = 0.043$, CI [0.9, 4.2]), 5.8 breaths·min^{-1} (SD 6.7) ($P = 0.017$, CI [1.3, 10.3]) and 5.7 breaths·min^{-1} (SD 5.8) ($P = 0.008$, CI [1.8, 9.6]) respectively.

Across the steady-state exercises phases during the normothermic condition there were no significant changes in T_I or T_E (Fig 3.4A&B) from E1 at 1.48 s (SD 0.25) and 1.48 s (SD 0.21) to H1 at 1.32 s (SD 0.17) ($P = 0.355$) and 1.50 (SD 0.16) ($P = 1.000$) and E2 at 1.44 s (SD 0.14) ($P = 1.000$) and 1.44 (SD 0.18) ($P = 0.835$) respectively. For the hyperthermic condition during steady-state exercise there were also no significant changes indicated for T_E from E1 at 1.39 s (SD 0.16) to H1 at 1.24 s (SD 0.33) ($P = 0.457$) and E2 at 1.22 s (SD 0.27) ($P = 0.113$). Inspiratory time however showed a decrease during the hyperthermic condition from E1 at 1.32 s (SD 0.23) to H1 at 1.13 s (SD 0.27) which bordered a significant reduction of 0.20s (SD 0.23) ($P = 0.057$, CI [-0.40, 0.01]) but showed no significant change during E2 at 1.18 s (SD 0.33) ($P = 0.146$). Inspiratory time and T_E were both shortened during the hyperthermic condition as compared to the normothermic condition for H1 by 0.19 s (SD 0.24) ($P = 0.023$, CI [0.03, 0.35]) and 0.25 s (SD 0.32) ($P = 0.023$, CI [0.04, 0.46]) and for E2 by 0.26 s (SD 0.36) ($P = 0.034$, CI [0.02, 0.50]) and 0.22 s (SD 0.29) ($P = 0.030$, CI [0.03, 0.42]) respectively. For the hyperthermic relative to the normothermic condition at E1 there was only a trend for a reduction observed in T_E of 0.09 s (SD 0.16) ($P = 0.081$).

Across the steady-state exercise phases $V_T \cdot T_I^{-1}$ (Fig. 3.4 C) for the normothermic condition increased from 0.76 $L \cdot s^{-1}$ (SD 0.10) at E1 to 1.26 $L \cdot s^{-1}$ (SD 0.19) at H1, a significant increase of 0.50 $L \cdot s^{-1}$ (SD 0.21) ($P = 0.001$, CI [0.36, 0.64]) and returned to steady-state levels during E2 at 0.75 $L \cdot s^{-1}$ (SD 0.10), a non-significant change from E1 ($P = 1.000$). During the hyperthermic condition $V_T \cdot T_I^{-1}$ also increased from 0.85 $L \cdot s^{-1}$ (SD 0.11) at E1 to 1.57 $L \cdot s^{-1}$ (SD 0.33) at H1, a significant increase of 0.72 $L \cdot s^{-1}$ (SD 0.21) (P

= 0.001, CI [0.50, 0.94]) and returned to steady-state levels during E2 at 0.95 $L \cdot s^{-1}$ (SD 0.32), a non-significant change from E1 ($P = 0.708$). Inspiratory drive was elevated during the hyperthermic condition in all steady-state exercises phases ($P = 0.003$) as compared to the normothermic condition. For E1, H1 and E2 $V_T \cdot T_I^{-1}$ increased by 0.10 $L \cdot s^{-1}$ (SD 0.13) ($P = 0.031$, CI [0.01, 0.18]), 0.32 $L \cdot s^{-1}$ (SD 0.01) ($P = 0.002$, CI [0.15, 0.48]) and 0.20 $L \cdot min^{-1}$ (SD 0.26) ($P = 0.030$, CI [0.02, 0.38]) respectively.

A significant Core Temperature and Gas Type interaction was evident for $\dot{V}_E$ (F = 5.8, $P = 0.012$) and $V_T \cdot T_I^{-1}$ (F = 5.2, $P = 0.023$), while a trend for a Core Temperature and Gas Type interaction was evident for f_v (F = 3.4, $P = 0.076$) (Fig. 3.5). On comparison of the increases in $\dot{V}_E$ from the normothermic to hyperthermic condition, the elevation in H1 was significantly greater than that at E1 (F = 8.2, $P = 0.017$), while there was no difference between the elevations from the normothermic to the hyperthermic condition between E1 and E2 (P = 0.226) (Fig. 3.5A). For f_v a trend for a greater increase of f_v was evident from the normothermic to hyperthermic condition at both H1 ($P =$ 0.099) and E2 ($P = 0.062$) as compared to E1 (Fig. 3.5B). For $V_T \cdot T_I^{-1}$ the elevation in H1 was significantly greater than that at E1 (F = 9.2, $P = 0.013$), while there was no difference between the elevations from the normothermic to the hyperthermic condition evident between E1 and E2 (P = 0.235) (Fig. 3.5C).

Oxygen saturation (Fig 3.6A) decreased during H1 to 85.6 % (SD 5.7) ($P = 0.001$, [-19.2, -9.4]) in the normothermic condition and to 83.5 % (SD 5.7) (P = 0.001, [-18.9, -10.1]) in the hyperthermic condition, both significant reductions of 14.3 % (SD 5.6) ($P = 0.001$, [-10.5, -18.1]) and 14.5 % (SD 5.1) (P = 0.001, [-11.1, -17.9]) as compared to E1 at 99.9 % (SD 0.6) and 98.0 % (SD 1.0) respectively. A Core Temperature effect was also indicated as S_aO_2 values decreased significantly from the normothermic levels during euoxic conditions (E1 and E2) by 2.0 % (SD 0.8) ($P = 0.001$, [1.4, 2.5]) and 2.5 % (SD 1.1) ($P = 0.001$, [1.8, 3.3]) respectively during the hyperthermic condition. During H1, there was no significant difference ($P = 0.368$) for S_aO_2 levels between the hyperthermic and normothermic condition.

For $P_{ET}CO_2$ (Fig 3.6B) the main effect of Gas Type bordered significant (F = 4.7, $P = 0.051$) and there was no significant main effect of Core Temperature (F = 0.3, $P = 0.623$). An effective isocapnic hypoxia was achieved, as $P_{ET}CO_2$ levels remained relatively constant across both the normothermic and hyperthermic conditions during H1 as compared to E1

3.5 Discussion

3.5.1 Hypoxic ventilation and core temperature

The main finding of the present study was that the increase in $\dot{V}_E$ observed during hypoxic was significantly greater during steady-state hyperthermic exercise as compared to steady-state normothermic exercise (Fig 3.3A). The increase in $\dot{V}_E$ appears to be related to a significant increase in f_v (Fig 3.3C) since V_T (Fig 3.3B) was not significantly influenced by the elevation of T_{es}. A hyperthermic-induced hyperpnea was also observed independent of changes to inspired gas composition (Fig 3.3A) and a hypoxic hyperventilation was evident (Fig 3.3A) during hypoxic exposure independent of core temperature changes. Together these results support the working research hypothesis that the sensitivity to blood borne metabolites by the peripheral chemoreceptors in the carotid and aortic bodies is elevated in hyperthermia. Since in humans, lower arterial oxygen tension is only sensed by these peripheral chemoreceptors, it suggests part of the elevation in $\dot{V}_E$ during exercise could be a result of increased firing from warmed peripheral chemoreceptors relative to the firing rate of normothermic peripheral chemoreceptors.

The hyperthermic-induced hyperpnea observed in this current study was in agreement with results from previous studies (2, 23). This was observed by comparing

the normothermic and hyperthermic temperature conditions in the two euoxic phases (E1 and E2) of the study (Fig. 3.3A). Petersen and Vejby-Christensen (22) suggested that a core temperature threshold for ventilation existed around 38°C above which a significant hyperpnea was evident. Cabanac and White (2) further defined this core temperature threshold for ventilation to exist at a T_{es} of ~38.0 to 38.5°C during passive warming. In a following study, White and Cabanac (40) illustrated that this core temperature threshold appeared to be also evident during an active hyperthermia but at a lower level of ~37.3 to ~37.8°C depending on the site of core temperature measurement. They also indicated that above this threshold, with passive or active passive warming, ventilation increased at a proportional rate to core temperature (2, 40). We reasoned this proportionality between T_{es} and ventilation accounts for the higher $\dot{V}_E$ in the hyperthermic exercise during E1 and E2 relative to that during normothermia (Fig. 3.2A).

The HVR observed in this present study during low intensity exercise was also in agreement with a previous study by Weil and colleagues (38). Mean $\dot{V}_E$ increased significantly during both hypoxic conditions, however the hyperthermic hypoxia-induced increase in $\dot{V}_E$ was almost twice that of the normothermic hypoxia-induced increase in $\dot{V}_E$. There was no significant difference in steady-state $\dot{V}_E$ during the normothermic condition between E1 and E2, which supported there was no order effect of hypoxia between the three phases of exercise (E1, H1 and E2). The HVR during normothermic exercise was mediated completely by V_T (Fig 3.3B) with no significant influence from f_v (Fig 3.3C). This result differed slightly from those of Savourey et al. (30) who showed that only at rest was the HVR a result of an increased V_T and during moderate exercise it

was a result of a both an increased V_T and f_v. The difference presently from Savourey et al.'s study (30), however, was that T_{es} was clamped at resting levels throughout the hypoxic exercise and not allowed to increase. During the hyperthermic hypoxic exercise condition V_T increased in a relatively equal magnitude as during the normothermic hypoxic condition, yet the HVR was enhanced. This can be attributed primarily to the elevated f_v as a result of the increased core temperature, which has been described as a thermal tachypnea (2, 20). This would lead to the suggestion that an elevated core temperature may influence the sensitivity of the peripheral chemoreceptors helping to explain the elevated HVR during hyperthermia (Fig 3.3A).

Previous studies have shown the existence of a thermal tachypnea during an active hyperthermia (22, 40). The need for this thermal tachypnea remains unknown but there have been several plausible explanations. Petersen and Vejby-Christensen (22) have proposed that the thermal tachypnea could be part of a vestigial panting response that is still present in humans suggested to be needed for heat loss. White and Cabanac (40) have extended this theory to suggest that the panting mechanism observed may be a significant avenue of respiratory heat loss contributing to selective brain cooling in humans. It can be argued that in exercising humans eccrine sweating and skin vasodilatation would be the main source of heat loss, however, Rasch et al. (26) demonstrated that respiratory heat loss stills provides a significant portion of total cephalic heat loss during hyperthermia. Mariak et al. (14) showed directly for the first time an existence of ventilation-induced intracranial cooling in hyperthermic humans directly supporting existence of this heat loss response.

The most probable explanation for the observed thermal tachypnea in the current study would be a direct temperature effect on the peripheral chemoreceptors increasing their sensitivity to arterial O_2, CO_2 and pH. The peripheral chemoreceptors are located in the carotid body and aortic bodies, which is a highly perfussed tissue with a high metabolic rate. It would be plausible to suggest significant increases in core temperature would cause blood warming around the carotid or aortic bodies that could increase their sensitivity to arterial O_2. This would explain why the HVR was significantly increased during hyperthermia as compared to normothermia (Fig 3.2). Furthermore, the increase in $\dot{V}_E$ during hyperthermic hypoxia relative to hyperthermic euoxia was greater than the increase from normothermic euoxia to normothermic hypoxia, which would support that the observed $\dot{V}_E$ enhancement during hyperthermic hypoxia was a peripheral response. Cunningham and O'Riordan (5) and Petersen and Vejby-Christensen (23) have previously suggested a similar hypothesis in studies on passive hyperthermia and hypoxia. Present results may also help explain the results of Weil et al. (38) that showed the HVR becomes enhanced with increasing exercise intensity. It is well known that higher levels of exercise are associated with increasing core temperature (12, 19). On this basis it could be suggested the enhancement of the HVR due to increasing exercise intensity is in part a function of the concomitant increasing core temperature. Furthermore, during the hypoxic hyperthermic phase it would be expected that pH may increase in response to the hypoxic hyperventilation, however, during the current study $P_{ET}CO_2$ was clamped at isocapnic levels which should have prevented any increases in pH (22).

Independent of hypoxia the mechanism of thermal-induced tachypnea in panting animals has been shown to be mediated by the hypothalamus (11). It has recently been indicated in mice through surgical isolation of the brain stem that heating directly modifies the respiratory neural activity generated in the ventral respiratory group causing an increase in f_v (34). This would agree with previous studies in humans, which have suggested that the thermal tachypnea observed during exercise may be a direct effect of temperature on the cells of the respiratory control centres in the medulla (5, 15). MacDougall et al. (13) suggested another possible explanation for the thermal tachypnea. They indicated increasing H^+ stimulus as a possible mediator acting at the peripheral or central chemoreceptors. This hypothesis however would seem unlikely for the present study, as it has been shown by Petersen and Vejby-Christensen (22) that there is no change in arterial pH observed at hyperthermic states. Furthermore during low intensity euoxic exercise, as in this present study, arterial and cerebrospinal fluid pH are not thought to change (39). As such, the mechanism of the thermal tachypnea remains to be established in humans.

A consideration during hyperthermic hypoxia is that an increase in body temperature shifts the oxy-hemoglobin dissociation curve to the right causing a reduction in the O_2 affinity for hemoglobin. This was evident to a small degree in the present study as S_aO_2 was slightly reduced during the hyperthermic condition by ~2 % in E1 and E2 (Fig 3.6). This would have little effect during the euoxic conditions as the S_aO_2 was still at ~98 % for both E1 and E2, which should not be low enough to influence $\dot{V}_E$

significantly. During the hypoxic phase between the normothermic and hyperthermic condition S_aO_2 was not significantly different and would appear not to have had a significant influence on $\dot{V}_E$.

3.5.2 The Pattern of Breathing

Inspiratory time was significantly shortened from rest to exercise with a further reduction evident during hyperthermic exercise (Fig 3.4A). These findings are in agreement with previous studies showing that exercise-induced hyperthermia (15) and passive hyperthermia (23) are both associated with a lowering of the ventilatory timing components. It has been suggested for anaesthetized cats that an increase core temperature stimulates the dorsal respiratory "pacemaker" and vagal neurons of the central respiratory control centre decreasing T_I and consequently increasing f_v (9). Similar suggestions have been made in humans (15, 23). Petersen and Vejby-Christensen (23) proposed the existence of an inspiratory "off-switch" pool of neurons that are influenced by temperature and are the main mediators of the shortened f_v evident during hyperthermia. These neurons were further investigated in animal studies and during expiration the pneumotaxic centre of the upper pons showed increased neural activity and was suggested to be responsible for the termination of inspiration (37).

Expiratory time followed a very similar pattern to T_I during the present study (Fig 3.4B). This occurred despite any significant changes in V_T between temperature

conditions and would suggest the involvement of the ventral respiratory neurons in increasing the T_E during hyperthermia (34). The absence of any significant changes in V_T between temperature conditions however was in contrast to results of previous studies which showed a reduced V_T with passive (23) and active hyperthermia (15). In the present study however, a much lower level of exercise was used than in the previous study (15) suggesting that the variability in these results may be related in part to different levels of exercise intensity. It was also shown in this study that during the hyperthermic condition V_T decreased significantly from E1 to E2 (Fig 3.3B), which was accompanied by a small but significant rise in T_{es} from E1 to E2. This would advocate the possible existence of a temperature effect at higher levels of T_{es} on V_T, similar to that evident in previous studies (15, 23) and may suggest possible evidence of a vestigial panting response at higher core temperatures.

An increase in $V_T \cdot T_I^{-1}$ was also evident during the hyperthermic condition (Fig 3.4C) and was further enhanced during hyperthermic hypoxia (Fig 3.5C). The increased $V_T \cdot T_I^{-1}$ during hyperthermic euoxic and hypoxic exercise can be attributed mainly to the shortened T_I in each gas condition as V_T showed no significant change between temperature conditions. This finding was in agreement with a study by Mekjavic et al. (17) who showed that the inspiratory flow component increases with exercise intensity and was further amplified during hypoxic exposure. Although core temperature was not measured in Mekjavic et al.'s study (17), the inspiratory flow during hypoxia was only augmented at higher intensity levels of exercise, which are generally concomitant with an increase in body temperature (19). This would suggest that there might have been a small

core temperature effect on the ventilatory drive during hypoxia in Mekjavic et al.'s (17) study, which would be similar to that seen in the present study. In the present study two possible explanations are suggested by which an increase in core temperature influences the inspiratory flow. The first explanation would be a direct temperature effect on the central respiratory centre, particularly the dorsal respiratory neurons and/or the pneumotaxic respiratory centre. The second would be a direct warming effect on the peripheral chemoreceptors increasing their sensitivity and firing rate to a low arterial oxygen tension. The later explanation would be the most plausible cause of the augmented inspiratory flow during hyperthermic hypoxia as it has been shown that over 50 % of the HVR is under peripheral chemoreceptor control (8).

3.5.3 Variability in the hyperthermic and hypoxic ventilatory response

There was considerable inter-participant variation evident in the present study in regards to the magnitude of the ventilatory response to temperature and/or hypoxia. For hypoxia this inter-individual variability in $\dot{V}_E$ response characteristics has been well documented (29, 36). There are several considerations that can account for the variation evident in the HVR among individuals, which include the type of hypoxic stimulus, the duration and previous exposure. These were all controlled for in the present experiment; however inter-individual variability in chemoreceptor sensitivity has been shown to exist (36). Furthermore exercise has been shown to amplify the variability of this chemoreceptor sensitivity to hypoxia (29), which can help explain the significant inter-participant variation in the HVR evident in the present study.

There was also variability evident in the magnitude of the temperature response to $\dot{V}_E$. Particularly it was noted that several participants increased their f_v significantly during euoxic hyperthermia while others showed little change in f_v from the normothermic condition. This observation was similar to that made by Petersen and Vejby-Christensen et al. (23) who showed that during passive hyperthermia they also had variability in the f_v response between participants for which they further classified into low and high "f_v-responders" to elevations in core temperature. Further variability was evident in the participant's f_v response to hyperthermic hypoxia with several participants showing an exaggerated increase as compared to others. This response can be attributed to both the $\dot{V}_E$ variability in the HVR and thermal tachypnea.

In the present study we have controlled for this inter-participant variability by using a repeated measures design but there were still apparent hypoxic and temperature "responders" and non-responders" during the study. The intra-participant variability cannot be completely controlled for and therefore must be taken into account when interpreting the results. Randomizing the order of the temperature conditions for each participant however, helped control for the possible learning effect of repeated hypoxic exposure from one temperature condition to the other. The cause of the hypoxic and thermal-induced variability in $\dot{V}_E$ among individuals remains unknown and requires further investigation.

3.5.4 Core temperature regulation

In this study, we used shoulder level water immersion as a method to regulate core temperature during sub-maximal exercise at a normothermic and hyperthermic level. Esophageal temperature was used to estimate core temperature as it has been shown to closely follow cardiac temperature (10) while rectal temperature has been shown to respond sluggishly to changes in core temperature (14). A key finding of this study was the ability to maintain a steady-state core temperature during sub-maximal exercise for each temperature condition. This allowed the observation of the interaction of hypoxia and T_{es}. Previous studies attempting to provide thermal clamps during exercise were not able to maintain a steady-state normothermic or hyperthermic core temperature (4, 27). Two of the possible reasons for this result was that in these studies during normothermia the water temperature was set to low at 23°C (27) and 18°C (4) and the work rate was set to high at a $\dot{V}O_2$ of ~2 $L \cdot min^{-1}$ (4). The lower water temperatures of 18 and 23°C would have induced a metabolic response from skin (i.e. shivering) and or core cooling. In preliminary testing for our experiment, when performing exercise at water temperatures between 18°C and 25°C, we observed a thermogenic shivering response in several of our participants after about 10 min of immersion. To prevent shivering thermogenesis we used a predictive equation as described by Park et al. (21) to determine a thermoneutral water temperature based on the exercise work rate and our participants body composition. The water temperatures we employed were between 28-32°C (Table 3.1) for the normothermic conditions, which were much higher than previously reported (4, 27). Our observations did not indicate any visual signs of perspiration or shivering throughout the

protocol and this result was confirmed by the participant's comments. For the hyperthermic condition we used a similar water temperature to the two previous studies (4, 27) but we lowered the work rate in both core temperature conditions to a mean level $\dot{V}O_2$ of ~ 0.87 L·min^{-1}. This allowed our participant's T_{es} to rise steadily and reach a relative plateau after a 25-min warm-up period. As such our study was unlike the previous studies where core temperature rose at linear rate over time after the onset of exercise (4, 27).

3.5.5 Clamping end-tidal carbon dioxide

One of the consequences of the HVR is a fall in P_aCO_2. Hypocapnia can be a confounding factor to the HVR as it can depress the peripheral chemoreceptor response that is responsible for the hypoxic-induced increase in ventilation. As such a hypocapnic hypoxia allows P_aCO_2 levels to return towards normal values during sustained hypoxia (25). In goats this effect of hypocapnia was suggested to function by blunting the carotid body chemoreceptor sensitivity to a low P_aO_2 (6). In the present study the possibility of a hypocapnic response during hypoxia was eliminated by clamping $P_{ET}CO_2$ during the hypoxic phases at resting immersion levels for each participant. The results indicated that $P_{ET}CO_2$ levels for the hypoxic phase were maintained close to resting immersion values indicating that an isocapnic hypoxia was achieved.

3.5.6 The effects of water immersion on ventilation

Water immersion was used in this study to regulate T_{es}. There are several considerations of water immersion on ventilation that should be noted. It has been suggested that due to the pressure exerted on the chest from the water, the diaphragm may shift upwards decreasing the functional residual capacity (FRC) of the lungs and consequently changing the ventilation-to-perfusion ratio possibly making gas exchange in the lungs more difficult (24). Conversely, other studies have shown that water immersion is marked by a global increase in cardiac output, blood volume, and pulmonary artery pressure, which could enhance gas exchange (1).

Another possible consequence of water immersion on ventilation is an increase CO_2 storage capacity that could enhance the accumulation of metabolically produced CO_2 in the peripheral tissues. This mechanism was proposed by Chang and Lundgren (3) to occur due to the increase in CO_2 and tissue perfusion evident during whole body water immersion. They suggested that the increased tissue perfusion would cause CO_2 to be redistributed throughout the body causing an overall increase in resting $P_{ET}CO_2$ (3). In the present study a similar finding was made as $P_{ET}CO_2$ was significantly increased during water immersion along with $\dot{V}_E$ and V_T (Table 3.2). Oxygen consumption was also slightly increased, which has been suggested to be due to the increased hydrostatic pressure of water immersion causing a shift of venous blood towards the thoracic region and a transient increase in the uptake of oxygen into the blood (16).

In order to account for the possible effects of water immersion on $\dot{V}_E$ and perfusion of the lungs in the present study we employed a repeated measures design so the hydrostatic effect of immersion was constant across the two exercise conditions and would not appear to confound the expression of these results.

3.5.7 Conclusion

In conclusion, $\dot{V}_E$ was significantly increased by a hyperthermic core temperature as compared to a normothermic core temperature during low intensity euoxic exercise. The hyperthermic-induced hyperpnea appears to be mediated solely by an increase in f_v suggesting the existence of a thermal-induced tachypnea. This was also associated with a decrease in T_I which implicates the possibility of a temperature effect on the pneumotaxic centre of the central respiratory control centre which regulates inspiration. During hyperthermic hypoxic exercise an enhancement of the HVR was indicated. The augmentation of the HVR in hyperthermic hypoxia appears to be mediated primarily by f_v as no significant changes were evident in V_T from the normothermic to hyperthermic hypoxic levels. This response is also associated with an increased $V_T \cdot T_I^{-1}$ during hyperthermic hypoxia which would support the hypothesis that increased core temperature increases peripheral chemoreceptor sensitivity to hypoxia. Overall the results support the hypothesis that temperature plays a significant role in the control of ventilation, particularly during hypoxic exercise.

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3.8 References

1. **Arborelius M, Jr., Ballidin UI, Lilja B, and Lundgren CE.** Hemodynamic changes in man during immersion with the head above water. *Aerosp Med* 43: 592-598, 1972.

2. **Cabanac M and White MD.** Core temperature thresholds for hyperpnea during passive hyperthermia in humans. *Eur J Appl Physiol* 71: 71-76, 1995.

3. **Chang LP and Lundgren CE.** CO2 chemosensitivity during immersion in humans. *Chin J Physiol* 38: 7-12, 1995.

4. **Cross MC, Radomski MW, VanHelder WP, Rhind SG, and Shephard RJ.** Endurance exercise with and without a thermal clamp: effects on leukocytes and leukocyte subsets. *J Appl Physiol* 81: 822-829, 1996.

5. **Cunningham DJC and O'Riordan JLH.** The effect of a rise in temperature of the body on respiratory response to carbon dioxide at rest. *QJ Exp Physiol* 42: 329-345, 1957.

6. **Daristotle L, Berssenbrugge AD, Engwall MJ, and Bisgard GE.** The effects of carotid body hypocapnia on ventilation in goats. *Respir Physiol* 79: 123-135, 1990.

7. **Dejours P.** Chemoreflexes in breathing. *Physiol Rev* 42: 335-358, 1962.

8. **Griffiths TL, Henson LC, and Whipp BJ.** Influence of inspired oxygen concentration on the dynamics of the exercise hyperpnoea in man. *J Physiol* 380: 387-403, 1986.

9. **Grunstein MM, Fisk WM, Leiter LA, and Milic-Emili J.** Effect of body temperature on respiratory frequency in anesthetized cats. *J Appl Physiol* 34: 154-159, 1973.

10. **Hayward JS, Eckerson JD, and Kemna D.** Thermal and cardiovascular changes during three methods of resuscitation from mild hypothermia. *Resuscitation* 11: 21-33, 1984.

11. **Inomoto T, Mercer JB, and Simon E.** Interaction between hypothalamic and extrahypothalamic body temperatures in the control of panting in rabbits. *Pflugers Arch* 398: 142-146, 1983.

12. **Lambertsen CJ.** Physical, chemical, and nervous interactions in respiratory control. In: *Medical Physiology* (14 ed.), edited by Mountcastle VB, 1980, p. 1873-1900.

13. **MacDougall JD, Reddan WG, Layton CR, and Dempsey JA.** Effects of metabolic hyperthermia on performance during heavy prolonged exercise. *J Appl Physiol* 36: 538-544, 1974.

14. **Mariak Z, White MD, Lewko J, Lyson T, and Piekarski P.** Direct cooling of the human brain by heat loss from the upper respiratory tract. *J Appl Physiol* 87: 1609-1613, 1999.

15. **Martin BJ, Morgan EJ, Zwillich CW, and Weil JV.** Influence of exercise hyperthermia on exercise breathing pattern. *J Appl Physiol* 47: 1039-1042, 1979.

16. **Mekjavic IB and Bligh J.** The increased oxygen uptake upon immersion. The raised external pressure could be a causative factor. *Eur J Appl Physiol Occup Physiol* 58: 556-562, 1989.

17. **Mekjavic IB, Eiken O, LaPrairie A, and Banister EW.** The pattern of breathing during hypoxic exercise. *Eur J Appl Physiol Occup Physiol* 56: 619-622, 1987.

18. **Mekjavic IB and Rempel ME.** Determination of esophageal probe insertion length based on standing and sitting height. *J Appl Physiol* 69: 376-379, 1990.

19. **Nielsen M.** Regulation der Korpertemperatur bei Muskelarbeit. *Skand Arch Physiol* 79: 197-217, 1938.

20. **Nybo L and Nielsen B.** Middle cerebral artery blood velocity is reduced with hyperthermia during prolonged exercise in humans. *J Physiol* 534: 279-286, 2001.

21. **Park YS, Pendergast DR, and Rennie DW.** Decrease in body insulation with exercise in cool water. *Undersea Biomed Res* 11: 159-168, 1984.

22. **Petersen ES and Vejby-Christensen H.** Effect of Body Temperature on Steady State Ventilation and Metabolism in Exercise. *Acta Physiol Scand* 89: 342-351, 1973.

23. **Petersen ES and Vejby-Christensen H.** Effects of body temperature on ventilatory response to hypoxia and breathing pattern in man. *J Appl Physiol* 42: 492-500, 1977.

24. **Prefaut C, Ramonatxo M, Boyer R, and Chardon G.** Human gas exchange during water immersion. *Respir Physiol* 34: 307-318, 1978.

25. **Rapanos T and Duffin J.** The ventilatory response to hypoxia below the carbon dioxide threshold. *Can J Appl Physiol* 22: 23-36, 1997.

26. **Rasch W, Samson P, Cote J, and Cabanac M.** Heat loss from the human head during exercise. *J Appl Physiol* 71: 590-595, 1991.

27. **Rhind SG, Gannon GA, Shek PN, Brenner IK, Severs Y, Zamecnik J, Buguet A, Natale VM, Shephard RJ, and Radomski MW.** Contribution of exertional hyperthermia to sympathoadrenal-mediated lymphocyte subset redistribution. *J Appl Physiol* 87: 1178-1185, 1999.

28. **Sancheti A and White MD.** Human minute ventilation responses to carbon dioxide levels prior to and following an exercise induced hyperthermia. *International Union of Physiological Sciences Thermal Physiology Symposium*, Wollongong, Australia. Australian Physiological and Pharmacological Society, 2001, p. 134P.

29. **Sato F, Nishimura M, Igarashi T, Yamamoto M, Miyamoto K, and Kawakami Y.** Effects of exercise and CO2 inhalation on intersubject variability in ventilatory and heart rate responses to progressive hypoxia. *Eur Respir J* 9: 960-967, 1996.

30. **Savourey G, Besnard Y, Launay JC, Guinet A, Hanniquet AM, Caterini R, and Bittel J.** Short hypobaric hypoxia and breathing pattern: effect of positive end expiratory pressure. *Aviat Space Environ Med* 70: 863-866, 1999.

31. **Saxton C.** Effects of severe heat stress on respiration and metabolic rate in resting man. *Aviat Space Environ Med* 52: 281-286, 1981.

32. **Sommer LZ, Iscoe S, Robicsek A, Kruger J, Silverman J, Rucker J, Dickstein J, Volgyesi GA, and Fisher JA.** A simple breathing circuit minimizing changes in alveolar ventilation during hyperpnoea. *Eur Respir J* 12: 698-701, 1998.

33. **Stadie WC, Austin JH, and Robinson HW.** The effect of temperature on the acid-base protein equilibrium and its influence on the CO_2 absorption curve of whole blood, true and separated serum. *J Biol Chem* 66: 901, 1925.

34. **Tryba AK and Ramirez JM.** Response of the respiratory network of mice to hyperthermia. *J Neurophysiol* 89: 2975-2983, 2003.

35. **Veicsteinas A and Rennie DW.** Thermal insulation and shivering threshold in Greek sponge divers. *J Appl Physiol* 52: 845-850, 1982.

36. **Vizek M, Pickett CK, and Weil JV.** Interindividual variation in hypoxic ventilatory response: potential role of carotid body. *J Appl Physiol* 63: 1884-1889, 1987.

37. **von Euler C.** The functional organization of the respiratory phase-switching mechanisms. *Fed Proc* 36: 2375-2380, 1977.

38. **Weil JV, Byrne-Quinn E, Sodal IE, Kline JS, McCullough RE, and Filley GF.** Augmentation of chemosensitivity during mild exercise in normal man. *J Appl Physiol* 33: 813-819, 1972.

39. **Whipp BJ.** Ventilatory control during exercise in humans. *Annu Rev Physiol* 45: 393-413, 1983.

40. **White MD and Cabanac M.** Exercise hyperpnea and hyperthermia in humans. *J Appl Physiol* 81: 1249-1254, 1996.

3.9 Tables

Table 3.1 Participant physical characteristics and water temperature (T_w) calculated for each exercise condition.

Participant	Age (yr)	Weight (kg)	Height (m)	BSA (m^2)	SS (mm)	I_{rest}	T_w (°C) Normothermic	T_w (°C) Hyperthermic
1	27	97.2	1.84	2.19	157.2	0.197	28.2	38.1
2	21	76.4	1.88	2.02	81.2	0.119	31.8	38.3
3	22	71.4	1.75	1.86	85.8	0.124	31.6	38.3
4	22	72.7	1.80	1.91	66.4	0.104	32.5	38.3
5	22	62.3	1.68	1.71	79.8	0.118	31.9	38.3
6	29	79.0	1.78	1.97	122.8	0.162	29.9	38.2
7	21	66.5	1.67	1.75	65.7	0.103	32.6	38.3
8	34	69.0	1.83	1.90	56.9	0.094	33.0	38.3
9	22	77.3	1.75	1.93	80.2	0.118	31.9	38.3
10	22	71.5	1.74	1.86	88.0	0.126	31.5	38.2
11	19	72.0	1.73	1.85	85.3	0.123	31.6	38.3
Mean	**23.7**	**74.1**	**1.77**	**1.9**	**88.1**	**0.126**	**31.5**	**38.2**
SD	4.4	9.0	0.06	0.1	28.5	0.031	1.4	0.1

Body surface area (BSA); Sum of skinfolds (SS); Overall body insulation at rest (I_{rest}).

Table 3.2 Mean resting ventilatory values for pre-immersion and immersion in the water filled tub.

The mean for the pre-immersion rest period was taken over a 30 min steady-state period. The mean for the immersion rest period was taken over a 5 min steady-state period.

	$P_{ET}CO_2$ (mmHg)	$\dot{V}_E$ ($L \cdot min^{-1}$)	V_T (L)	f_v ($breaths \cdot min^{-1}$)	$\dot{V}O_2$ ($L \cdot min^{-1}$)
Pre-immersion	4.76 (0.35)	9.8 (1.0)	0.66 (.09)	15.7 (1.8)	0.22 (.03)
Immersion	5.19 (0.44)	11.5 (1.6)	0.75 (.14)	16.4 (2.5)	0.32 (.06)
Δ (Immersion – pre-immersion)	+0.42*	+1.8*	+0.09*	+0.8	+0.1*
P (2-tailed)	0.002	0.001	0.004	0.089	0.001
95 % [CI]	[0.2, 0.65]	[1.0, 2.6]	[0.04, 0.15]	[-0.1, 1.7]	[0.06, 0.13]

Values are mean values (SD) for normothermic immersion sessions (* = significant at $P < 0.05$).

3.10 Figures

Fig. 3.1 Time course of ventilation (V_E), oxygen consumption (VO_2), end-tidal CO_2 ($P_{ET}CO_2$), arterial oxygen saturation (S_aO_2), and esophageal temperature (T_{es}) for a typical participant (participant 5) during the normothermic condition.
R1 represents rest out of water; R2 represents rest in-water; Warm-up represents the warm-up exercise period; E1 represents the first steady-state euoxic exercise period; H1 represents the steady-state hypoxic exercise period; E2 represents the second steady-state euoxic exercise period. , normothermic condition; ■, hyperthermic condition.

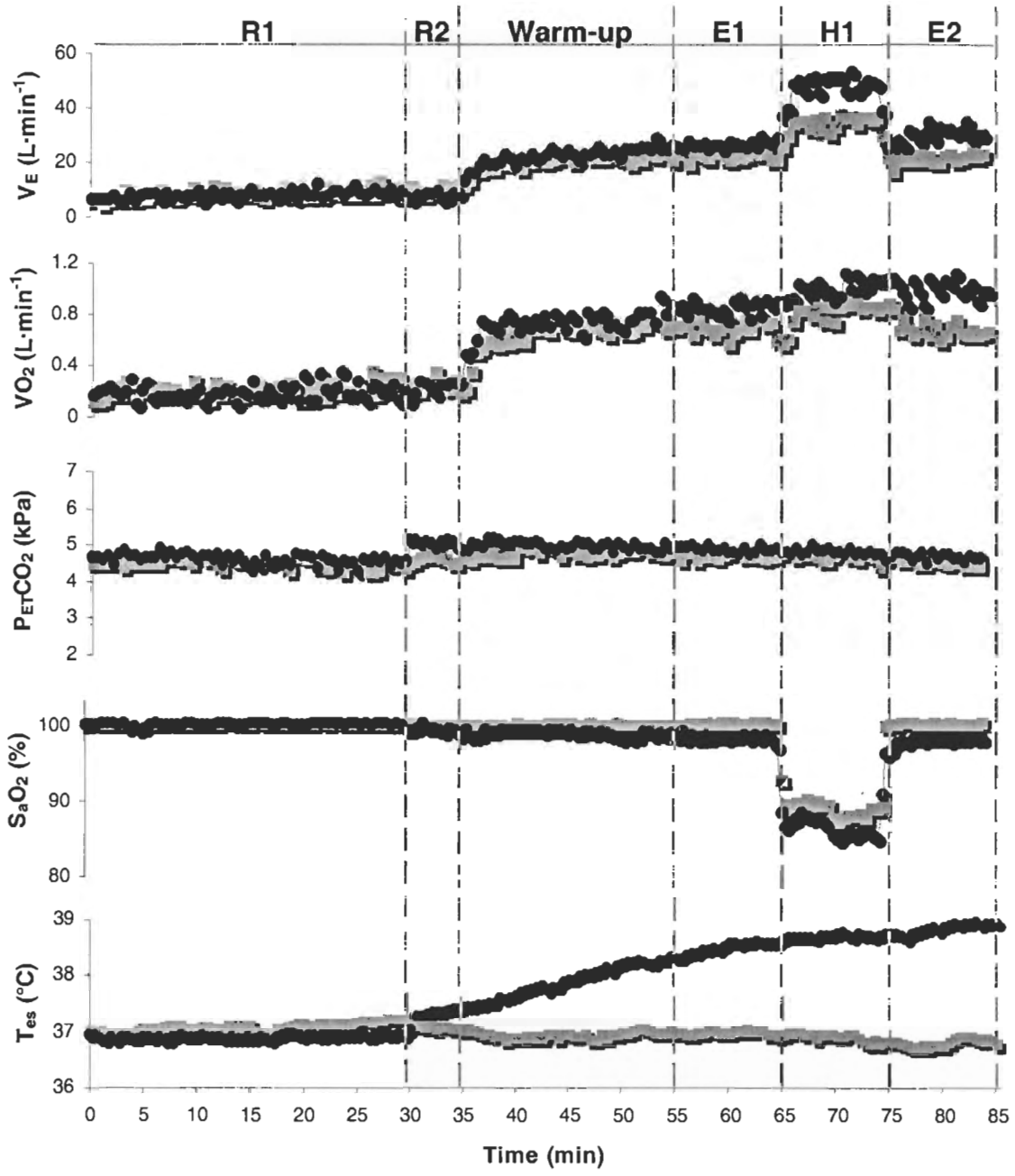


Fig. 3.2 Esophageal temperature (T_{es}) for pre-immersion rest and each exercise phase. Values are means for 11 participants. Rest period represents the 30-min pre-immersion period, E1 represents the 1st 10-min euoxic exercise period, H1 represents the 10-min hypoxic period, and E2 represents the 2nd 10-min euoxic period. , normothermic condition; ■, hyperthermic condition. Error bars represent the SD (**significant at $P < 0.01$, NS non-significant at $P > 0.1$).

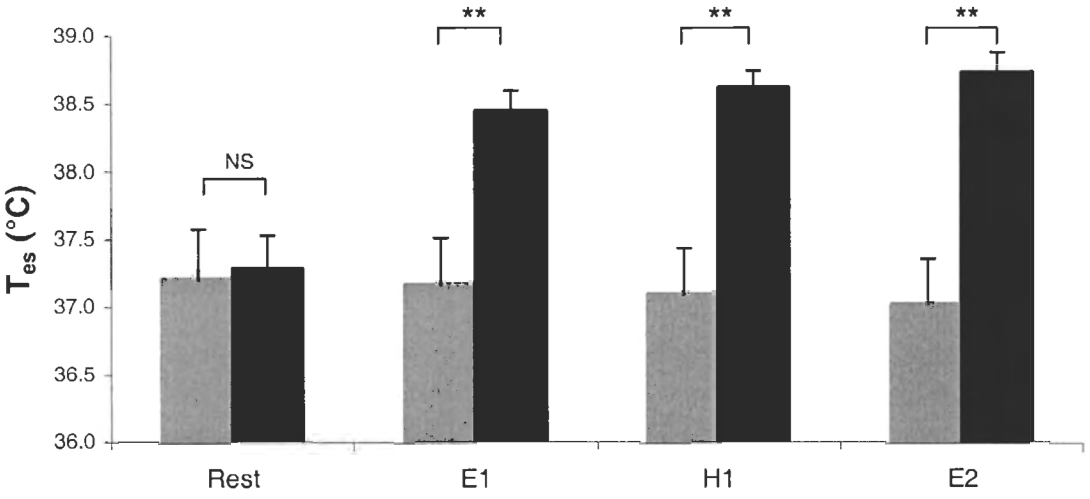


Fig. 3.3 Time course of mean ventilation (V_E), tidal volume (V_T) and ventilation frequency (f_v) for each exercise phase.

E1, euoxic exercise phase; H1, hypoxic exercise phase; E2, recovery euoxic exercise phase. ▒, normothermic condition; ■, hyperthermic condition. Error bars represent the SD (*significant at $P < 0.05$, **significant at $P < 0.01$, † significant from E1 at $P < 0.05$, ‡ significant from E1 at $P < 0.01$, NS non-significant at $P > 0.1$).

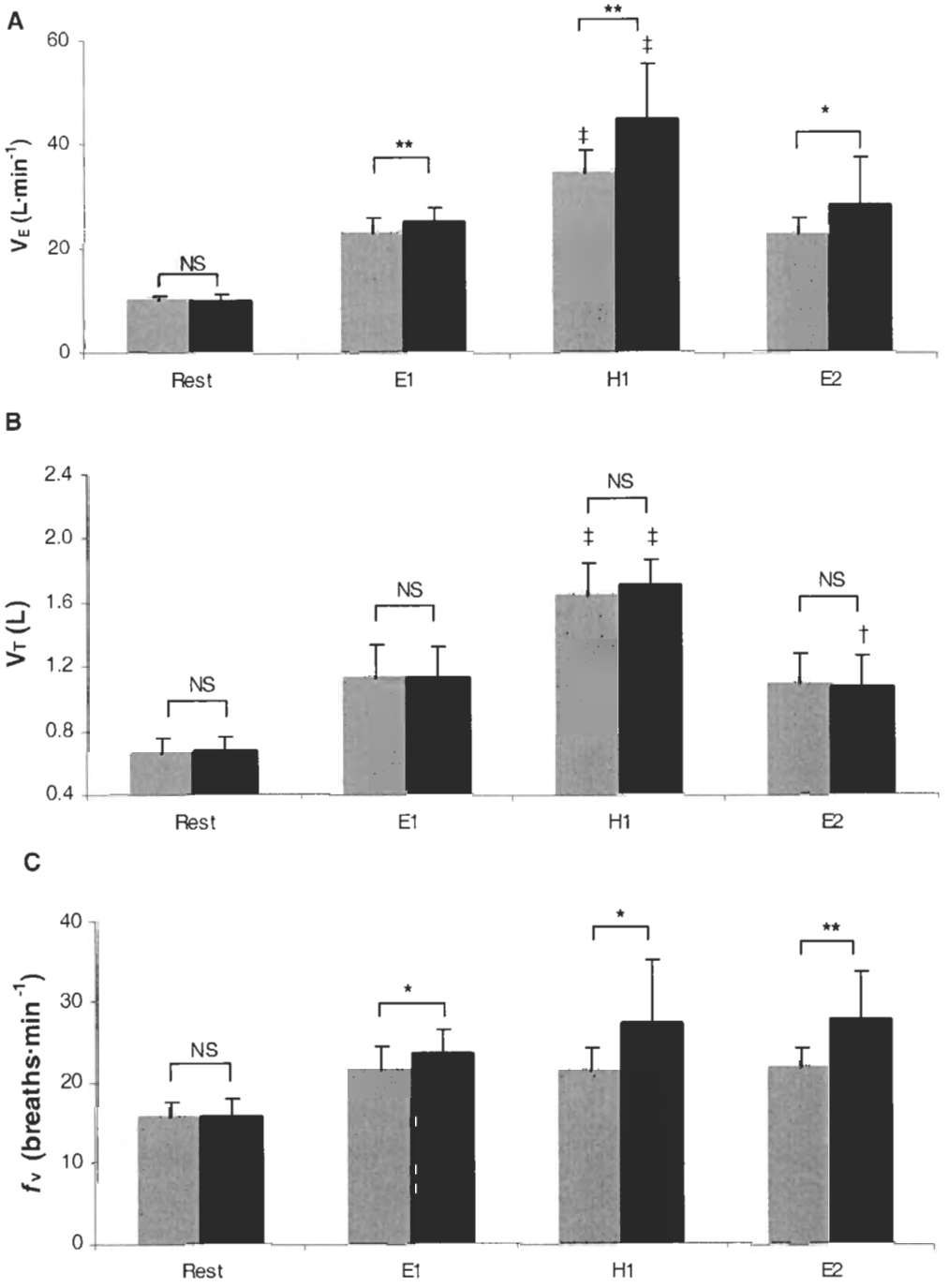


Fig. 3.4 **Time course of mean inspiratory time (T_I), expiratory time (T_E) and inspiratory flow or "drive" ($V_T \cdot T_I^{-1}$) for each exercise phase.**
E1, euoxic exercise phase; H1, hypoxic exercise phase; E2, recovery euoxic exercise phase. ■, normothermic condition; ■, hyperthermic condition. Error bars represent the SD (*significant at P < 0.05, **significant at P < 0.01, ‡ significant from E1 at $P < 0.01$, NS non-significant at $P > 0.1$, $P = 0.06$ bordered significance from E1)

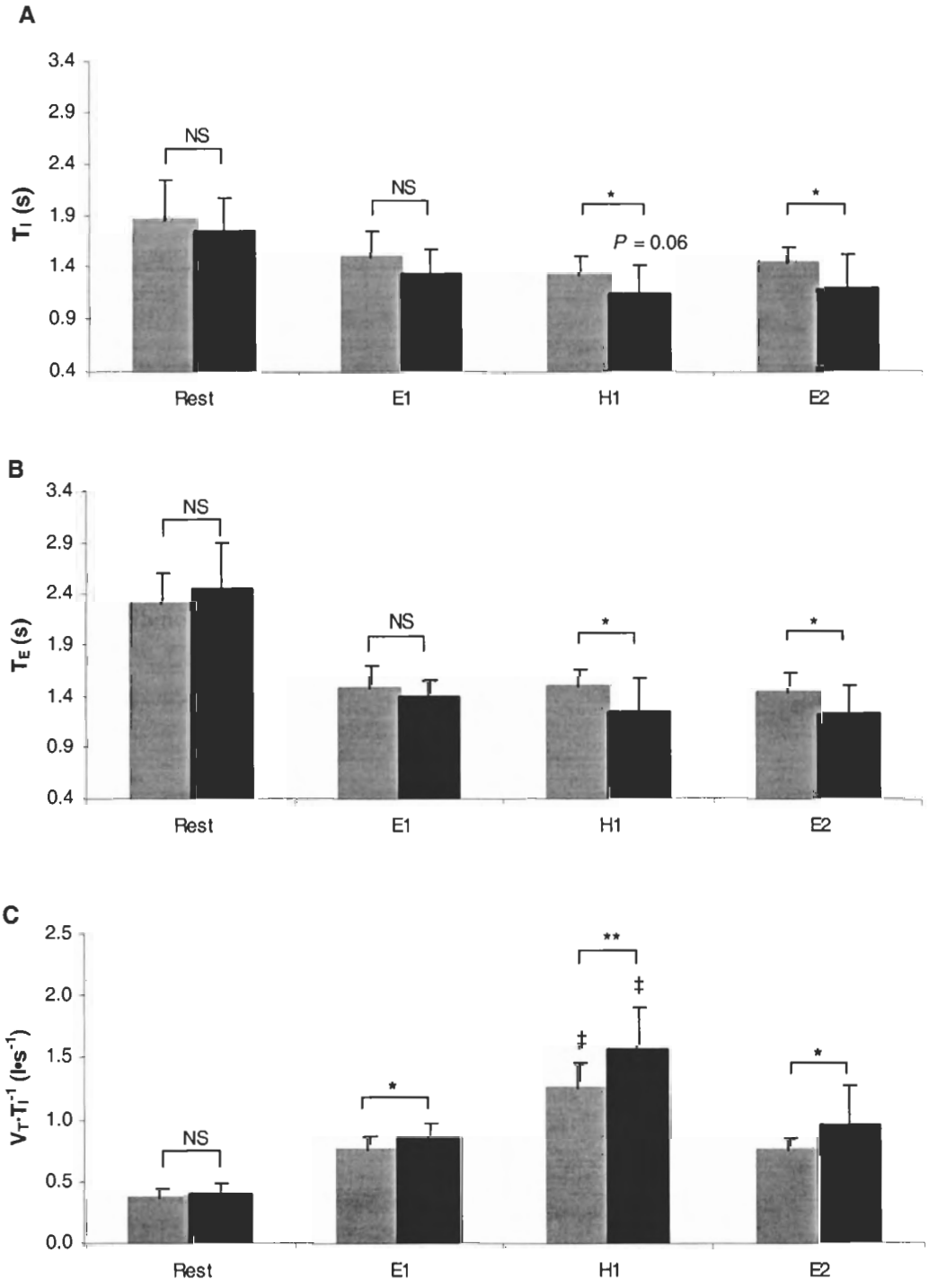


Fig. 3.5 Interaction effects of Core Temperature and Gas Type for ventilation (V_E), ventilation frequency (f_v), and mean inspiratory flow ($V_T \cdot T_I^{-1}$).
Values represent the mean increase from the normothermic to hyperthermic condition in V_E, f_v, and $V_T \cdot T_I^{-1}$ for each exercise phase. E1, euoxic exercise phase; H1, hypoxic exercise phase; E2, recovery euoxic exercise phase. Error bars represent the SD (*significant at $P < 0.05$, **significant at $P < 0.01$, NS non-significant at $P > 0.1$)

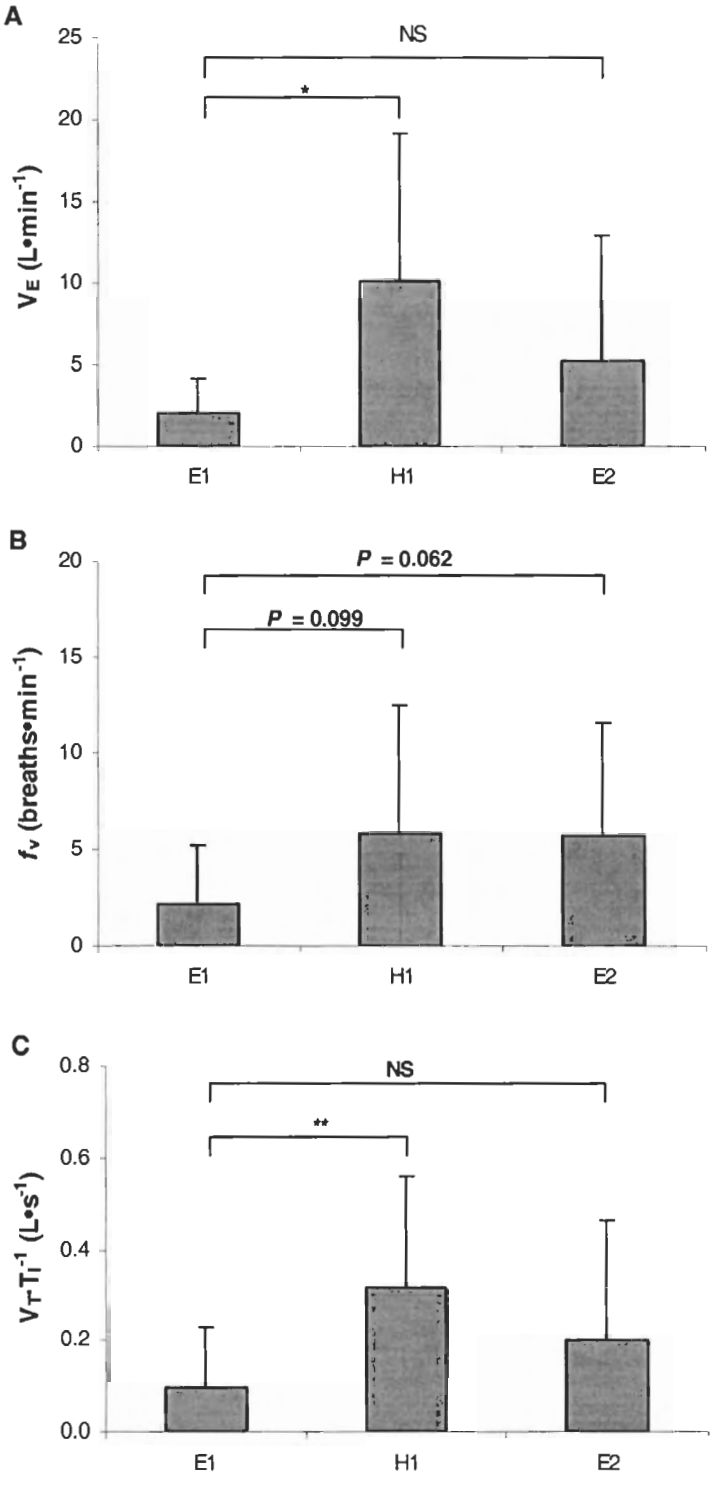
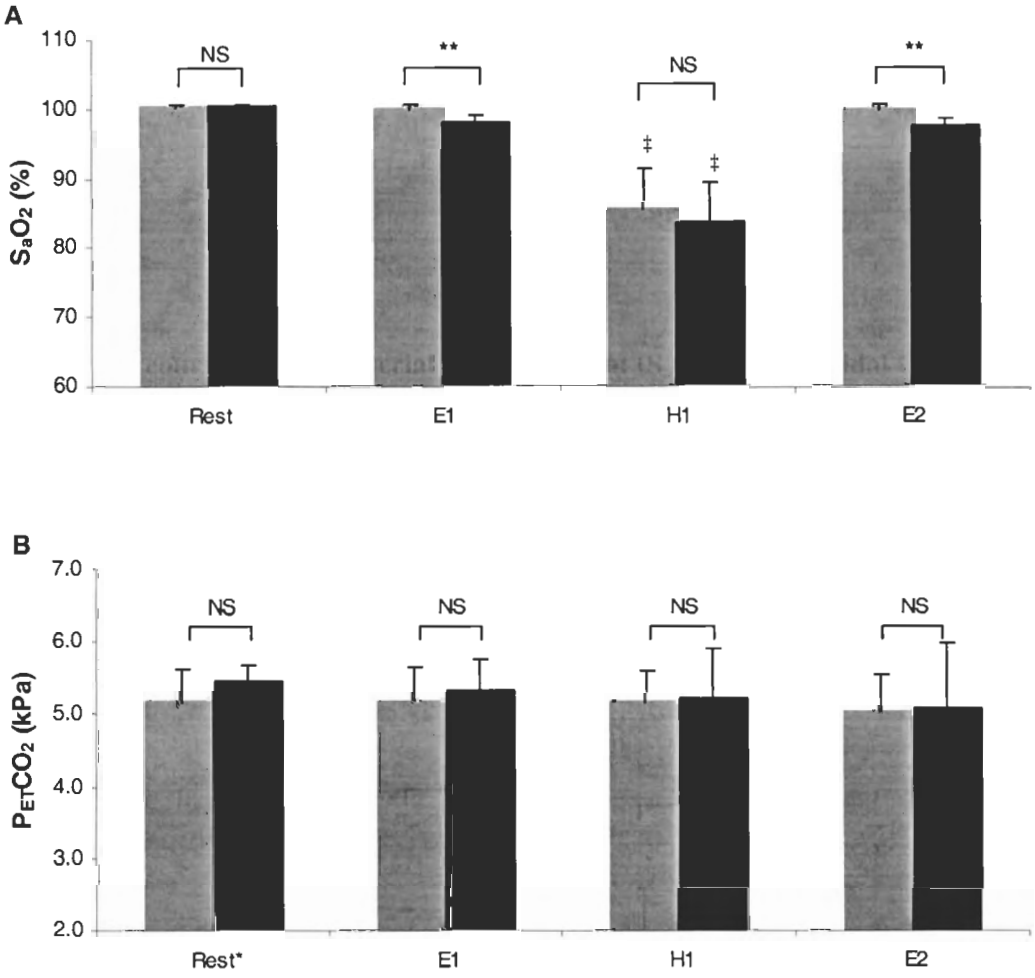


Fig 3.6 Time course of mean arterial oxygen content (S_aO_2) and end-tidal CO_2 ($P_{ET}CO_2$) for each exercise phase.

$P_{ET}CO_2$ was clamped for the hypoxic (H1) condition by the titration of 100 % CO2 to the inspirate. E1, euoxic exercise phase; H1, hypoxic exercise phase; E2, recovery euoxic exercise phase. ■, normothermic condition; ■, hyperthermic condition. Rest* represents the mean of the 5 min in-water resting period. Error bars represent the SD (**significant at $P < 0.01$, NS non-significant at $P > 0.1$, ‡ significant from E1 at $P < 0.01$).



CHAPTER 4 STUDY 2

Body temperature modulation of ventilatory kinetics during the onset of low intensity exercise and hypoxia in humans

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Running Head: "Hyperthermia and hypoxia ventilation kinetics"

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4.1 Abstract

The effects of elevated esophageal temperature (T_{es}) and skin temperature (T_{sk}) were investigated for their potential influence on the ventilation ($\dot{V}_E$) response during both the transition from rest to low intensity exercise and from low intensity exercise with air to that with hypoxia. In either a 'hyperthermic' core temperature or a 'normothermic' core temperature session, 11 college-aged, healthy male volunteers were immersed to the shoulders and pedalled on an underwater cycle ergometer at a steady-state oxygen consumption ($\dot{V}O_2$) of 0.87 $L \cdot min^{-1}$ (SD 0.07). Following a 30-min rest and 20-min warm-up, a 20-min steady-state cycling period was divided into two 10-min gas phases when participants inhaled: air (Euoxia 1 (E1)) or hypoxic gas (12 % O_2 and 88 % N_2 (H1)). End-tidal CO_2 ($P_{ET}CO_2$) was maintained at an isocapnic level of 5.19 kPa (SD 0.71) throughout the exercise. A mono-exponential model was fitted to the $\dot{V}_E$ response to the onsets of exercise and of hypoxia. For the $\dot{V}_E$ response from rest to exercise, results indicated a significantly shortened time constant (τ) of 49.3 s (SD 20.3) (P = 0.032) for the hyperthermic condition as compared to the τ of 109.6 s (SD 84.4) for the normothermic condition. Between the two temperature conditions for the $\dot{V}_E$ response from rest to exercise the difference in τ was also found to negatively correlate with the difference in T_{es} ($R^2 = 0.829$, $P = 0.011$). In contrast, between the temperature conditions there was no significant difference for the τ values of the $\dot{V}_E$ kinetic response to the onset of hypoxia during low intensity exercise. The responses of tidal volume (V_T)

and ventilation frequency (f_v) during both transition from rest to exercise and euoxic to hypoxic exercise showed no core temperature-induced difference suggesting they do not independently influence the $\dot{V}_E$ response. In conclusion, results supported an elevated T_{es} but not T_{sk} influenced the $\dot{V}_E$ response during the onset of exercise. As well, T_{es} and T_{sk} both had no influence on the $\dot{V}_E$ response during the transition from low intensity euoxic to low intensity hypoxic exercise.

4.2 Introduction

In response to a step increase in work rate both $\dot{V}O_2$ and carbon dioxide production ($\dot{V}CO_2$) abruptly increase due to an increase in metabolic demand at the exercising muscles and this is followed by an increase in pulmonary gas exchange. With the start of exercise at a fixed low to moderate intensity ($\leq$ ~60 % of $\dot{V}O_{2peak}$), ventilation increases proportionately to $\dot{V}O_2$ and a new steady state of ventilation is established at these exercise intensities. (30). The kinetics of this response is characterized by a mono-exponential function (13, 27, 34).

During rest the lowering of arterial oxygen content (S_aO_2) to ~80 % has been shown to stimulate an acute proportionate increase in ventilation (9, 14). The increase is mediated primarily by the stimulation of the peripheral chemoreceptors due to low P_aO_2 levels (7, 12). This initial increase in ventilation has been further shown to be proceeded by a gradual fall in ventilation which is commonly evident in progressive hypoxia tests (9). However, during isocapnic hypoxia ventilation remains consistently elevated for up to 15 minutes after the initial peak increase before a significant ventilatory depression is evident (9, 14, 32). The ventilation response to acute isocapnic hypoxia can then also be described by a mono-exponential function as a new steady-state elevated ventilation is established (9, 14).

There are several established factors that can influence the increase of ventilation from rest to exercise and euoxic to hypoxic exercise. These factors include varying levels of exercise intensity (33), P_aO_2 (27), and P_aCO_2 (28). A less established mediator of the ventilation response to exercise is body temperature. In a study by Vejby-Christensen and Petersen (23) an elevated body temperature was shown to increase ventilation during the first 2 breaths immediately following the onset of exercise. They suggested this response may be due to an interaction of temperature on the respiratory control centres increasing their sensitivity to neural stimuli from exercise (23). In this study however the effects of skin temperature were not separated from core temperature. For resting humans it is well established that increasing core temperature causes a hyperpnea (2, 16, 19) and it is has been suggested that core temperature influences hypoxic ventilation by possible stimulation of the peripheral chemoreceptors (20). Whether elevations in core and/or skin temperature cause the enhancement of ventilation from rest to exercise and/or the elevation of ventilation evident in the hypoxic ventilatory response (HVR) during steady-state moderate exercise is unknown and is the focus of this study.

The specific questions asked in this study were: 1) Do skin and core temperature influence the increase in $\dot{V}_E$ during the transition from rest to exercise and 2) Does an elevation in skin and core temperature influence the increase in $\dot{V}_E$ during the transition from euoxic to hypoxic exercise. As described in Chapter 3, the ability to study the effect of core temperature on the $\dot{V}_E$ response to the onset of exercise and to hypoxia was

possible by implementing an innovative approach (18) that allows a clamping of core temperature at normothermic levels during exercise.

4.3 Methods

4.3.1 Participants

Eleven healthy male university participants, age 19-34 years old (height 1.77 m (SD 0.06), weight 74.1 kg (SD 9.0) and body surface area 1.9 m^2 (0.1)) volunteered to participate in the study. Power calculation results for sample size justification are given in Appendix C. All participants were non-smokers, non-asthmatics and refrained from caffeine for 12 h prior to each test. Prior to the experimentation the participants were informed of the potential risk associated with the protocol and after a 24 h reflection period gave their written, informed consent to participate in the experiment. The participants all attended a preliminary testing period where they were familiarized with the experimental protocol and instrumentation. During the preliminary testing period the participants performed a sub-maximal exercise protocol on an underwater cycle ergometer to determine their level of fitness and ensure they would be able to undergo the experimental protocol (Appendix B). Ethics approval for the study was received from the S.F.U. Office of Research Ethics prior to experimentation.

All experimental sessions were within ± 60 min of each other and started at between 10am or 1pm. Participants were also required to fast, exercise and refrain from drinking any warm beverages for a minimum of 5 hours prior each experimental session.

Participants were clad in shorts and kayak boots during the experiments. A medical emergency kit including a defibrillator was available at all times.

4.3.2 Instrumentation

Pulmonary function variables and ventilatory excursions were measured using a breath-by-breath Sensormedics V_{max} 229c metabolic cart (Sensormedics, Yorba Linda, CA, USA). Participants wore a nose clip and were fitted with a mouthpiece connected to a Mass Flow Sensor. The mouthpiece was connected to a two-way flow sensor housing, which was connected to a 2-way non-rebreathing valve (NRB 2700, Hans Rudolph Inc, Kansas Cit, MO, USA) that was connected with 3.8 cm diameter corrugated Collins tubing to a 350 L Tissot spirometer. Breath-by-breath gas samples were drawn from the inspired and expired air to the metabolic cart at a rate of 500 $ml \cdot min^{-1}$. Carbon dioxide partial pressure was measured using non-dispersive infrared Spectroscopy and oxygen concentration was measured using a paramagnetic sensor. A premixed hypoxic gas of 12 % O_2 and balanced nitrogen (N_2) from a compressed gas bottle was used to fill the Tissot spirometer for the hypoxic condition. A fan mounted on the Tissot spirometer was used to mixed gas within its bell during the hypoxic condition. In addition, between conditions the Tissot was flushed with room air to remove any residual gases from the hypoxic trials.

Arterial oxygen saturation (S_aO_2) was continuously measured with a pulse oximeter (Masimo Radical, Irvine, CA, USA) positioned on the participants' left ear lobe. Esophageal temperature was measured by placing a paediatric size temperature thermocouple probe of approximately 2 mm in diameter through the participants' nostril, while they were asked to sip water through a straw. The location of the tip of the probe in the oesophagus was past the nares, at the T8/T9 level, a position bounded by the left ventricle and aorta. This position is based on the equation of Mekjavic and Rempel (17) for standing height: L (cm) = 0.228 x (standing height) - 0.194. The participant was then immersed to the level of the shoulders in a water-filled tub and sat on a hydraulically braked, underwater cycle ergometer. Water temperature was maintained at a specific temperature so as to maintain T_{es} at either a normothermic or hyperthermic level. The determination of these water temperature (T_w) levels and their values for each participant is described in Chapter 3 under the subheading 'Water Temperature calculations'.

An analog signal for f_v from the V_{max} cart was used to trigger data collection for body temperatures, heart rate and hemoglobin saturation on acquired a National Instruments data acquisition system SCXI-1000 (Austin, USA) that was controlled by LabVIEW program (National Instruments, Austin, USA, version 5.1).

4.3.3 Protocol

All participants volunteered for 2 separate exercise-testing sessions, with each session separated by at least one week. Half of the participants were randomly chosen to

start with the hyperthermic session and the other half started with the normothermic session. After instrumentation each protocol began with a 30-min rest period in room air to establish a stable resting T_{es}. For the exercise session, the participants were seated on a stationary underwater bicycle ergometer in water up to their shoulder level and instrumented with a weight belt to avoid floatation. A metronome was used to maintain the pedalling cadence and the participant was monitored continuously to assure adherence. The determination for the prescribed work rate for the participants is given in Chapter 3 under the subheading 'Protocol'.

Each exercise session was performed at a constant work rate and was preceded by a 5-min in-water rest period. This was followed by a 20-min warm-up cycle period where a steady state $\dot{V}_E$ and core temperature were achieved and a 20-min testing cycle period. For the normothermic condition T_{es} was held at 37.09°C (SD 0.33) and for the hyperthermic condition T_{es} was held at 38.60°C (SD 0.14) for the 20-min testing cycle (Chapter 3, Fig 3.2). Both the warm-up and testing period were completed at the same work rate and cadence and there were no rest phases between each period. The 20-min testing period was divided into two continuous 10-min steady state exercise phases: a 10-min euoxic exercise period where the participant breathed room air and a 10-min hypoxic exercise period where the participant breathed the hypoxic gas mixture (12 % O_2, balanced N_2). All participants followed this protocol in the same order for all sessions. Arterial oxygen content (S_aO_2) was lowered to 85.6 % (SD 5.7) (Chapter 3, Fig 3.6A) in the normothermic condition and 83.5 % (SD 5.7) in the hyperthermic condition during the hypoxic exercise phase. If the $P_{ET}CO_2$ fell below resting water-immersed values, 100

% CO_2 was manually titrated into the inspirate via a non-re-breathing demand valve apparatus as described by Sommer et al. (22) to bring the $P_{ET}CO_2$ back to resting, water-immersed levels. The purpose for clamping of $P_{ET}CO_2$ was to maintain an isocapnic hypoxia, which would alleviate the possibly confounding effects of a hyperventilation-induced hypocapnia, which is often associated with hypoxia, and was suggested to diminish the HVR (21). The resting water-immersed $P_{ET}CO_2$ levels (3) were determined during the 5-min rest session immediately prior to commencing the exercise session. End-tidal CO_2 ($P_{ET}CO_2$) was maintained at an isocapnic level of 5.19 kPa (SD 0.71) during all exercise conditions (Chapter 3, Fig 3.6B).

4.3.4 Calibrations and Analysis

Calibrations of esophageal thermocouple probes were completed in regulated temperature hot water baths (Appendix A). Gas analyzers were calibrated against two gases of known concentrations (4 % CO_2, 16 % O_2, balanced N_2 and 26 % O_2, balanced N_2, and air) and the mass flow sensor was calibrated manually by the use of a 3 litre syringe prior to each experiment.

To mathematically evaluate the ventilatory response during transition from rest to moderate exercise and euoxic to hypoxic exercise the following mono-exponential function was employed (27):

$$\dot{V}_E(t) = \dot{V}_E(ss) \bullet (1 - e^{t/\tau})$$

Where $\dot{V}_E(t)$ is the increase in the $\dot{V}_E$ above the previous steady state value at any given time (t); $\dot{V}_E(ss)$ is the difference between the first steady state and the second steady state level; and τ is the time to reach 63 % of $\dot{V}_E(t)$. This equation was also used to evaluate the kinetics of the ventilatory components: V_T and f_v.

In order to investigate the whether the difference in time constants (τ) of the $\dot{V}_E$ response between the temperature conditions can be better explained by the difference in ΔT_{es} or ΔT_{sk}, a univariate correlation analysis was employed. A step-wise multiple regression was then employed using a general linear model (GLM) to determine the contributions of ΔT_{es} and/or ΔT_{sk} to the explanation of the variance in $\Delta\tau$. The GLM incorporated the parameters of ΔT_{es} and ΔT_{sk} in both normothermic and hyperthermic conditions and subsequently analyzed the variance of $\Delta\tau$ for the effects of ΔT_{es} and ΔT_{sk}. The exclusion criterion for the stepwise model was a non-significant contribution to the explanation of the variance of $\Delta\tau$ (i.e. $P > 0.05$). To detect for possible outliers in the regression analysis, Cook's distance D values were determined for the values of each participant. A case with a D value greater than 1.0 has been shown to have unusual leverage on the model and is the suggested exclusion criterion for outliers (15). In the current study cases with D values > 1.0 were excluded from the regression model.

A paired-samples *t*-test was used to compare the parameters of the mono-exponential function for the $\dot{V}_E$ response during both the normothermic and

hyperthermic condition. A P value of < 0.05 was considered significant. All values are expressed as the mean ± the Standard Deviation (SD) and 95 % Confidence Intervals [CI] of the difference between means are given in square brackets following each P value stated. Sigma Plot 8.0 (Systat Inc., Evanston, Ill., USA) was used to derive the mono-exponential equation. SPSS 12.0 (SPSS Inc., Chicago, Ill., USA) was used for all the statistical analyses.

4.4 Results

All participants were able to complete the full exercise protocol including 10 min of hypoxic exposure with only mild signs or symptoms of hypoxia including hyperventilation, lethargy, and slight nausea. The mean water temperature for the normothermic condition was 31.5°C (SD 1.3) and for the hyperthermic condition was 38.2°C (SD 0.1)

During the 30-min rest period prior to the commencement of the normothermic exercise sessions, resting T_{es} was 37.20°C (SD 0.37) and prior to the hyperthermic exercise sessions resting T_{es} was not significantly different at 37.28°C (SD 0.24) (P = 0.386, CI [-0.1, 0.3]). After immersion in water for a 5-min period T_{es} was maintained at a thermoneutral level of 37.13°C (SD 0.41) for the normothermic condition and was elevated to 37.53°C (SD 0.16) in the hyperthermic condition; this gave a significant difference of 0.40°C (P = 0.002, CI [0.19, 0.62]) between temperature conditions. The chest T_{sk} after 5 min of immersion was 31.97°C (SD 0.85) in the normothermic condition and was elevated to 37.44°C (SD 0.32) in the hyperthermic condition, a significant difference between temperature conditions by 5.47°C (P = 0.000, CI [4.78, 6.16]) (Table 4.1).

For both the normothermic and hyperthermic conditions a typical sample participant's ventilatory response for the transition from rest to exercise is given in Figure 4.1. The increase in $\dot{V}_E$ followed the pattern of a mono-exponential function attaining a new steady state within ~5 min from the onset of exercise. The time constants (τ) for this transition phase in the normothermic and hyperthermic conditions are given Table 4.2. The mean τ for the normothermic condition was 109.6 s (SD 84.4) and for the hyperthermic condition was 49.3 s (SD 20.3) producing a mean significant difference of 60.4 s (SD 80.5) ($P = 0.032$, CI [6.3, 114.5]). There was no significant difference between temperature conditions for the amplitude or baseline of the $\dot{V}_E$ response to exercise.

Results from the stepwise multiple regression indicated that the variance in $\Delta\tau$ was significantly explained by ΔT_{es} ($R^2 = -0.829$, $P = 0.001$) and ΔT_{sk} did not significantly contribute to the explanation of variance of τ ($R^2 = 0.123$, $P = 0.196$) (Fig. 4.2). Participant 4 was excluded from the regression model as their Cook's distance, D value of 1.13 was greater than the outlier exclusion value of 1.0.

For both the normothermic and hyperthermic conditions a typical sample participant's $\dot{V}_E$ response to the transition from the euoxic steady state to hypoxic steady state exercise is given in Figure 4.3. The increase in $\dot{V}_E$ followed the pattern of a mono-exponential function attaining a new steady state within ~5 min from the transition from steady state euoxic to steady state hypoxic exercise. The τ for this transition phase in the

normothermic and hyperthermic conditions is given Table 4.4. The time course to reach the steady-state level was variable between both temperature conditions and the mean τ for the normothermic and hyperthermic condition was not significantly different at 83.2 s (SD 44.4) and 80.7 s (SD 25.8) respectively ($P = 0.880$).

The components of $\dot{V}_E$ (i.e. f_v and V_T) were also analyzed for their changes from rest to exercise and euoxic to hypoxic exercise for both the normothermic and hyperthermic condition. For the V_T response, 10 of the 11 participants from rest to exercise, and 9 out of 11 participants from euoxic to hypoxic exercise fit the mono-exponential model. One of the participants showed no evident step change in V_T during the transition periods from rest to exercise and two participants similarly showed no evident step change in V_T during the step change from euoxic to hypoxic exercise. Since their responses did not follow a mono-exponential pattern the τ value and amplitude was not calculated. For the participants that fit the model, the results indicated that there was no significant temperature effect on the kinetic of responses by V_T for both the transition from rest to exercise (Table 4.3) or for the transition from euoxic to hypoxic exercise (Table 4.5). For f_v there was no consistent change indicated from rest to exercise or euoxic to hypoxic exercise and therefore f_v cannot be characterized under the mono-exponential model. For both the V_T and f_v a typical sample participant's response to the transition from the rest to exercise in Figure 4.4 and from euoxic steady state to hypoxic steady state exercise is given in Figure 4.5.

4.5 Discussion

4.5.1 Body temperature modulation of ventilatory dynamics during exercise

The first main finding of the present study was that the time constants for $\dot{V}_E$ during the transition from rest to exercise were significantly less in the hyperthermic relative to the normothermic condition (Table 4.2). This was in agreement with a previous study by Vejby-Christensen and Petersen who showed a hyperthermic enhancement of the ventilation response to exercise. However in Vejby-Christensen and Petersen's study (23) only 3 subjects were investigated and only the first two breaths were analyzed. In the current study $\dot{V}_E$ response for both temperature conditions to exercise followed the pattern of a mono-exponential function, which was in agreement with previous studies (27, 30) and thus we were able to look at the full dynamic response of the change in $\dot{V}_E$ from resting levels to steady-state exercise levels.

The ventilation response from rest to low intensity exercise has been proposed to increase in two distinct temporal phases (7). Phase I (ϕ_I) represents the initial, usually rapid ventilatory increase evident with the onset of exercise. This initial increase is maintained on average for approximately 10 to 20 seconds (7, 29), and was suggested to be neurally mediated with little influence from the peripheral chemoreceptors (33). This was inferred by studies showing that hypoxia (7, 27) and surgical resection of the carotid bodies (12, 31) did not influence the magnitude or onset of this initial ventilatory

response. Phase II (ϕ_2) represents the slower, exponential increase in ventilation which begins approximately 20 seconds after the onset of exercise and lasts about 2 to 3 minutes (34). The increase in ventilation at this phase was shown to be mediated by the carotid bodies (27, 31, 35). Following ϕ_2 ventilation begins to plateau, reaching steady-state which characterizes the third phase (34).

In the present study a significant shortening of the τ value for $\dot{V}_E$ was evident while the participants began exercising in hot water at ~38.2°C (hyperthermic condition) relative to that in thermoneutral water of ~31.5°C. Both T_{sk} and T_{es} were significantly increased during the hyperthermic condition when exercise was initiated (Table 4.1). To determine which variable could better explain the changes in τ a multiple regression model was employed. The variance in τ showed a significant negative association with the variance in T_{es} (Fig. 4.2A), while the variance in T_{sk} showed no significant association with the variance in τ and was excluded from the regression model (Fig. 4.2B). This would indicate that T_{es} can explain the variance in τ better than T_{sk} and suggests that it may be a significant mediator of the change in τ evident between temperature conditions. The mechanism by which increasing core temperature might shorten the kinetics of the ventilatory response to exercise has not yet to our knowledge been investigated. However, it has been shown previously that the sensitivity to the carotid bodies increases during warming (10), which would suggest the possible involvement of the peripheral chemoreceptors in mediating this enhanced ventilatory kinetic response.

It has been previously suggested by Cunningham et al. (5) that there may be a direct physical effect of increased temperature on the cells of the central respiratory centres in the medulla oblongata and/or on the peripheral chemoreceptors thereby enhancing the reactivity of these respiratory control mechanisms to their normal stimuli. This hypothesis has been further supported in studies on passive body core warming that indicated an increased peripheral chemoreceptor sensitivity during hyperthermic states suggesting this to be a proponent of the increased core temperature (20). The dorsal respiratory "pacemaker" and vagal neurons of the central respiratory control centre have also been implicated in mediating an increase in ventilation during hyperthermia in cats (11). In humans a similar association has been made (16, 20) and the pneumotaxic centre of the upper pons has been suggested to be the area influenced by an increase in core temperature (25). This would be in agreement with the findings of the present study and support the possibility that the small increase in T_{es} may have influenced the sensitivity of both the peripheral chemoreceptors and the central respiratory control centre and enhanced the dynamics of the $\dot{V}_E$ response to the onset of exercise.

For kinetics of the transition from rest to exercise, a consideration of the present results is that the T_{es} was only slightly elevated in the warming condition and a true hyperthermia was not achieved. All previous studies (5, 20) suggesting a core temperature effect on the peripheral chemoreceptors were done under true hyperthermic states (a minimum of 1°C increase). However, despite being only a minor increase, the change in T_{es} was still significantly different from the normothermic condition when T_{es}

was effectively clamped and prevented from rising. This suggests even a small increase in core temperature of ~0.4°C (Table 4.2) may have a significant effect on the peripheral chemoreceptor and/or central control of the ventilatory dynamics to exercise. It would be beneficial in a future study to look at varied degrees of body warming and its effect on ventilatory kinetics during the onset of moderate exercise. This may help establish if there is a graded influence of temperature for the kinetics of the change in $\dot{V}_E$ from rest to exercise. A challenge in a potential future study will be to separate the central and peripheral effects of temperature on $\dot{V}_E$ kinetics from rest to low intensity exercise.

Another consideration is that T_{es} rose gradually during the onset of exercise in the hyperthermic condition, as the participants had not yet reached a steady-state core temperature. It has been demonstrated by Cunningham (5) that the respiratory response to warming was greater while the core temperature was rising than it was to a constant elevated temperature. The mechanism that may account for this hypothesis is unknown however it does not preclude the possibility that an increasing core temperature could influence peripheral chemoreceptor control in a similar fashion as that of a constant elevated core temperature.

4.5.2 Body temperature modulation of the ventilatory dynamic response to hypoxia during low intensity exercise

The second main finding of the present study was that the ventilatory 'on-kinetics' of hypoxia were not significantly influenced by a steady-state elevation in T_{es}

and T_{sk}. The $\dot{V}_E$ response for both temperature conditions to hypoxia appeared to follow the pattern of a mono-exponential function, but the τ values for the responses were variable (Table 4.4) with no significant difference between core temperature conditions. A significant temperature effect however was evident for the amplitude of the $\dot{V}_E$ response to hypoxia (Table 4.4). It is well known that the HVR is primarily under peripheral chemoreceptor control (6, 12). It has further been proposed that the enhanced HVR during hyperthermia is due to an increased peripheral chemoreceptor sensitivity (20) and this is reasoned to be mediated by a direct temperature effect on the carotid bodies (10). This hypothesis would suggest the involvement of an elevated body temperature stimulating the peripheral chemoreceptors and possibly having an effect on the kinetics of the HVR. Our results however showed while there was an evident increase in amplitude of the HVR the time course was uninfluenced by an elevated body temperature. There are several possibilities why the kinetics of the hypoxic response may not have been affected by changes in body temperature during steady state exercise.

One possibility why the kinetics of the hypoxia onset was not affected is that elevated body temperatures may only influence certain components of the time course of the HVR. The time course of the HVR in cats is mediated by three components, two peripheral stimulatory components and one central depressant component (1). The peripheral components have been shown to develop faster in most cases and cause a consequent stimulation of ventilation (9, 14, 24). The peripheral components can be divided further into a fast and slow acting component in the peripheral chemoreceptors, which counter the slow acting central depressing component in the central nervous

system (1). The fast acting component of the peripheral chemoreceptors seems to be responsible for the initial increase in ventilation evident in the HVR (1). The central depressant component in cats has been shown to have a time course of up to 10 minutes (24, 26), which is a similar duration to the slow component of the peripheral chemoreceptors (1) and both have a time course too long to be account for the ventilation kinetics during transition from euoxic to hypoxic exercise. The overall magnitude of the effects of the peripheral and central components determines the magnitude of the HVR (1). In the present study we found an effect of temperature on the amplitude of the HVR (Table 4.4), which we suggest is mediated in part by increased peripheral chemoreceptor sensitivity. This would indicate the possibility that the sensitivity of the slow component of the peripheral chemoreceptors may have been increased during hyperthermia (i.e. an increase in amplitude of the $\dot{V}_E$ response), while the fast component of the peripheral chemoreceptors may have not been significantly influenced by temperature.

Another possibility is that the mono-exponential model may not be able to fully describe the hypoxic ventilatory dynamics. In a study by Clement and Robbins (4) they showed the kinetics of the HVR were highly variable between and within participants. They suggested that a single set of dynamic parameters could not describe all the responses and that a first order model could not fully describe the hypoxic ventilatory dynamics. An alternative model has been suggested by Berkenbosch et al.(1), which takes into account the individual variation in hypoxic sensitivity, the level of hypoxia and shape parameter of the hypoxic response. Yet another model has been described by Dutton et al. (8) who suggest a fourth-order function to describe the ventilatory response

to hypoxia. It appears there is no current standardized model to accurately explain the kinetics of the HVR. Thus, although all the participants' responses to hypoxia in the present study appeared to fit the mono-exponential model, a more comprehensive model that involves pre-determined inter-participant hypoxic sensitivities may be necessary to detect for smaller changes in the kinetics that may be brought about by influencing factors such as core and skin temperatures.

4.5.3 The response of the components of ventilation and their influence on ventilation kinetics

Analysis of the V_T and f_v during the $\dot{V}_E$ kinetic response from rest to exercise and from euoxic to hypoxic exercise showed similar results. Between temperature conditions V_T showed no significant changes in τ values for the kinetics of the response, while f_v didn't follow a mono-exponential model. This would provide further evidence that the changes in ventilatory kinetics from euoxia to hypoxia are not mediated solely by V_T or f_v but are more likely mediated by a combination of changes in both components.

4.5.4 Conclusion

In conclusion, as evidenced by an enhancement of the ventilatory dynamics from rest to exercise during body warming, there is a strong support for the hypothesis that increased core but not skin temperature influences the kinetics of $\dot{V}_E$ during the transition from resting to exercise $\dot{V}_E$. The results also suggest that only a small change in T_{es} (~0.4°C) is needed to demonstrate this effect. It is also concluded during low to

moderate steady exercise, that the overall time course for the change in $\dot{V}_E$ from euoxic to hypoxic breathing can be described by a mono-exponential model but appears to be uninfluenced by increased core or skin temperature. Finally the initial increase in $\dot{V}_E$ during the transition from rest to exercise and from euoxic to hypoxic exercise appears to be mediated primarily by V_T with little influence from f_v.

4.6 Acknowledgements

The authors would like to thank Julia P. H. Christensen, Duncan Milne and Darryl Whitney for tireless help during this study. Special thanks are also given to the Airevac Paramedics who provided medical supervision during the study.

4.7 Grants

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4.8 References

1. **Berkenbosch A, DeGoede J, Ward DS, Olievier CN, and VanHartevelt J.** Dynamic response of the peripheral chemoreflex loop to changes in end-tidal O2. *J Appl Physiol* 71: 1123-1128, 1991.

2. **Cabanac M and White MD.** Core temperature thresholds for hyperpnea during passive hyperthermia in humans. *Eur J Appl Physiol* 71: 71-76, 1995.

3. **Chang LP and Lundgren CE.** CO2 chemosensitivity during immersion in humans. *Chin J Physiol* 38: 7-12, 1995.

4. **Clement ID and Robbins PA.** Dynamics of the ventilatory response to hypoxia in humans. *Respir Physiol* 92: 253-275, 1993.

5. **Cunningham DJC and O'Riordan JLH.** The effect of a rise in temperature of the body on respiratory response to carbon dioxide at rest. *QJ Exp Physiol* 42: 329-345, 1957.

6. **Dejours P.** Chemoreflexes in breathing. *Physiol Rev* 42: 335-358, 1962.

7. **Dejours P.** Control of respiration in muscular exercise. In: *Handbook of Physiology*, edited by Society AP. Washington, DC: Williams & Wilkins, 1964, p. 631-648.

8. **Dutton RE, Smith EJ, Ghatak PK, and Davies DG.** Dynamics of the respiratory controller during carotid body hypoxia. *J Appl Physiol* 35: 844-850, 1973.

9. **Easton PA, Slykerman LJ, and Anthonisen NR.** Ventilatory response to sustained hypoxia in normal adults. *J Appl Physiol* 61: 906-911, 1986.

10. **Eyzaguirre C, Monti-Bloch L, and Hayashida Y.** Effects of temperature on denervated carotid body (glomus) cells. *Brain Res* 279: 282-285, 1983.

11. **Grunstein MM, Fisk WM, Leiter LA, and Milic-Emili J.** Effect of body temperature on respiratory frequency in anesthetized cats. *J Appl Physiol* 34: 154-159, 1973.

12. **Honda Y.** Role of carotid chemoreceptors in control of breathing at rest and in exercise: studies on human subjects with bilateral carotid body resection. *Jpn J Physiol* 35: 535-544, 1985.

13. **Hughson RL and Morrissey M.** Delayed kinetics of respiratory gas exchange in the transition from prior exercise. *J Appl Physiol* 52: 921-929, 1982.

14. **Kagawa S, Stafford MJ, Waggener TB, and Severinghaus JW.** No effect of naloxone on hypoxia-induced ventilatory depression in adults. *J Appl Physiol* 52: 1030-1034, 1982.

15. **Kleinbaum D, Kupper L, and Muller K.** *Applied regression analysis and other multivariable methods.* Boston: PWS-KENT Publishing Company, 1988.

16. **Martin BJ, Morgan EJ, Zwillich CW, and Weil JV.** Influence of exercise hyperthermia on exercise breathing pattern. *J Appl Physiol* 47: 1039-1042, 1979.

17. **Mekjavic IB and Rempel ME.** Determination of esophageal probe insertion length based on standing and sitting height. *J Appl Physiol* 69: 376-379, 1990.

18. **Park YS, Pendergast DR, and Rennie DW.** Decrease in body insulation with exercise in cool water. *Undersea Biomed Res* 11: 159-168, 1984.

19. **Petersen ES and Vejby-Christensen H.** Effect of Body Temperature on Steady State Ventilation and Metabolism in Exercise. *Acta Physiol Scand* 89: 342-351, 1973.

20. **Petersen ES and Vejby-Christensen H.** Effects of body temperature on ventilatory response to hypoxia and breathing pattern in man. *J Appl Physiol* 42: 492-500, 1977.

21. **Rapanos T and Duffin J.** The ventilatory response to hypoxia below the carbon dioxide threshold. *Can J Appl Physiol* 22: 23-36, 1997.

22. **Sommer LZ, Iscoe S, Robicsek A, Kruger J, Silverman J, Rucker J, Dickstein J, Volgyesi GA, and Fisher JA.** A simple breathing circuit minimizing changes in alveolar ventilation during hyperpnoea. *Eur Respir J* 12: 698-701, 1998.

23. **Vejby-Christensen H and Petersen ES.** Effect of body temperature on ventilatory transients at start and end of exercise in man. *Respir Physiol* 17: 315-324, 1973.

24. **Vizek M, Pickett CK, and Weil JV.** Interindividual variation in hypoxic ventilatory response: potential role of carotid body. *J Appl Physiol* 63: 1884-1889, 1987.

25. **von Euler C.** The functional organization of the respiratory phase-switching mechanisms. *Fed Proc* 36: 2375-2380, 1977.

26. **Ward DS, Berkenbosch A, DeGoede J, and Olievier CN.** Dynamics of the ventilatory response to central hypoxia in cats. *J Appl Physiol* 68: 1107-1113, 1990.

27. **Ward SA, Blesovsky L, Russak S, Ashjian A, and Whipp BJ.** Chemoreflex modulation of ventilatory dynamics during exercise in humans. *J Appl Physiol* 63: 2001-2007, 1987.

28. **Ward SA, Whipp BJ, Koyal S, and Wasserman K.** Influence of body CO2 stores on ventilatory dynamics during exercise. *J Appl Physiol* 55: 742-749, 1983.

29. **Wasserman K, Whipp BJ, Casaburi R, and Beaver WL.** Carbon dioxide flow and exercise hyperpnea. Cause and effect. *Am Rev Respir Dis* 115: 225-237, 1977.

30. **Wasserman K, Whipp BJ, and Davis JA.** Respiratory physiology of exercise: metabolism, gas exchange, and ventilatory control. *Int Rev Physiol* 23: 149-211, 1981.

31. **Wasserman K, Whipp BJ, Koyal SN, and Cleary MG.** Effect of carotid body resection on ventilatory and acid-base control during exercise. *J Appl Physiol* 39: 354-358, 1975.

32. **Weil JV and Zwillich CW.** Assessment of ventilatory response to hypoxia: methods and interpretation. *Chest* 70: 124-128, 1976.

33. **Whipp BJ.** Peripheral chemoreceptor control of exercise hyperpnea in humans. *Med Sci Sports Exerc* 26: 337-347, 1994.

34. **Whipp BJ, Ward SA, Lamarra N, Davis JA, and Wasserman K.** Parameters of ventilatory and gas exchange dynamics during exercise. *J Appl Physiol* 52: 1506-1513, 1982.

35. **Whipp BJ and Wasserman K.** Carotid bodies and ventilatory control dynamics in man. *Fed Proc* 39: 2668-2673, 1980.

4.9 Tables

Table 4.1 Esophageal and skin temperatures during the normothermic and hyperthermic condition for the mean of the last 30 s of in-water rest prior to the onset of low intensity exercise in each condition.
Participants performed a steady state, head-out exercise on an underwater ergometer at a low exercise intensity ($\dot{V}O_2$ ~ 0.8 to 1.0 L • min-1) in the normothermic and hyperthermic conditions.

Subject	T_{es} (°C) normo	T_{es} (°C) hyper	ΔT_{es} (°C)	T_{sk} (°C) normo	T_{sk} (°C) hyper	ΔT_{sk} (°C)
1	37.46	37.53	0.07	30.12	37.73	7.61
2	37.24	37.51	0.28	32.20	37.45	5.25
3	36.47	37.33	0.86	31.51	37.46	5.95
4	36.52	37.35	0.84	32.46	36.93	4.47
5	36.97	37.46	0.49	32.35	37.54	5.19
6	37.35	37.42	0.07	30.69	37.50	6.81
7	37.27	37.65	0.38	32.33	37.62	5.29
8	36.74	37.65	0.91	32.91	36.76	3.85
9	37.50	37.72	0.22	32.64	37.87	5.23
10	37.71	37.83	0.11	32.24	37.49	5.25
11	37.16	37.43	0.27	32.17	37.44	5.27
Mean	**37.13**	**37.53**	**0.41**	**31.97**	**37.44**	**5.47**
	**			**		
SD	0.41	0.16	0.33	0.85	0.32	1.03

T_{es} represents the esophageal temperature, T_{sk} represents the chest skin temperature expressed, "normo" and "hyper" represent the normothermic and hyperthermic condition respectively (** = significant at $P < 0.01$).

Table 4.2 The parameters of the mono-exponential model fitted to the ventilation ($\dot{V}_E$) data for a step change in work rate from rest to a low intensity exercise level. Participants performed a steady state, head-out exercise on an underwater ergometer at a low exercise intensity ($\dot{V}O_2$ ~ 0.8 to 1.0 L • min-1) in the normothermic and hyperthermic conditions.

Subject	τ (s) normo	τ (s) hyper	Δτ (s)	Amp (L) normo	Amp (L) hyper	Baseline (L) normo	Baseline (L) hyper
1	79.8	79.1	-0.7	8.1	9.8	9.8	11.4
2	50.5	39.7	-10.8	10.3	13.1	11.8	13.1
3	287.5	53.0	-234.5	11.5	13.1	12.7	12.7
4	28.4	20.2	-8.2	10.5	12.7	11.7	11.3
5	118.0	65.9	-52.1	11.7	13.7	10.2	7.9
6	100.5	61.6	-38.9	9.0	11.6	10.3	11.6
7	58.0	39.1	-18.9	10.5	11.3	13.3	14.2
8	244.3	41.8	-202.5	13.7	10.2	13.5	13.0
9	64.3	42.7	-21.6	9.8	7.0	12.4	12.7
10	39.1	20.7	-18.4	7.9	8.2	11.0	11.2
11	135.1	78.4	-56.7	10.9	10.7	10.3	9.2
Mean	**109.6**	**49.3**	**-60.3**	**10.4**	**11.0**	**11.5**	**11.7**
	*			NS		NS	
SD	84.4	20.3	80.5	1.7	2.1	1.3	1.8

τ is the time constant for the ventilatory kinetic response, T_{es} represents the esophageal temperature, T_{sk} represents the chest skin temperature expressed, "normo" and "hyper" represent the normothermic and hyperthermic condition respectively (* = significant $P < 0.05$, NS non significant at $P > 0.1$).

Table 4.3 The parameters of the mono-exponential model fitted to the tidal volume (V_T) data for a step change in work rate from rest to a low intensity exercise level. Participants performed a steady state, head-out exercise on an underwater ergometer at a low exercise intensity ($\dot{V}O_2$ ~ 0.8 to 1.0 L • min-1) in the normothermic or hyperthermic conditions.

Subject	τ (s) normo	τ (s) hyper	Δτ (s)	Amp (L) normo	Amp (L) hyper	Baseline (L) normo	Baseline (L) hyper
1	23.7	72.8	49.1	0.36	0.55	0.81	0.73
2	64.2	30.7	-33.5	0.47	0.53	0.62	0.68
3	28.4	7.3	-21.1	0.74	0.60	0.81	0.68
4	15.1	6.3	-8.8	0.48	0.51	0.67	0.61
5	160.9	232.9	72.0	0.27	0.31	0.54	0.66
6	56.3	74.1	17.8	0.32	0.47	0.54	0.55
7	30.6	92.8	62.2	0.41	0.66	0.69	0.76
8	97.0	61.8	-35.2	0.55	0.60	0.85	0.79
9	140.4	57.8	-82.6	0.43	0.27	0.79	0.73
10	57.9	49.6	-8.3	0.39	0.37	0.58	0.62
11	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Mean	**67.5**	**68.6**	**1.2**	**0.44**	**0.49**	**0.69**	**0.68**
	NS			NS		NS	
SD	50.2	64.3	48.9	0.13	0.13	0.12	0.07

τ is the time constant for the V_T kinetic response, Amp is the amplitude of the step change in V_T expressed, Baseline is the steady-state V_T level prior to the hypoxic stimulus, "normo" and "hyper" represent the normothermic and hyperthermic condition respectively (NS non significant at $P > 0.1$).

Table 4.4 The parameters of the mono-exponential model fitted to the ventilation ($\dot{V}_E$) data for a step change from euoxic (E1) exercise (F_IO_2 = 0.2093) to a hypoxic (H1) exercise (F_IO_2 = 0.12)

Participants performed a steady state, head-out exercise on an underwater ergometer at a low exercise intensity ($\dot{V}O_2$ ~ 0.8 to 1.0 L • min-1) in the normothermic or hyperthermic conditions.

Subject	τ (s) normo	τ (s) hyper	Δτ (s)	Amp ($L \cdot min^{-1}$) normo	Amp ($L \cdot min^{-1}$) hyper	Baseline ($L \cdot min^{-1}$) normo	Baseline ($L \cdot min^{-1}$) hyper
1	93.5	103.7	10.2	13.6	14.4	19.1	23.3
2	46.9	109.8	62.9	17.9	21.3	22.0	26.3
3	74.8	66.2	-8.6	15.6	35.8	25.1	27.2
4	166.4	99.3	-67.1	5.4	11.6	26.7	27.4
5	74.6	65.6	-9.0	14.2	26.6	22.3	26.8
6	56.8	55.4	-1.4	10.1	11.8	20.4	23.1
7	96.9	117.8	20.9	17.6	16.9	23.9	28.8
8	144.3	31.6	359.8	12.0	32.2	22.6	29.2
9	30.1	79.2	49.1	10.6	11.3	22.7	21.3
10	105.2	73.2	-32.0	12.4	18.1	19.8	21.2
11	25.5	85.7	60.2	13.2	21.3	21.3	21.4
Mean	**83.2** NS	**80.7**	**40.5**	**13.0** **	**20.1**	**22.4** **	**25.1**
SD	44.4	25.8	113.0	3.6	8.4	2.3	3.1

τ is the time constant for the ventilatory kinetic response, T_{es} represents the esophageal temperature, T_{sk} represents the chest skin temperature expressed, "normo" and "hyper" represent the normothermic and hyperthermic condition respectively (= significantly different from the normothermic condition at $P < 0.01$, NS non significant at $P > 0.1$).**

Table 4.5 The parameters of the mono-exponential model fitted to the tidal volume (V_T) data for a step change from euoxic (E1) exercise (F_IO_2 = 0.2093) to a hypoxic (H1) exercise (F_IO_2 = 0.12).

Participants performed a steady state, head-out exercise on an underwater ergometer at a low exercise intensity ($\dot{V}O_2$ ~ 0.8 to 1.0 L • min-1) in the normothermic or hyperthermic conditions.

Subject	τ (s) normo	τ (s) hyper	Δτ (s)	Amp (L) normo	Amp (L) hyper	Baseline (L) normo	Baseline (L) hyper
1	48.2	70.8	22.6	0.69	0.71	1.05	1.11
2	12.2	54.9	42.7	0.92	0.84	1.03	1.04
3	136.3	62.8	-73.5	0.34	0.51	1.49	1.12
4	n/a	n/a	-8.0	n/a	n/a	n/a	n/a
5	17.5	9.5	1.8	0.45	0.47	0.79	0.87
6	25.2	27.0	8.7	0.48	0.47	0.88	1.02
7	35.6	44.3	47.7	0.76	0.74	1.10	1.16
8	n/a	n/a	n/a	n/a	n/a	n/a	n/a
9	25.8	73.5	-18.5	0.54	0.73	1.08	0.95
10	71.4	34.6	-1.5	0.58	0.63	0.97	0.97
11	25.6	7.1	38.5	0.79	0.82	0.94	0.94
Mean	**44.2**	**42.7**	**6.0**	**0.62**	**0.66**	**1.04**	**1.02**
	NS			NS		NS	
SD	38.9	24.9	35.9	0.19	0.14	0.20	0.10

τ is the time constant for the V_T kinetic response, Amp is the amplitude of the step change in V_T expressed, Baseline is the steady-state V_T level prior to the hypoxic stimulus, "normo" and "hyper" represent the normothermic and hyperthermic condition respectively (NS non significant at $P > 0.1$).

4.10 Figures

Fig. 4.1 **A sample participant's (Participant 5) ventilation ($\dot{V}_E$) response to the onset of low intensity exercise in the normothermic and hyperthermic condition.** The smooth curve running between points is the model fit for the mono-exponential function. The τ values are the time constant for each curve, T_{es} represents esophageal temperature and T_{sk} represents chest skin temperature.

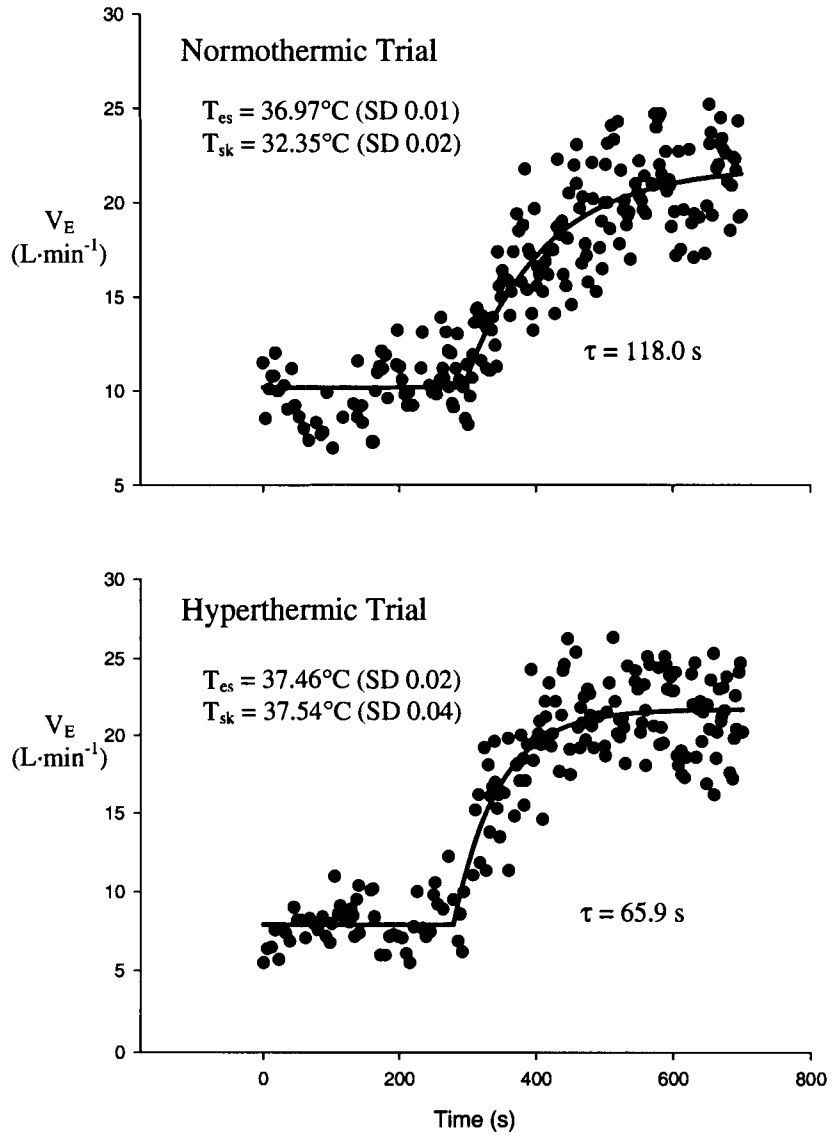


Fig 4.2 Simple correlation plots of the regression analysis for the ventilation response from rest to low intensity exercise.

The difference in time constants ($\triangle\tau$) between the normothermic and hyperthermic condition are plotted against the difference in esophageal temperature ($\triangle T_{es}$) in (A), and skin temperature ($\triangle T_{sk}$) in (B). (Regression analysis was done with 10 participants. Participant 4 showed a Cook's distance, D value of 1.13 which was above the outlier cut-off of 1.0 and was thereby excluded from the regression model.)

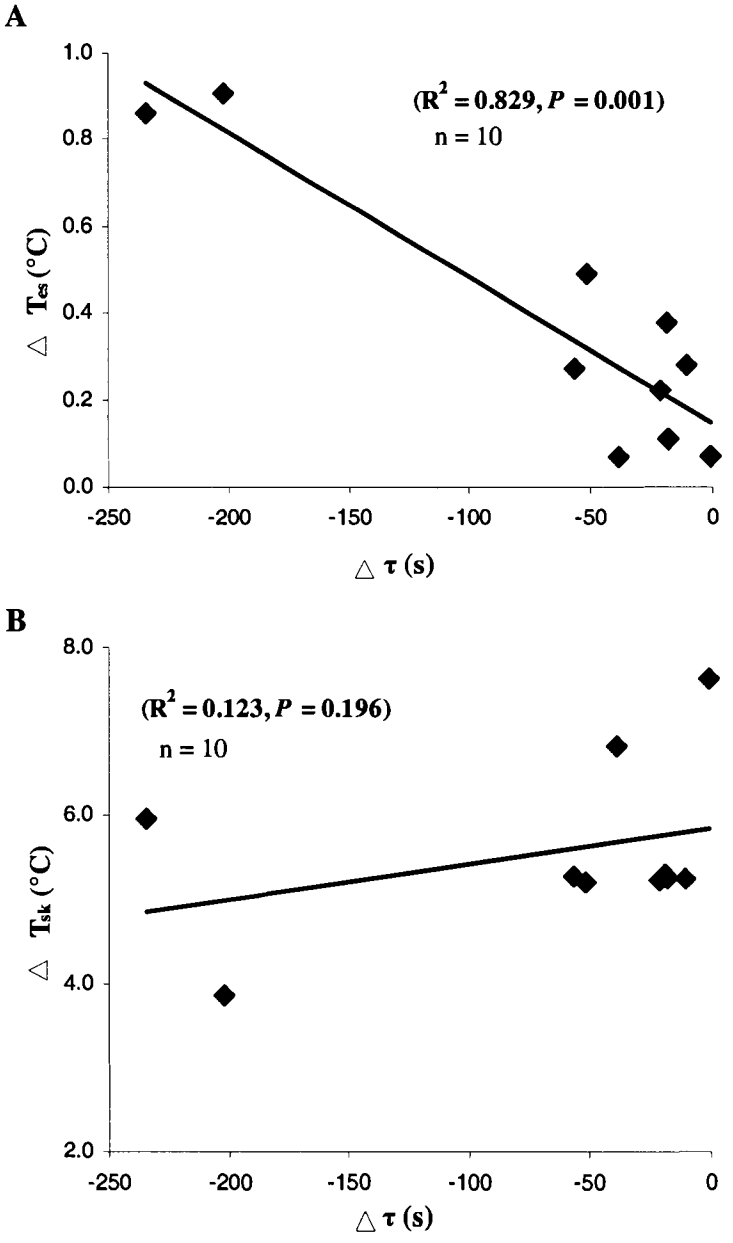


Fig. 4.3 A sample participant's (Participant 5) ventilation ($\dot{V}_E$) response from euoxia (E1) to hypoxia (H1) during low intensity exercise for the normothermic and hyperthermic conditions.

The smooth curve running between points is the model fit for the mono-exponential function. The τ values are the time constants for each curve, T_{es} represents esophageal temperature.

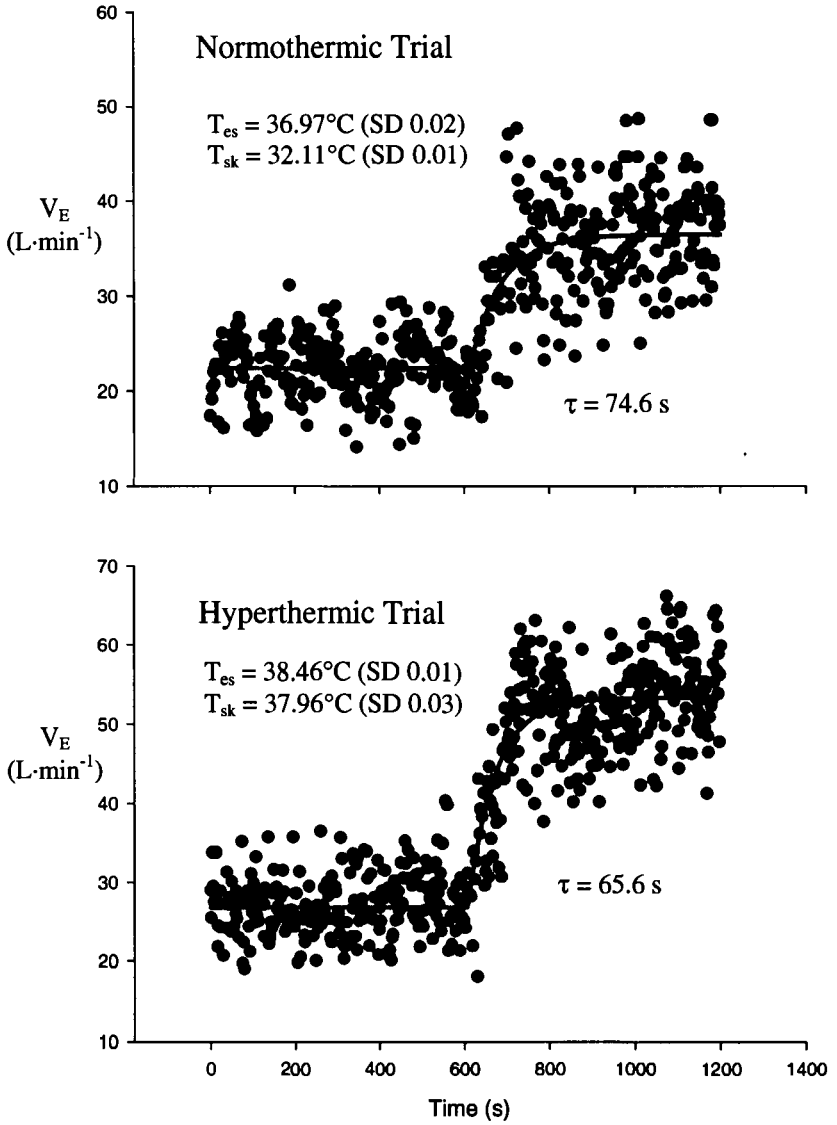


Fig. 4.4 A sample participant's (Participant 10) ventilation frequency (f_v) and tidal volume (V_T) response to the step change from rest to low intensity exercise for the hyperthermic condition.

The smooth curve running between points is the model fit for the mono-exponential function. The τ values are the time constants for each curve, T_{es} represents esophageal temperature.

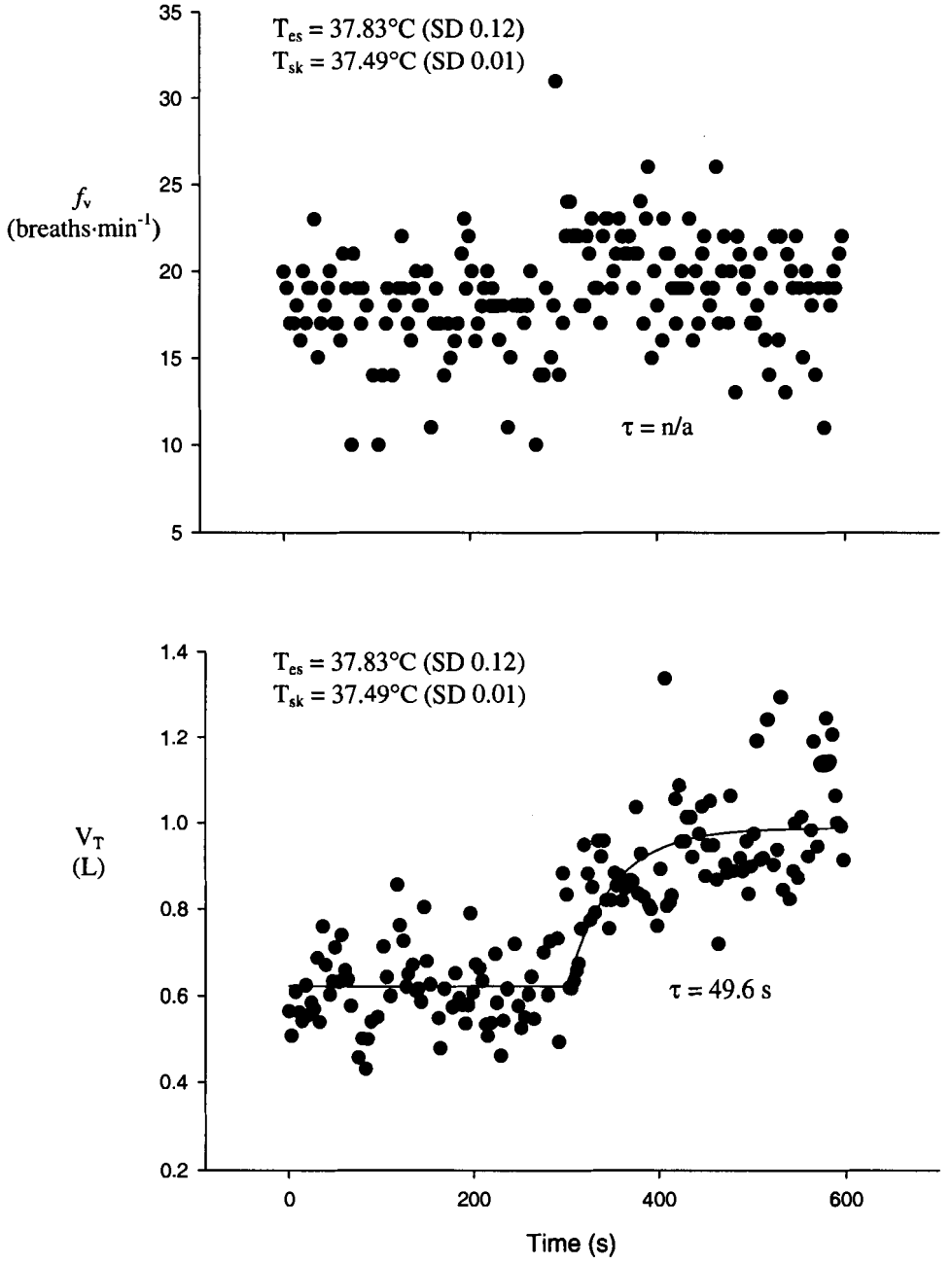
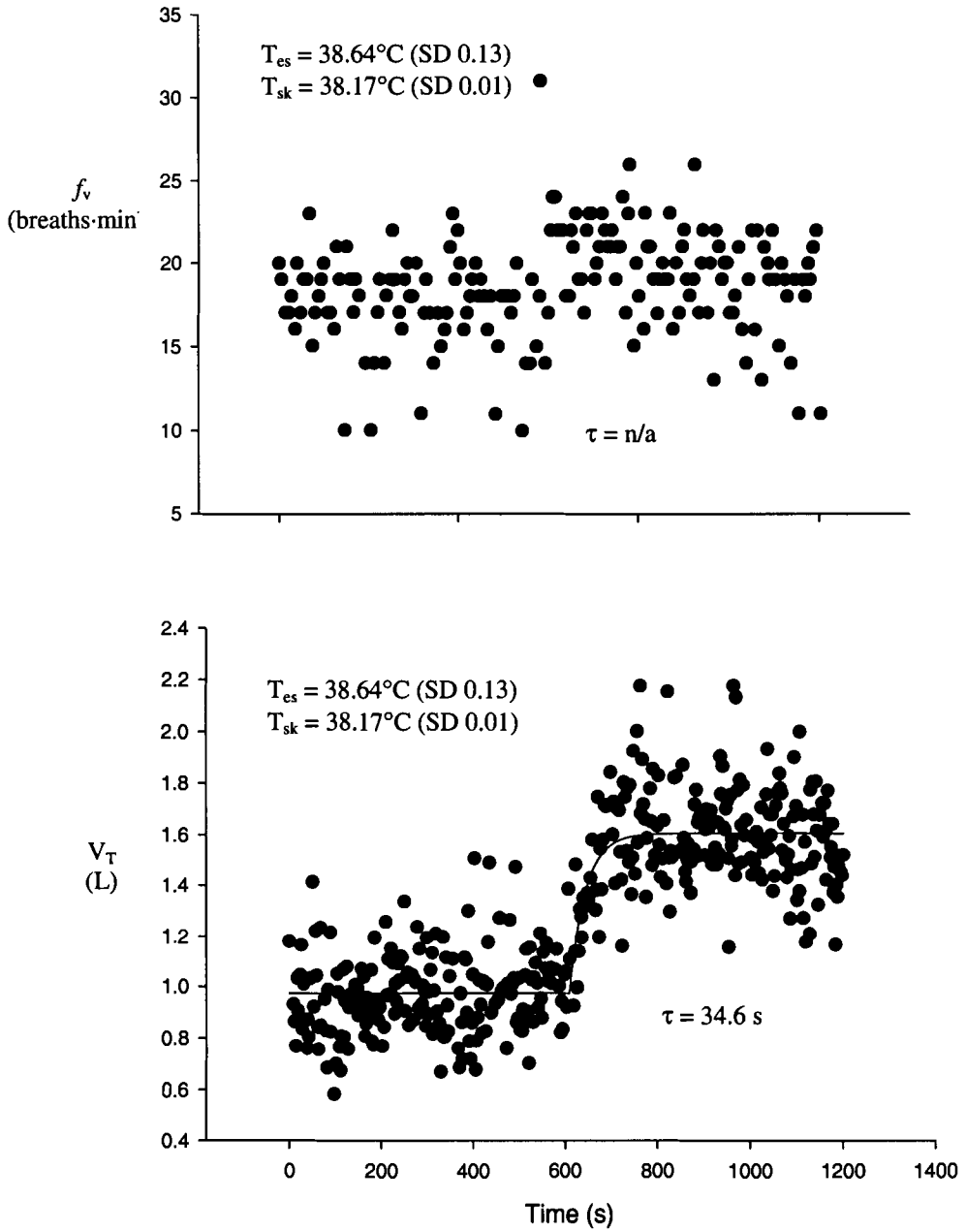


Fig. 4.5 A sample participant's (Participant 10) ventilation frequency (f_v) and tidal volume (V_T) response to the step change from euoxic (E1) to hypoxic (H1) low intensity exercise for the hyperthermic condition.
The smooth curve running between points is the model fit for the mono-exponential function. The τ values are the time constants for each curve, T_{es} represents esophageal temperature.



CHAPTER 5 STUDY 3

Do metabolic changes during hyperthermia and hypoxia influence ventilation during low intensity steady-state exercise?

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Running Head: "Ventilation, Core Temperature and Metabolism"

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5.1 Abstract

The levels of metabolic rate, plasma lactate and potassium (K^+) were investigated for their potential effects on body temperature- or hypoxia-induced changes in ventilation ($\dot{V}_E$). In either a 'hyperthermic' T_{es} or a 'normothermic' T_{es} session, 11 college-aged, healthy male volunteers were immersed to the shoulders and pedalled on an underwater cycle ergometer at a steady-state oxygen consumption ($\dot{V}O_2$) of 0.87 $L \cdot min^{-1}$ (SD 0.07). Following a 30-min rest and 20-min warm-up, a 30-min steady-state cycling period was divided into three 10 min gas phases when participants inhaled: air (Euoxia 1 (E1)), hypoxic gas (12 % O_2 and 88 % N_2 (H1)), and air (Euoxia 2 (E2)). End-tidal CO_2 ($P_{ET}CO_2$) was maintained at an isocapnic level of 5.19 kPa (SD 0.71) throughout the exercise. Blood samples were drawn at rest, and 5 min into all gas phases. For euoxic exercise (E1) results indicated the 9.4 % (SD 9.7) increase in $\dot{V}_E$ was not different than the 6.9 % (SD 10.7) increase evident in $\dot{V}O_2$ during the hyperthermic condition relative to the normothermic condition. Similarly, for euoxic recovery exercise results indicated the 22.0 % (SD 28.8) increase in $\dot{V}_E$ was not different than the 13.2 % (SD 18.1) increase evident in $\dot{V}O_2$ during the hyperthermic condition relative to the normothermic condition. However, for hypoxic exercise $\dot{V}_E$ and $\dot{V}O_2$ increased by 29.2 % (SD 25.5) and 13.5 % (SD 10.1) respectively, which bordered a significant difference ($P = 0.056$). For heart rate (HR) there was a significant main effect of Core Temperature ($P = 0.001$) and Gas Type ($P = 0.001$). Hyperthermic HR relative to normothermic HR was significantly elevated ($P = 0.001$) at all levels of Gas Type. There were no significant

main effects of Gas Type or Core Temperature on blood lactate or potassium (K^+) levels. In conclusion, during low intensity exercise, $\dot{V}O_2$, K^+ and lactate do not appear to significantly contribute to the augmented hypoxic ventilatory response (HVR) during the hyperthermic condition as compared to the normothermic condition.

5.2 Introduction

The onset of low to moderate intensity exercise is marked by an increase in metabolic rate, which is mediated mainly by the increased metabolic demand of the skeletal muscle (33). A by-product of elevated metabolism during exercise with progressively greater intensity, is a proportionate increase in body core temperature (2). This concomitant increase in core temperature during exercise has been suggested to be a possible mediator of ventilation (25, 35), as it has been established that a passive increase in core temperature increases ventilation (9, 12). In Chapters 3 and 4 of this thesis we have hypothesized that the enhanced HVR during exercise with hyperthermia, are due to either an increased sensitivity of peripheral chemoreceptors to low arterial oxygen saturation (S_aO_2), and/or a central effect of elevated core temperature on the respiratory control centre's pneumotaxic area. As such, presently we examined if changes in $\dot{V}_E$ evident during elevations in core temperature and during hypoxia are due to a direct temperature effect on $\dot{V}O_2$ (i.e. a Q_{10} effect) or due to possible elevations of lactate (11, 30) or K^+ (15, 26) that may be evident with exercise and/or hyperthermia. Another factor that was considered in this study is the possible influence of HR on ventilation during hyperthermia. Increased pulmonary perfusion in hyperthermia or exercise increases CO_2 flow across the lungs and is hypothesized to increase ventilation by the CO_2 flow hypothesis (31).

To investigate the potential effects of $\dot{V}O_2$, HR and blood borne metabolites on ventilation, we studied participants at a low level of exercise ($\dot{V}O_2$ 0.87 $L \cdot min^{-1}$ (SD 0.07)) with a superimposed passive hyperthermia. Changes in the blood borne metabolites that were analyzed included plasma lactate and K^+, which have each been associated with changes in core temperature (8, 11), hypoxia (4, 26) and are suggested modulators of exercise ventilation (18, 34). The specific questions we asked in these exercise conditions were if: 1) increases in $\dot{V}O_2$ or HR and/or 2) increases in plasma levels of plasma lactate or potassium can explain the elevations evident in $\dot{V}_E$ during low intensity hypoxic exercise and hyperthermia.

5.3 Methods

5.3.1 Participants

Eleven healthy male university participants, age 19-34 years old (height 1.77 m (SD 0.06), weight 74.1 kg (SD 9.0) and body surface area 1.9 m^2 (0.1)) volunteered to participate in the study. Power calculation results for sample size justification are given in Appendix C. All participants were non-smokers, non-asthmatics and refrained from caffeine for 12 h prior to each test. Prior to the experimentation the participants were informed of the potential risk associated with the protocol and after a 24 h reflection period gave their written, informed consent to participate in the experiment. The participants all attended a preliminary testing period where they were familiarized with the experimental protocol and instrumentation. During the preliminary testing period the participants performed a sub-maximal exercise protocol on an underwater cycle ergometer to determine their level of fitness and ensure they would be able to undergo the experimental protocol (Appendix B). Ethics approval for the study was received from the S.F.U. Office of Research Ethics prior to experimentation.

All experimental sessions were within ± 60 min of each other and started at between 10am or 1pm. Participants were also required to fast, exercise and refrain from drinking any warm beverages for a minimum of 5 hours prior each experimental session.

Participants were clad in shorts and kayak boots during the experiments. A medical emergency kit including a defibrillator was available at all times.

5.3.2 Instrumentation

Pulmonary function variables and ventilatory excursions were measured using a breath-by-breath Sensormedics V_{max} 229c metabolic cart (Sensormedics, Yorba Linda, CA, USA). Participants wore a nose clip and were fitted with a mouthpiece connected to a Mass Flow Sensor. The mouthpiece was connected to a two-way flow sensor housing, which was connected to a 2-way non-rebreathing valve (NRB 2700, Hans Rudolph Inc, Kansas Cit, MO, USA) that was connected with 3.8 cm diameter corrugated Collins tubing to a 350 L Tissot spirometer. Breath-by-breath gas samples were drawn from the inspired and expired air to the metabolic cart at a rate of 500 $ml \cdot min^{-1}$. Carbon dioxide partial pressure was measured using non-dispersive infrared Spectroscopy and oxygen concentration was measured using a paramagnetic sensor. A premixed hypoxic gas of 12 % O_2 and balanced nitrogen (N_2) from a compressed gas bottle was used to fill the Tissot spirometer for the hypoxic condition. A fan mounted on the Tissot spirometer was used to mixed gas within its bell during the hypoxic condition. In addition, between conditions the Tissot was flushed with room air to remove any residual gases from the hypoxic trials.

Heart rate and arterial oxygen saturation were continuously measured with a pulse oximeter (Masimo Radical, Irvine, CA, USA) positioned on the participants' left ear lobe.

Esophageal temperature was measured by placing a paediatric size temperature thermocouple probe of approximately 2 mm in diameter through the participants' nostril, while they were asked to sip water through a straw. The location of the tip of the probe in the oesophagus was past the nares, at the T8/T9 level, a position bounded by the left ventricle and aorta. This position is based on the equation of Mekjavic and Rempel (17) for standing height: L (cm) = 0.228 x (standing height) - 0.194. The participant was then immersed to the level of the shoulders in a water-filled tub and sat on a hydraulically braked, underwater cycle ergometer. Water temperature was maintained at a specific temperature so as to maintain T_{es} at either a normothermic or hyperthermic level. The determination of these water temperature (T_w) levels is described in Chapter 3 under the subheading 'Water Temperature calculations'.

An analog signal for f_v from the V_{max} cart was used to trigger data collection for body temperatures, HR and hemoglobin saturation on acquired a National Instruments data acquisition system SCXI-1000 (Austin, Texas, USA) that was controlled by LabVIEW program (National Instruments, Austin, USA, version 5.1).

Blood samples were drawn via an indwelling venous catheter (BD Insyte, 18 gauge) inserted in the antecubital vein of the left arm. Each sample consisted of approximately 4 ml of blood. The participants were instrumented with the catheter prior to each exercise protocol.

5.3.3 Protocol

All participants volunteered for 2 separate exercise-testing sessions, with each session separated by at least one week. Half of the participants were randomly chosen to start with the hyperthermic session and the other half started with the normothermic session. After instrumentation each protocol began with a 30-min rest period in room air to establish a stable resting T_{es}. The exercise began with a 5-min rest period with the participant seated on a stationary underwater bicycle ergometer in water up to their shoulder level and instrumented with a weight belt to avoid floatation. A metronome was used to maintain the pedalling cadence and the participant was monitored continuously to assure adherence. The determination for the prescribed work rate for the participants is given in Chapter 3 under the subheading 'Protocol'.

Each exercise session was performed at a constant work rate and consisted of a 20-min warm-up period where a steady state $\dot{V}_E$ and T_{es} were achieved and a 30-min testing period. Both the warm-up and testing period were completed at the same work rate and cadence and there were no rest phases between each period. The 30-min testing period was divided into three continuous 10-min steady state exercise phases: a 10-min euoxic exercise period (E1) where the participant breathed room air, a 10-min hypoxic exercise period (H1) where the participant breathed the hypoxic gas mixture (12 % O_2, balanced N_2), and a 10-min euoxic recovery exercise period (E2) when the participant again breathed room air. All participants followed this protocol in the same order for all sessions. Arterial oxygen content (S_aO_2) was lowered to 85.6 % (SD 5.7) in the

normothermic condition and 83.5 % (SD 5.7) (Chapter 3, Fig 3.6A) in the hyperthermic condition during the hypoxic exercise phase. If the $P_{ET}CO_2$ fell below resting water-immersed values, 100 % CO_2 was manually titrated into the inspirate via a non-re-breathing demand valve apparatus as described by Sommer et al. (29) to bring the $P_{ET}CO_2$ back to resting, water-immersed $P_{ET}CO_2$ levels. The purpose for clamping of $P_{ET}CO_2$ was to maintain an isocapnic hypoxia, which would alleviate the possibly confounding effects of a hyperventilation-induced hypocapnia, which is often associated with hypoxia and was suggested to diminish the HVR (27). The resting water-immersed $P_{ET}CO_2$ levels (7) were determined during the 5-min rest session immediately prior to commencing the exercise session. End-tidal CO_2 ($P_{ET}CO_2$) was maintained at an isocapnic level of 5.19 kPa (SD 0.71) during all exercise conditions (Chapter 3, Fig 3.6B).

Blood samples were drawn in 4 ml increments at rest, and at 5 min of the E1, H1 and E2 steady-state exercise phases. The catheter was flushed with saline between each sample to assure heterogeneity of samples. Blood was collected into collection tubes containing the anti-coagulant lithium heparin (BD Vacutainers, Franklin Lakes, NJ, USA). Samples were immediately placed on ice and centrifuged within 30 minutes of being drawn at 4°C and a speed of 3500 rpm. Plasma was removed after centrifugation and allocated into in 1.5 ml eppendorf tubes. There were 2 alloquots from each sample, for 2 different analyses (Lactate and K^+). The eppendorf tubes were stored at -80°C until the analyses, which was carried out within 3 months of the sampling date.

5.3.4 Blood analysis

Plasma K^+ concentrations were determined using an ion-selective electrode (Cole Parmer, Vernon Hills, Ill., USA). Samples of 100 μL plasma were diluted (100 x) to 10 ml with distilled water and the electrode was submerged in the 21°C solution. Electrode potential readings (mV) correspond to the concentration of K^+ in the sample (mM). Lactate concentration in plasma samples was determined using a colorimetric, enzymatic diagnostic kit (Pointe Scientific, Lincoln Park, Michigan) as previously described by Lin et al. (16). A volume of 10μL of plasma was used for each determination of lactate.

5.3.5 Calibrations and Analysis

Calibrations of esophageal thermocouple probes were completed in regulated temperature hot water baths (Appendix A). Gas analyzers were calibrated against two gases of known concentrations (4 % CO_2, 16 % O_2, balanced N_2 and 26 % O_2, balanced N_2, and air) and the mass flow sensor was calibrated manually by the use of a 3 litre syringe prior to each experiment.

Oxygen consumption, HR, respiratory exchange ratio (RER), $P_{ET}CO_2$, T_{es}, K^+ and lactate for the steady-state exercise phases were analyzed using a two-way ANOVA for repeated measures. The factors were Core Temperature (Levels: normothermic and hyperthermic) and Gas Type (Levels: euoxia (E1), hypoxia (H1), and euoxic recovery (E2)). Dependent *t*-tests with the Bonferroni correction for multiple comparisons of were

used to compare the means so as to explain the interactions of Core Temperature and Gas Type. A paired samples t-test was used to compare the percent change in $\dot{V}_E$ and VO_2 from the normothermic to hyperthermic at both E1 and H1. A P value of < 0.05 was considered significant. For comparisons values are expressed as the mean $\pm$ the Standard Deviation (SD) and 95 % Confidence Intervals [CI] of the difference between means are given in square brackets following each P value stated. SPSS 12.0 (SPSS Inc., Chicago, Ill., USA) was used for all the statistical analyses.

5.4 Results

All participants were able to complete the full exercise protocol including 10 min of hypoxic exposure with only mild signs or symptoms of hypoxia including hyperventilation, lethargy, and slight nausea. The mean water temperature for the normothermic condition was 31.5°C (SD 1.3) and for the hyperthermic condition was 38.2°C (SD 0.1)

During the 30-min rest period prior to the commencement of the normothermic exercise sessions the mean resting T_{es} was 37.2°C (SD 0.4) and prior to the hyperthermic exercise sessions the mean resting T_{es} was not significantly different at 37.3°C (SD 0.2) ($P = 0.386$, CI [-0.1, 0.3]). As shown in Chapter 3, T_{es} was maintained relatively constant during the normothermic condition at 37.2°C (SD 0.3), 37.1°C (SD 0.3), and 37.0°C (SD 0.3) during E1, H1 and E2 respectively. For the hyperthermic exercise condition T_{es} increased steadily from rest and approached a gradual plateau after the completion of the warm-up exercise period at 38.4°C (SD 0.1), 38.6°C (SD 0.1), and 38.7°C (SD 0.1) during. See Fig 3.2 for a more detailed description of the T_{es} results.

Comparisons of the elevations in $\dot{V}O_2$ in and the elevations in $\dot{V}_E$ evident during the hyperthermic condition relative to the normothermic condition are given in Figure 5.1. During E1, $\dot{V}O_2$ increased by 0.05 $L \cdot min^{-1}$ (SD 0.08) an elevation of 6.9 % (SD

10.7) from the normothermic to hyperthermic condition. Ventilation in E1 from the normothermic to the hyperthermic condition increased by 2.1 $L \cdot min^{-1}$ (SD 2.1) an elevation of 9.4 % (SD 9.7), which was not a significantly different increase than that for $\dot{V}O_2$ ($P = 0.303$). During H1 results indicated $\dot{V}O_2$ increased by 0.12 $L \cdot min^{-1}$ (SD 0.09) an elevation of 13.5 % (SD 10.1) from the normothermic to hyperthermic condition. Ventilation increased by 10.2 $L \cdot min^{-1}$ (SD 9.0) an elevation of 29.2 % (SD 25.5) from the normothermic to hyperthermic condition, which bordered on a significantly greater increase than that for $\dot{V}O_2$ ($P = 0.056$, CI [-0.5, 31.9]). During E2 results indicated $\dot{V}O_2$ increased by 0.10 $L \cdot min^{-1}$ (SD 0.13) an elevation of 13.2 % (SD 18.1) from the normothermic to hyperthermic condition. Ventilation increased by 5.2 $L \cdot min^{-1}$ (SD 7.7) an elevation of 22.0 % (SD 28.8) from the normothermic to hyperthermic condition, which was not a significantly different increase than that for $\dot{V}O_2$ ($P = 0.274$).

For $\dot{V}O_2$ there was a significant main effect of Gas Type ($F = 107.1$, $P = 0.001$) and a significant main effect of Core Temperature ($F = 10.3$, $P = 0.009$) observed (Fig. 5.2A). The normothermic condition the metabolic responses obtained from the three steady-state exercise phases indicated $\dot{V}O_2$ during E1 was 0.79 $L \cdot min^{-1}$ (SD 0.11) and significantly increased during H1 to 0.91 $L \cdot min^{-1}$ (SD 0.10) ($P = 0.001$, CI [0.08, 0.15]), which was followed by a return to steady-state euoxic levels during E2 at 0.80 $L \cdot min^{-1}$ (SD 0.10). For the hyperthermic condition $\dot{V}O_2$ during E1 was 0.83 $L \cdot min^{-1}$ (SD 0.07) and increased significantly during H1 to 1.02 $L \cdot min^{-1}$ (SD 0.05) ($P = 0.001$, CI [0.56, 0.66]), which was followed by a return to steady-state euoxic levels during E2 at 0.89 $L \cdot min^{-1}$ (SD 0.11). During hyperthermic relative to normothermic exercise $\dot{V}O_2$ was not

different in E1 ($P = 0.079$, CI [-0.10, 0.01]) and significantly elevated in both H1 by 0.12 $L \cdot min^{-1}$ (SD 0.09) ($P = 0.001$, CI [0.06, 0.17]) and in E2 by 0.09 $L \cdot min^{-1}$ (SD 0.13) ($P = 0.034$, CI [0.01, 0.18]) (Fig. 5.2A). A significant Core Temperature by Gas Type interaction was also observed for $\dot{V}O_2$ ($F = 4.2$, $P = 0.030$), as the increase in $\dot{V}O_2$ from the normothermic to hyperthermic condition was greater during H1 as compared to E1 ($F = 9.5$, $P = 0.012$) but not E2 ($P = 0.137$)

For RER there was a significant main effect of Gas Type ($F = 91.6$, $P = 0.001$) and no significant main effect of Core Temperature observed ($F = 2.8$, $P = 0.123$) (Fig. 5.2 B). The pooled mean RER values between Core Temperature conditions increased significantly by 0.28 (SD 0.11) ($P = 0.001$, CI [0.18, 0.37]) from E1 at 0.83 (SD 0.05) to H1 at 1.11 (SD 0.11) and decreased below E1 levels by 0.05 (SD 0.03) ($P = 0.001$, CI [-0.07, -0.03]) on return to euoxic levels during E2 at 0.78 (SD 0.05).

For HR there was a significant main effect of Gas Type ($F = 130.0$, $P = 0.001$) and a significant main effect of Core Temperature ($F = 51.9$, $P = 0.001$) observed (Fig. 5.2C). For the normothermic condition HR increased significantly by 12.9 $beats \cdot min^{-1}$ (SD 6.1) ($P = 0.001$, CI [8.8, 17.0]) from E1 at 87.4 $beats \cdot min^{-1}$ (SD 11.5) to H1 at 100.3 $beats \cdot min^{-1}$ (SD 15.9), and returned close to E1 levels during E2 at 87.6 $beats \cdot min^{-1}$ (SD 14.5). For the hyperthermic condition HR during E1 was 109.9 $beats \cdot min^{-1}$ (SD 9.5) and increased to 126.9 $beats \cdot min^{-1}$ (SD 10.7) during H1, a significant increase of 17.0 $beats \cdot min^{-1}$ (SD 4.3) ($P = 0.001$, CI [14.1, 19.9]). During E2, HR at 116.3 $beats \cdot min^{-1}$ (SD 9.4) remained significantly elevated ($P = 0.001$, CI [3.3, 9.5]) relative to E1 values.

During the hyperthermic condition relative to the normothermic condition HR was significantly elevated ($P = 0.001$, CI [15.8, 29.3]) in E1 by 22.6 beats·min^{-1} (SD 10.0), in H1 by 26.7 beats·min^{-1} (SD 14.6) ($P = 0.001$, CI [16.9, 36.5]) and in E2 by 28.7 beats·min^{-1} (SD 12.7) ($P = 0.001$, CI [20.2, 37.3]).

Analysis of blood borne metabolites indicated there was no significant main effect of Gas Type for lactate ($F = 2.3$, $P = 0.121$) and K^+ ($F = 2.1$, $P = 0.119$) (Fig. 5.3 A&B). Similarly there was no significant main effect of Core Temperature for lactate ($F = 0.8$, $P = 0.395$) and K^+ ($F = 1.0$, $P = 0.352$).

5.5 Discussion

5.5.1 The effect of hyperthermia on oxygen consumption during euoxic and hypoxic exercise

The main finding of the current study was during hypoxic hyperthermia $\dot{V}O_2$ increased significantly from the normothermic hypoxic condition (Fig. 5.2A), however, in comparison to the change in $\dot{V}_E$ under the same conditions there was a trend observed for a disproportionate increase in $\dot{V}_E$ as compared to the increase in $\dot{V}O_2$ (Fig 5.1). This disproportionate increase in $\dot{V}_E$ was also in lieu of any significant changes in blood lactate or K^+ levels between temperature conditions and would therefore suggest that the augmentation of the HVR during hyperthermia is influenced to a greater extent by temperature rather than metabolic rate or by blood borne metabolites (Fig 5.3).

The influence of an increased metabolic rate during hyperthermia hypoxia however cannot be completely discounted. Previous studies have shown an enhancement of ventilation during hypoxia that was concomitant with an increase in exercise intensity (32) and with ingestion of a meal (36), each that gave an increase in body temperature. In a study by Natalino et al. (22) with passive hyperthermia, they also showed a hyperthermic enhancement of ventilation during hypoxia which was associated with an increase in $\dot{V}O_2$. It appears therefore to be a significant association between body temperature and $\dot{V}O_2$, however, whether $\dot{V}O_2$ is the cause or the effect of the enhanced

HVR during body warming has not been established. We suggest that there are several possibilities for which an increase in $\dot{V}O_2$ could be coupled with an increased ventilation which include an increased energy cost associated with an increase in RER, a Q_{10} effect during body warming, thermoregulatory effector responses during body warming and an increase in HR associated with hyperthermia and hypoxia.

In the current study there was a significant increase in RER observed during hypoxia for both temperature conditions indicating a significant hypoxic-induced hyperventilation. Furthermore, as shown in Chapter 3, there was also an enhancement of the inspiratory flow during hypoxic hyperthermia. This would suggest that the significant increase in $\dot{V}O_2$ during hyperthermic hypoxia might be due in part to the combined metabolic cost of the enhanced hypoxic-induced hyperventilation (i.e. an increase in tidal volume) and the enhanced thermal tachypnea (i.e. an increase in ventilation frequency).

There is also a well-known Q_{10} effect of an increase in metabolic rate of ~13 % associated with an increase in core temperature of ~1°C (28). This Q_{10} effect appears evident in our results where $\dot{V}O_2$ was elevated in the hyperthermic condition by 12 % during H1 and 11 % during E2 (Fig. 5.2A). The absence of hyperthermic-induced increase in $\dot{V}O_2$ in E1 appears to be explained by a lower T_{es} in E1 as compared to H1 and E2 (Chapter 3, Fig. 3.2).

There also remains the possibility that the increased $\dot{V}O_2$ in the hyperthermic relative to the normothermic condition was due to the energy requirement for heat dissipation through peripheral circulation, an elevated HR and eccrine sweat gland activity (17). This energy cost would increase with increasing core temperature. What portion of the increase in $\dot{V}O_2$ during hypoxic hyperthermia is due to the Q_{10} effect or due to the metabolic cost of the thermal- and/or hypoxic-induced increase in $\dot{V}_E$ is unknown. However, it remains in the current study during hyperthermic hypoxic low intensity exercise a trend for a disproportionate increase in $\dot{V}_E$ is observed that would support a direct effect of temperature on the peripheral chemoreceptors. It would appear then that $\dot{V}O_2$ plays a lesser role in the control of $\dot{V}_E$ during hyperthermic hypoxia and the associated increases may be due in part to the metabolic cost of breathing and thermoregulation at higher body temperatures and lower P_aO_2 levels.

5.5.2 The effect of hyperthermia and hypoxia on heart rate and its possible influences on ventilation

Heart rate increased from rest during low intensity steady-state exercise, however the increase was significantly greater during the hyperthermic condition across all gas phases as compared to the normothermic condition (Fig. 5.2C). The increased HR during hyperthermia can be primarily attributed to the increased peripheral blood flow requirement during body warming for heat dissipation (21).

During hypoxia in both temperature conditions HR was significantly elevated compared to the euoxic conditions despite maintaining a steady-state exercise and T_{es} (Fig. 5.2C). This is in agreement with previous studies (3, 13) that showed an increased

HR during isocapnic hypoxia. It has been suggested by Halliwill et al. (13) that the augmented HR response during isocapnic hypoxia is due to the activation of the peripheral chemoreceptors indirectly mediating a resetting of the arterial baroreflex control for both HR and sympathetic nerve activity to higher pressures.

In the current study there appears to be a strong association then between changes in HR and changes in $\dot{V}_E$. Particularly in hypoxia the changes in HR appear to occur by similar mechanisms to the changes in $\dot{V}_E$, which could help explain this association. Whether an increase in HR has any direct influence on $\dot{V}_E$ is unknown, but the CO_2 flow hypothesis suggested by Wasserman et al (31) may indirectly implicate changes in HR as a possibly mediator of ventilation. The CO_2 flow hypothesis is based on the premise that ventilation increases in proportion to CO_2 flow across the lungs and is irrespective of any changes in P_aCO_2 (31). This suggests little involvement of the peripheral and central chemoreceptors and possible involvement of a CO_2 flow receptor in the pulmonary circulation (31). According to this hypothesis an increase in cardiac output, which can be coupled with an increase in HR, could stimulate these CO_2 flow receptors by increasing pulmonary perfusion and thereby increasing ventilation. At present a CO_2 flow receptor still has not been identified and this hypothesis remains unsubstantiated.

5.5.3 *The influence of blood lactate and potassium on ventilation during hyperthermia and hypoxia*

There are several metabolic by-products that can influence ventilation, one of the more prominent modulators has been suggested to be lactate (18, 30). Lactate has been thought to modulate ventilation at higher exercise intensity levels at or above the anaerobic threshold (19). The current study was therefore designed to be well below the anaerobic threshold to prevent any confounding effects on $\dot{V}_E$ due to increased lactate concentrations. Consequently in the current study results indicated that there were no significant changes in lactate from rest to exercise (Fig. 5.3) under all conditions and as such lactate does not appear to be implicated in the changes of $\dot{V}_E$ during low intensity exercise.

In response to increases in body temperature, there have been associations made between hyperthermia and lactic acid production. In a study by Gaudio et al. (11) lactic acid was shown to increase in small proportions of ~0.4 mM after a passively–induced hyperthermia. They suggested the slight increase in lactate to be a result of the respiratory alkalosis created by the hyperthermic-induced hyperpnea (11). Druml et al. (10) who had their participants perform a controlled hyperventilation to induce a respiratory alkalosis further supported this finding. They observed a similar overall increase in the basal concentration of plasma lactate after the hyperventilation suggesting this to be a consequence of the fall in P_aCO_2 (10). There appears then to be an association between a respiratory alkalosis and increased lactic acid production, however the extent of lactic acid production is minimal as shown by Gaudio and colleagues (11).

In the present study an isocapnic clamp was used preventing any significant falls in P_aCO_2, thereby preventing a possible respiratory alkalosis in the participants. This may account for the lack of change in lactate concentration evident during hyperthermia and would also explain why no change in lactate was evident during the isocapnic hypoxic periods.

Another possible modulator of ventilation is blood borne K^+. There is a significant increase in plasma K^+ concentration evident during heavy exercise that has been suggested to be a result of an increased muscle cell depolarization (23). Patterson et al. indicated this increase in plasma K^+ was correlated with an increase in ventilation during exercise and suggested it to be a possible mediator of this ventilatory response, particularly at higher intensity levels (24). Studies by Band et al. (1) and Burger et al. (5) have shown that K^+ stimulates ventilation via peripheral chemoreceptors, as cats with denervated carotid bodies showed no increase in ventilation. In the present study there were no significant changes evident in plasma K^+ levels from rest to exercise, however again this can be primarily attributed to the low level of exercise. In previous studies the associations made between plasma K^+ and exercise ventilation were done at moderate to high intensity exercise levels (23, 24). Furthermore, in a previous study by Qayyum et al. (26) they showed that the addition of K^+ orally in the form of potassium chloride did not affect ventilation during light exercise, suggesting that K^+ does not influence ventilation at low exercise intensities.

The levels of plasma K^+ were also not significantly influenced by temperature or hypoxia in the current study (Fig. 5.3). Previous studies on the effects of temperature and hypoxia on K^+ concentrations in the blood are conflicting. Kozlowski and Saltin (15) reported a rise in plasma K^+ with combined exercise and heat exposure, but no increase with heat exposure alone. In contrast, Coburn et al. (8) showed a significant increase in plasma K^+ following passive heat exposure, however, this study was only done with four participants who were heated over a five hour period. During hypoxia several studies have suggested that K^+ may help mediate the HVR by stimulation of the peripheral chemoreceptors (23, 26). Conversely, a study by Khan et al. (14) found in humans that plasma K^+ does not increase at high altitudes (4424 m). In the current study there were no changes indicated in plasma K^+ during hypoxia which would support the later study and suggest that the HVR was not mediated by plasma K^+.

5.5.4 Conclusion

In conclusion, as evidenced by a trend for a greater ventilatory response to hyperthermic hypoxia than the associated metabolic responses (Figure 5.1), there is a support for the hypothesis that the augmentation of hypoxic $\dot{V}_E$ during hyperthermia is mediated primarily by body temperature. The evidence that no significant changes in plasma lactate and K^+ were observed during hyperthermia or hypoxia further supports this hypothesis. Finally, the increase in HR observed during the hyperthermia and hypoxia possibly influences $\dot{V}_E$ and could help explain the enhanced $\dot{V}_E$ by an increase in lung perfusion if the CO_2 flow hypothesis is accepted as valid (31).

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5.8 References

1. **Band DM, Linton RA, Kent R, and Kurer FL.** The effect of peripheral chemodenervation on the ventilatory response to potassium. *Respir Physiol* 60: 217-225, 1985.

2. **Berggren G and Hohwu Christensen E.** Heart rate and body temperature as indices of metabolic rate during work. *Arbeitsphysiologie* 14: 255-260, 1950.

3. **Bhattacharva J, Cunningham DJ, Howson MG, Lee MJ, and Sleight P.** Proceedings: The effects of mild hypoxia with constant PA, C02 and ventilation on the setting and sensitivity of the baroreceptor-cardiac-depressor reflex in man. *J Physiol (Lond)* 234: 112P-114P, 1973.

4. **Brooks GA.** Current concepts in lactate exchange. *Med Sci Sports Exerc* 23: 895-906, 1991.

5. **Burger RE, Estavillo JA, Kumar P, Nye PC, and Paterson DJ.** Effects of potassium, oxygen and carbon dioxide on the steady-state discharge of cat carotid body chemoreceptors. *J Physiol (Lond)* 401: 519-531, 1988.

6. **Chang LP and Lundgren CE.** CO2 chemosensitivity during immersion in humans. *Chin J Physiol* 38: 7-12, 1995.

7. **Coburn JW, Reba RC, and Craig FN.** Effect of potassium depletion on response to acute heat exposure in unacclimatized man. *Am J Physiol* 211: 117-124, 1966.

8. **Cunningham DJC and O'Riordan JLH.** The effect of a rise in temperature of the body on respiratory response to carbon dioxide at rest. *QJ Exp Physiol* 42: 329-345, 1957.

9. **Druml W, Grimm G, Laggner AN, Lenz K, and Schneeweiss B.** Lactic acid kinetics in respiratory alkalosis. *Crit Care Med* 19: 1120-1124, 1991.

10. **Gaudio RJ and Abrahamson N.** Heat-induced hyperventilation. *J Appl Physiol* 25: 742-746, 1968.

11. **Haldane JS.** The influence of high air temperatures. *J Hyg* 55: 497-513, 1905.

12. **Halliwill JR, Morgan BJ, and Charkoudian N.** Peripheral chemoreflex and baroreflex interactions in cardiovascular regulation in humans. *J Physiol (Lond)* 552: 295-302, 2003.

13. **Khan DA, Aslam M, and Khan ZU.** Changes in plasma electrolytes during acclimatization at high altitude. *J Pak Med Assoc* 46: 128-131, 1996.

14. **Kozlowski S and Saltin B.** Effect of Sweat Loss on Body Fluids. *J Appl Physiol* 19: 1119-1124, 1964.

15. **Lin C, Chen S, Kou G, and Kuo C.** An enzymatic microassay for lactate concentration in blood and hemolymph. *Acta Zool Taiw* 10: 91-101, 1999.

16. **MacDougall JD, Reddan WG, Layton CR, and Dempsey JA.** Effects of metabolic hyperthermia on performance during heavy prolonged exercise. *J Appl Physiol* 36: 538-544, 1974.

17. **Mateika JH and Duffin J.** A review of the control of breathing during exercise. *Eur J Appl Physiol Occup Physiol* 71: 1-27, 1995.

18. **Mateika JH and Duffin J.** The ventilation, lactate and electromyographic thresholds during incremental exercise tests in normoxia, hypoxia and hyperoxia. *Eur J Appl Physiol Occup Physiol* 69: 110-118, 1994.

19. **Mekjavic IB and Rempel ME.** Determination of esophageal probe insertion length based on standing and sitting height. *J Appl Physiol* 69: 376-379, 1990.

20. **Nadel ER.** Circulatory and thermal regulations during exercise. *Fed Proc* 39: 1491-1497, 1980.

21. **Natalino MR, Zwillich CW, and Weil JV.** Effects of hyperthermia on hypoxic ventilatory response in normal man. *J Lab Clin Med* 89: 564-572, 1977.

22. **Paterson DJ.** Potassium and ventilation in exercise. *J Appl Physiol* 72: 811-820, 1992.

23. **Paterson DJ, Robbins PA, and Conway J.** Changes in arterial plasma potassium and ventilation during exercise in man. *Respir Physiol* 78: 323-330, 1989.

24. **Petersen ES and Vejby-Christensen H.** Effect of Body Temperature on Steady State Ventilation and Metabolism in Exercise. *Acta Physiol Scand* 89: 342-351, 1973.

25. **Qayyum MS, Barlow CW, O'Connor DF, Paterson DJ, and Robbins PA.** Effect of raised potassium on ventilation in euoxia, hypoxia and hyperoxia at rest and during light exercise in man. *J Physiol (Lond)* 476: 365-372, 1994.

26. **Rapanos T and Duffin J.** The ventilatory response to hypoxia below the carbon dioxide threshold. *Can J Appl Physiol* 22: 23-36, 1997.

27. **Rhoades R.** The regulation of body temperature. In: *Medical Physiology*, edited by Rhoades R and Tanner G. Boston: Little, Brown and Company, 1995.

28. **Sommer LZ, Iscoe S, Robicsek A, Kruger J, Silverman J, Rucker J, Dickstein J, Volgyesi GA, and Fisher JA.** A simple breathing circuit minimizing changes in alveolar ventilation during hyperpnoea. *Eur Respir J* 12: 698-701, 1998.

29. **Wasserman K.** Breathing during exercise. *N Engl J Med* 298: 780-785, 1978.

30. **Wasserman K, Whipp BJ, Casaburi R, and Beaver WL.** Carbon dioxide flow and exercise hyperpnea. Cause and effect. *Am Rev Respir Dis* 115: 225-237, 1977.

31. **Weil JV, Byrne-Quinn E, Sodal IE, Kline JS, McCullough RE, and Filley GF.** Augmentation of chemosensitivity during mild exercise in normal man. *J Appl Physiol* 33: 813-819, 1972.

32. **Whipp BJ.** Peripheral chemoreceptor control of exercise hyperpnea in humans. *Med Sci Sports Exerc* 26: 337-347, 1994.

33. **Whipp BJ.** Ventilatory control during exercise in humans. *Annu Rev Physiol* 45: 393-413, 1983.

34. **White MD and Cabanac M.** Exercise hyperpnea and hyperthermia in humans. *J Appl Physiol* 81: 1249-1254, 1996.

35. **Zwillich CW, Sahn SA, and Weil JV.** Effects of hypermetabolism on ventilation and chemosensitivity. *J Clin Invest* 60: 900-906, 1977.

5.9 Figures

Fig, 5.1 Percent change from the normothermic to hyperthermic condition for oxygen consumption ($\dot{V}O_2$) and ventilation ($\dot{V}_E$) during euoxic exercise (E1), hypoxic exercise (H1) and recovery euoxic exercise (E2).
Participants performed a steady state, head-out exercise on underwater ergometer at a low-level exercise intensity ($\dot{V}O2$ ~ 0.8 to 1.0 L•min-1) in the normothermic and hyperthermic conditions. Error bars represent the SD (NS non significant at $P > 0.1$)

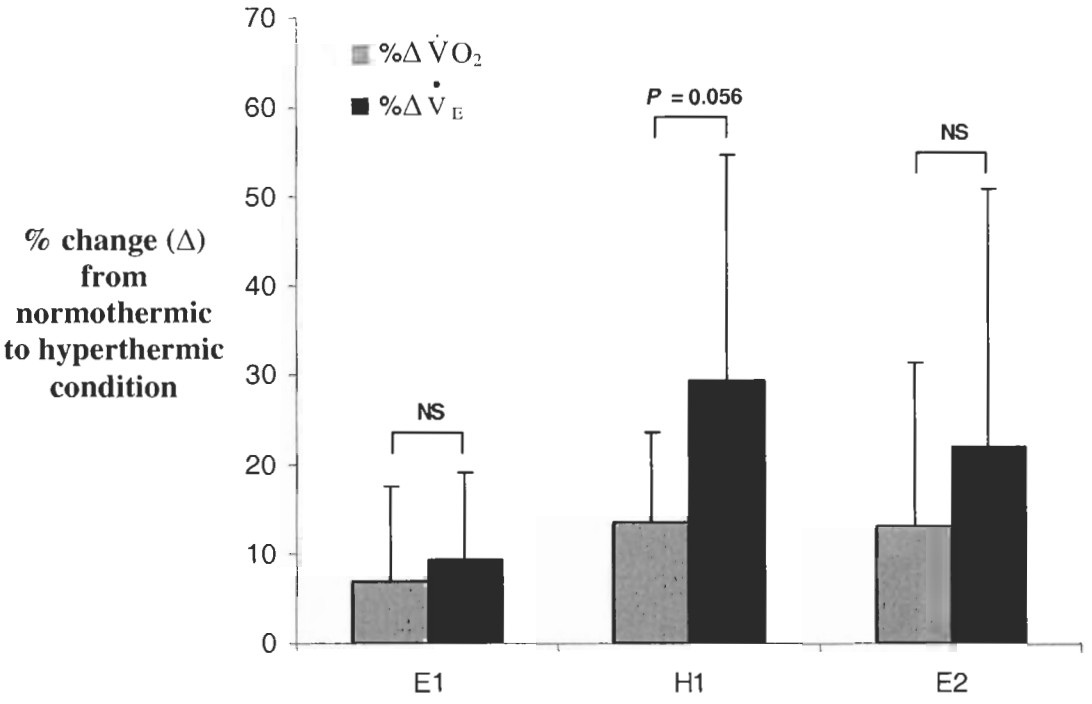


Fig. 5.2 **Course of mean oxygen consumption ($\dot{V}O_2$), respiratory exchange ratio (RER), heart rate (HR) for rest, euoxic exercise (E1), hypoxic exercise (H1) and recovery euoxic exercise (E2).**
, normothermic condition; ■, hyperthermic condition. Error bars represent the SD (**significant between temperature conditions at $P < 0.01$, ‡ significant from E1 at $P < 0.01$, NS non-significant at $P > 1.0$).

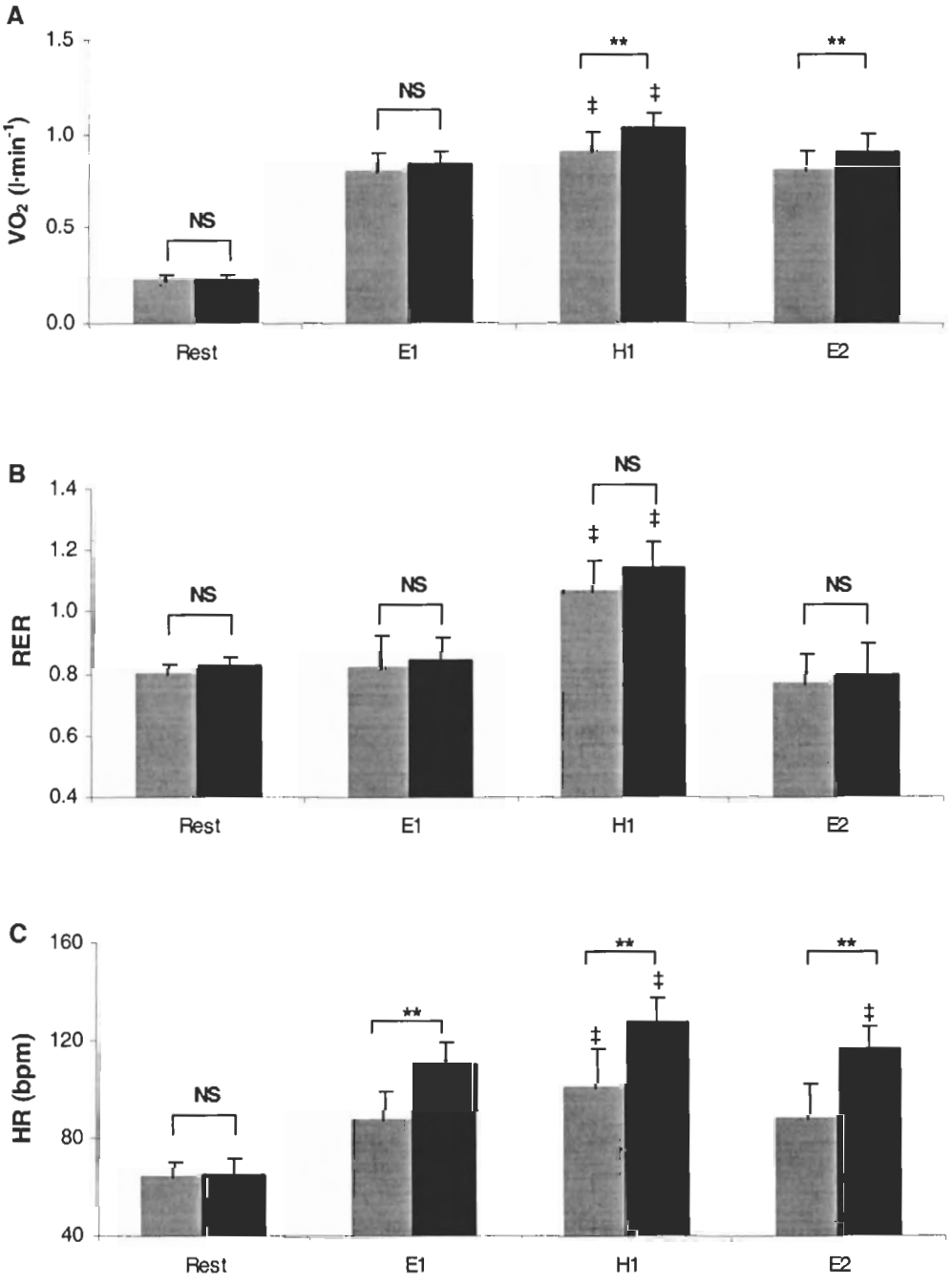
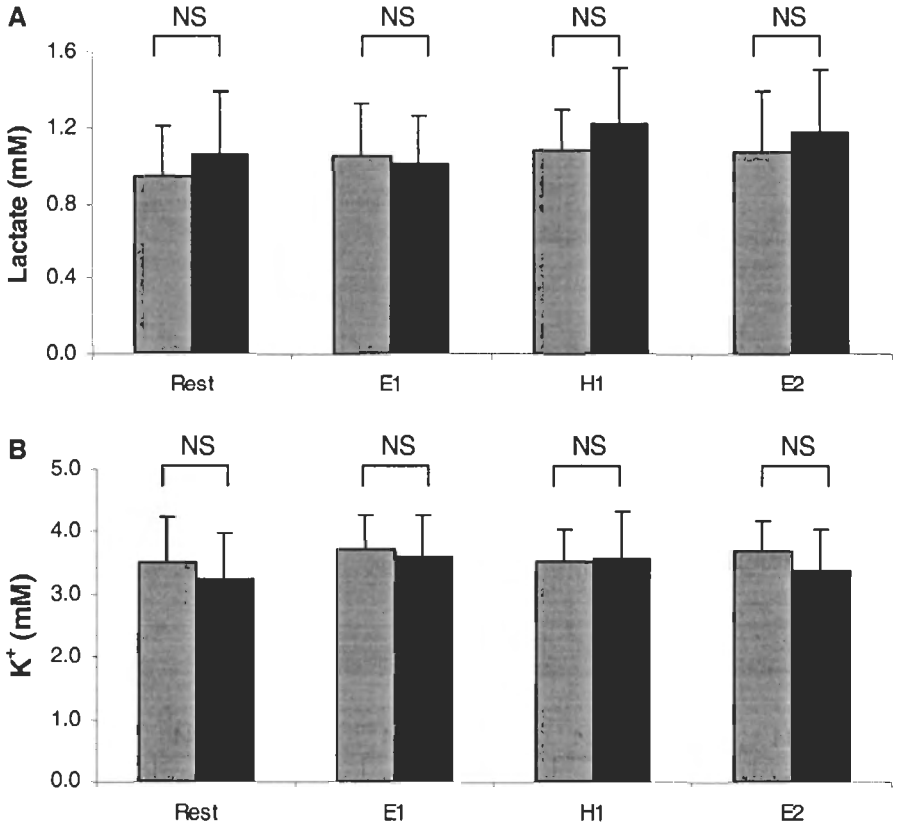


Fig. 5.3 **Course of mean serum lactate and potassium (K^+) concentration for rest, euoxic exercise (E1), hypoxic exercise (H1), and recovery euoxic exercise (E2).** ▪, normothermic condition; ■, hyperthermic condition. No significant differences (NS) found between Gas phases or Core Temperature conditions. Error bars represent the SD (NS non-significant at $P > 0.1$)



CHAPTER 6 THESIS SUMMARY

6.1 Testable Questions

1. **Is ventilation during low intensity exercise with an elevated hyperthermic Core Temperature different than ventilation during low intensity exercise with a normothermic Core Temperature?**

   Ventilation was significantly increased by a hyperthermic core temperature as compared to a normothermic core temperature during low intensity exercise. The hyperthermic-induced hyperpnea appears to be mediated solely by an increase in f_v suggesting the existence of a thermal-induced tachypnea.

2. **Is there an interaction of body Core Temperature and Gas Type on ventilation during low intensity exercise? Is the effect additive or multiplicative?**

   There was a significant interaction for $\dot{V}_E$ observed between core temperature and hypoxia during low intensity exercise. During the hyperthermic hypoxia $\dot{V}_E$ increased disproportionately as compared to the normothermic hypoxia, suggesting the effect of an elevated core temperature on hypoxic $\dot{V}_E$ is multiplicative.

3. **If there is an interaction between Core Temperature and Gas Type on ventilation, what components of ventilation, f_v and/or V_T, mediate this change during low intensity exercise?**

The HVR at normothermic body temperatures appears to be mediated solely by an increase in V_T. However, during hyperthermic hypoxia there is an augmentation of the HVR which appears to be due to increases in f_v as no significant changes were evident in V_T from the normothermic to hyperthermic conditions. Ventilation frequency was elevated significantly during euoxic hyperthermia relative to euoxic normothermia and showed a trend for an even greater elevation during hypoxic hyperthermia relative to hypoxic normothermia suggesting a trend for an interaction of core temperature and hypoxia on f_v.

4. **How do Core Temperature and Gas Type influence the inspiratory flow and timing components of ventilation during low intensity exercise?**

An increase in core temperature elevates $V_T \cdot T_I^{-1}$ during euoxic exercise. This elevated $V_T \cdot T_I^{-1}$ is further enhanced during hypoxic hyperthermic exercise. A shortening of the T_I and T_E was also associated with increases in $V_T \cdot T_I^{-1}$ during the hyperthermic condition. This was in absence of any significant changes in V_T which would suggest the enhanced $V_T \cdot T_I^{-1}$ during euoxic and hypoxic hyperthermic exercise are due primarily to decreases in T_I.

5. **Is the kinetics of ventilation influenced by temperature during the onset of low intensity exercise and during the onset of hypoxia during steady-state exercise?**

The ventilatory kinetics appears to be influenced by increasing core temperature during the onset of exercise, which appears to be independent of changes in skin temperature. Particularly increasing core temperature appears to shorten the time course of the ventilatory kinetic response to the onset of exercise. A hyperthermic body temperature appears mediate the amplitude of the ventilatory kinetic response to hypoxia during low intensity steady-state exercise, however it does not appear to influence the time course of this response.

6. Do associated increases in metabolic rate and blood borne metabolites as evident with exercise, hyperthermia, and hypoxia significantly influence ventilation?

There was evidence of a significant metabolic response to both hyperthermia and hypoxia. These increases occurred despite any changes in blood lactate and K^+ levels. The resultant increase in $\dot{V}_E$ however, was significantly greater during hyperthermic hypoxia than the increase in $\dot{V}O_2$ which would suggest that the associated increase in metabolic rate during hyperthermic hypoxia was not the primary mediator of the $\dot{V}_E$ response.

6.2 Research Hypotheses

1. **It was hypothesized that if both the combined influences of exercise during hypoxia (2-4, 7) and passive hyperthermia during hypoxia (5, 6) would cause a multiplicative increase in $\dot{V}_E$, then with the removal of the exercise-induced hyperthermia there would be a marked reduction in $\dot{V}_E$ during hypoxic normothermic exercise.**

   The first hypothesis was validated as a marked reduction in $\dot{V}_E$ was evident during normothermic hypoxia as compared to hyperthermic hypoxia.

2. **If a hyperthermia-induced hyperpnea is a vestigial panting response, then the elevations in $\dot{V}_E$ during hyperthermic exercise would be due to increases in ventilation frequency.**

   The second hypothesis is validated as there was an evident thermal tachypnea evident during all hyperthermic exercise conditions which were independent of any changes in V_T.

3. **It was hypothesized that if core temperature influences steady-state $\dot{V}_E$ during rest (1) and exercise (8), then it may influence the ventilatory kinetics for the onset of exercise. Furthermore, if core temperature influences the HVR (5, 6) it**

was also hypothesized that an enhancement of the kinetics of this response may have been evident during an elevated core temperature.

The third hypothesis was validated in part as the results suggest an elevated core temperature influences the dynamics of $\dot{V}_E$ response shortening it in comparison to a normothermic core temperature during the onset of exercise. However the second part of the hypothesis was not validated as it appeared core temperature had no significant influence on the dynamics of the $\dot{V}_E$ response during the transition from low intensity euoxic to low intensity hypoxic exercise.

6.3 Thesis Summary and Future Directions

The main findings of the thesis are that an increase in body core temperature appears to enhance exercise ventilation, particularly during hypoxia. This response appears to be mediated through an increase in ventilation frequency and mean inspiratory flow without a metabolic influence. This would appear to support the concept of a possible direct temperature effect on the peripheral chemoreceptors and/or the central respiratory centres in the medulla and provide evidence for increasing body temperature as a possible mediator of ventilation during exercise.

In future studies it would be beneficial to look at higher levels of exercise and produce an active hyperthermia and normothermia to look at the effects of an increased metabolism on the ventilation response. The challenge would be to clamp body temperature at higher exercise intensities. Another possible avenue of study would be to look at individual variation in hypoxic sensitivity during a progressive hypoxia test and compare this to the responses of a protocol similar to the current study. This would allow for the investigation of hypoxic "responders" and "non-responders" and see how they are influenced by perturbations in body temperature.

6.4 References

1. **Cabanac M and White MD.** Core temperature thresholds for hyperpnea during passive hyperthermia in humans. *Eur J Appl Physiol* 71: 71-76, 1995.

2. **Hansen JE, Stelter GP, and Vogel JA.** Arterial pyruvate, lactate, pH, and PCO2 during work at sea level and high altitude. *J Appl Physiol* 23: 523-530, 1967.

3. **Klausen K, Robinson S, Micahel ED, and Myhre LG.** Effect of high altitude on maximal working capacity. *J Appl Physiol* 21: 1191-1194, 1966.

4. **Lahiri S.** Physiological responses and adaptations to high altitude. *Int Rev Physiol* 15: 217-251, 1977.

5. **Natalino MR, Zwillich CW, and Weil JV.** Effects of hyperthermia on hypoxic ventilatory response in normal man. *J Lab Clin Med* 89: 564-572, 1977.

6. **Petersen ES and Vejby-Christensen H.** Effects of body temperature on ventilatory response to hypoxia and breathing pattern in man. *J Appl Physiol* 42: 492-500, 1977.

7. **Pugh LG.** Man at high altitude: studies carried out in the Himalaya. *Sci Basis Med Annu Rev*: 32-54, 1964.

8. **White MD and Cabanac M.** Exercise hyperpnea and hyperthermia in humans. *J Appl Physiol* 81: 1249-1254, 1996.

CHAPTER 7 OVERALL REFERENCE LIST

1. **Anderton JL, Harris EA, and Slawson KB.** The Repeatability of Ventilatory Responses to Excess of Carbon Dioxide and Lack of Oxygen. *Q J Exp Physiol Cogn Med Sci* 49: 43-51, 1964.

2. **Arborelius M, Jr., Ballidin UI, Lilja B, and Lundgren CE.** Hemodynamic changes in man during immersion with the head above water. *Aerosp Med* 43: 592-598, 1972.

3. **Asmussen E and Nielsen M.** Pulmonary ventilation and effect of oxygen breathing in heavy exercise. *Acta Physiol Scand* 43: 365, 1958.

4. **Asmussen E and Nielsen M.** Studies on the regulation of respiration in heavy work. *Acta Physiol Scand* 12: 171, 1946.

5. **Baker MA, Hawkins MJ, and Rader RD.** Thermoregulatory influences on common carotid blood flow in the dog. *J Appl Physiol* 52: 1138-1146, 1982.

6. **Band DM, Linton RA, Kent R, and Kurer FL.** The effect of peripheral chemodenervation on the ventilatory response to potassium. *Respir Physiol* 60: 217-225, 1985.

7. **Barcroft H, Basnaykae V, Celander O, Cobbold A, Cunningham DA, Jukes M, and Young I.** The effect of carbon dioxide on the respiratory responses to noradrenalin in man. *J Physiol (Lond)* 137: 365, 1957.

8. **Benzinger TH.** The diminution of thermoregulatory sweating during cold-reception at the skin. *Proc Natl Acad Sci*, edited by Bard P, Bethesda, MD, 1961, p. 1683-1688.

9. **Benzinger TH.** The human thermostat. *Sci Am* January: 2-11, 1961.

10. **Benzinger TH.** The Thermal Homeostasis of Man. In: *Temperature, Part II: Thermal Homeostasis*. Stoudsburg: Dowden, Hutchinson & Ross, Inc., 1967, p. 289-325.

11. **Benzinger TH, Pratt AW, and Kitzinger C.** The thermostatic control of human metabolic heat production. *Proceedings of the NAS* 47: 730-738, 1961.

12. **Berggren G and Hohwu Christensen E.** Heart rate and body temperature as indices of metabolic rate during work. *Arbeitsphysiologie* 14: 255-260, 1950.

13. **Berkenbosch A, DeGoede J, Ward DS, Olievier CN, and VanHartevelt J.** Dynamic response of the peripheral chemoreflex loop to changes in end-tidal O2. *J Appl Physiol* 71: 1123-1128, 1991.

14. **Bhattacharva J, Cunningham DJ, Howson MG, Lee MJ, and Sleight P.** Proceedings: The effects of mild hypoxia with constant PA, C02 and ventilation on the setting and sensitivity of the baroreceptor-cardiac-depressor reflex in man. *J Physiol (Lond)* 234: 112P-114P, 1973.

15. **Bligh J.** Thermal Regulation: What is regulated and how? *Proc Symp Therm Reg*, edited by Houdas Y and Guieu JD, Lille, France. Masson, 1977, p. 1-9.

16. **Boulant JA.** Thermoregulation. In: *Fever: basic Mechanisms and Management*, edited by Mackowiak P. New York: Raven Press, Ltd, 1991, p. 1-22.

17. **Brice AG, Forster HV, Pan LG, Funahashi A, Hoffman MD, Murphy CL, and Lowry TF.** Is the hyperpnea of muscular contractions critically dependent on spinal afferents? *J Appl Physiol* 64: 226-233, 1988.

18. **Brooks GA.** Current concepts in lactate exchange. *Med Sci Sports Exerc* 23: 895-906, 1991.

19. **Burger RE, Estavillo JA, Kumar P, Nye PC, and Paterson DJ.** Effects of potassium, oxygen and carbon dioxide on the steady-state discharge of cat carotid body chemoreceptors. *J Physiol (Lond)* 401: 519-531, 1988.

20. **Cabanac M.** Heat Stress and Behaviour. In: *Handbook of Physiology, sect 4: Environmental Physiology*, edited by Fregly MJ and Blatteis CM. New York: Oxford University Press, 1996, p. 261-278.

21. **Cabanac M and Massonnet B.** Thermoregulatory responses as a function of core temperature in humans. *J Physiol (Lond)* 265: 587-596, 1977.

22. **Cabanac M and White MD.** Core temperature thresholds for hyperpnea during passive hyperthermia in humans. *Eur J Appl Physiol* 71: 71-76, 1995.

23. **Casaburi R, Daly J, Hansen JE, and Effros RM.** Abrupt changes in mixed venous blood gas composition after the onset of exercise. *J Appl Physiol* 67: 1106-1112, 1989.

24. **Chang LP and Lundgren CE.** CO2 chemosensitivity during immersion in humans. *Chin J Physiol* 38: 7-12, 1995.

25. **Chang LP and Lundgren CE.** Maximal breath-holding time and immediate tissue CO2 storage capacity during head-out immersion in humans. *Eur J Appl Physiol* 73: 210-218, 1996.

26. **Clement ID and Robbins PA.** Dynamics of the ventilatory response to hypoxia in humans. *Respir Physiol* 92: 253-275, 1993.

27. **Coburn JW, Reba RC, and Craig FN.** Effect of potassium depletion on response to acute heat exposure in unacclimatized man. *Am J Physiol* 211: 117-124, 1966.

28. **Comroe JHJ and Schmidt CF.** Reflexes from the limbs as a factor in the hyperpnea of muscular exercise. *Am J Physiol* 138: 536, 1943.

29. **Cormack RS, Cunningham DJ, and Gee JB.** The effect of carbon dioxide on the respiratory response to want of oxygen in man. *Q J Exp Physiol Cogn Med Sci* 42: 303-319, 1957.

30. **Craig AB, Jr. and Dvorak M.** Expiratory reserve volume and vital capacity of the lungs during immersion in water. *J Appl Physiol* 38: 5-9, 1975.

31. **Cross MC, Radomski MW, VanHelder WP, Rhind SG, and Shephard RJ.** Endurance exercise with and without a thermal clamp: effects on leukocytes and leukocyte subsets. *J Appl Physiol* 81: 822-829, 1996.

32. **Cunningham DJC.** The effect of noradrenaline infusions on the relation between pulmonary ventilation and the alveolar PO_2 and PCO_2 in man. *Ann N Y Acad Sci*: 756-771, 1961.

33. **Cunningham DJC and O'Riordan JLH.** The effect of a rise in temperature of the body on respiratory response to carbon dioxide at rest. *QJ Exp Physiol* 42: 329-345, 1957.

34. **Cunningham DJC, Spurr D, and Lloyd BB.** Ventilatory drive in hypoxic exercise. In: *Arterial Chemoreceptors*, edited by Torrance RW. Blackwell: Oxford, 1968, p. 310-323.

35. **D'Angelo E and Torelli G.** Neural stimuli increasing respiration during different types of exercise. *J Appl Physiol* 30: 116-121, 1971.

36. **Daristotle L, Berssenbrugge AD, Engwall MJ, and Bisgard GE.** The effects of carotid body hypocapnia on ventilation in goats. *Respir Physiol* 79: 123-135, 1990.

37. **Dejours P.** Chemoreflexes in breathing. *Physiol Rev* 42: 335-358, 1962.

38. **Dejours P.** Control of respiration in muscular exercise. In: *Handbook of Physiology*, edited by Society AP. Washington, DC: Williams & Wilkins, 1964, p. 631-648.

39. **Dejours P.** The regulation of breathing during muscular exercise in man: A neurohumoral theory. In: *The regulation of human respiration*, edited by Cunningham DJC and Lloyd BB. Oxford, England: Blackwell Scientific Publications, 1963, p. 535.

40. **Dempsey JA, Vidruk EH, and Mitchell GS.** Pulmonary control systems in exercise: update. *Fed Proc* 44: 2260-2270, 1985.

41. **Diaz FJ, Hagan RD, Wright JE, and Horvath SM.** Maximal and submaximal exercise in different positions. *Med Sci Sports Exerc* 10: 214-217, 1978.

42. **Druml W, Grimm G, Laggner AN, Lenz K, and Schneeweiss B.** Lactic acid kinetics in respiratory alkalosis. *Crit Care Med* 19: 1120-1124, 1991.

43. **DuBois EF.** *Fever and the regulation of body temperature.* Springfield, Il.: Charles C. Thomas, 1948.

44. **Dutton RE, Smith EJ, Ghatak PK, and Davies DG.** Dynamics of the respiratory controller during carotid body hypoxia. *J Appl Physiol* 35: 844-850, 1973.

45. **Easton PA, Slykerman LJ, and Anthonisen NR.** Ventilatory response to sustained hypoxia in normal adults. *J Appl Physiol* 61: 906-911, 1986.

46. **Eisele JH, Ritchie BC, and Severinghaus JW.** Effect of stellate ganglion blockade on the hyperpnea of exercise. *J Appl Physiol* 22: 966-969, 1967.

47. **Evans AB, Tsai LW, Oelberg DA, Kazemi H, and Systrom DM.** Skeletal muscle ECF pH error signal for exercise ventilatory control. *J Appl Physiol* 84: 90-96, 1998.

48. **Eyzaguirre C, Monti-Bloch L, and Hayashida Y.** Effects of temperature on denervated carotid body (glomus) cells. *Brain Res* 279: 282-285, 1983.

49. **Farhi LE and Linnarsson D.** Cardiopulmonary readjustments during graded immersion in water at 35 degrees C. *Respir Physiol* 30: 35-50, 1977.

50. **Fuller CA and Baker MA.** Selective regulation of brain and body temperatures in the squirrel monkey. *Am J Physiol* 245: R293-297, 1983.

51. **Gale CC.** Neuroendocrine aspects of thermoregulation. *Annu Rev Physiol* 35: 391-430, 1973.

52. **Gaudio RJ and Abrahamson N.** Heat-induced hyperventilation. *J Appl Physiol* 25: 742-746, 1968.

53. **Glass C, Knowlton RG, Sanjabi PB, and Sullivan JJ.** The effect of exercise induced glycogen depletion on the lactate, ventilatory and electromyographic thresholds. *J Sports Med Phys Fitness* 37: 32-40, 1997.

54. **Glotzbach SF and Heller HC.** Central nervous regulation of body temperature during sleep. *Science* 194: 537-539, 1976.

55. **Gonzalez RR, Kluger MJ, and Hardy JD.** Partitional calorimetry of the New Zealand white rabbit at temperatures 5-35 degrees C. *J Appl Physiol* 31: 728-734, 1971.

56. **Griffiths TL, Henson LC, and Whipp BJ.** Influence of inspired oxygen concentration on the dynamics of the exercise hyperpnoea in man. *J Physiol* 380: 387-403, 1986.

57. **Grunstein MM, Fisk WM, Leiter LA, and Milic-Emili J.** Effect of body temperature on respiratory frequency in anesthetized cats. *J Appl Physiol* 34: 154-159, 1973.

58. **Haldane JS.** The influence of high air temperatures. *J Hyg* 55: 497-513, 1905.

59. **Hales J.** Peripheral effector Mechanisms of Thermoregulation. *Regulation of Panting. Satelite of 28 Int. Congress of Physiol. Sci*, edited by Szelenyi ZaS, M., Pecs, Hungary., 1980.

60. **Halliwill JR, Morgan BJ, and Charkoudian N.** Peripheral chemoreflex and baroreflex interactions in cardiovascular regulation in humans. *J Physiol (Lond)* 552: 295-302, 2003.

61. **Hammel HT, Jackson DC, Stolwijk JAJ, Hardy JD, and Stromme SB.** Temperature regulation by hypothalamic proportional control with an adjustable set point. *J Appl Physiol* 18: 1146-1154, 1963.

62. **Hansen JE, Stelter GP, and Vogel JA.** Arterial pyruvate, lactate, pH, and PCO2 during work at sea level and high altitude. *J Appl Physiol* 23: 523-530, 1967.

63. **Hayward JS, Eckerson JD, and Kemna D.** Thermal and cardiovascular changes during three methods of resuscitation from mild hypothermia. *Resuscitation* 11: 21-33, 1984.

64. **Heigenhauser GJ, Sutton JR, and Jones NL.** Effect of glycogen depletion on the ventilatory response to exercise. *J Appl Physiol* 54: 470-474, 1983.

65. **Hensel H.** Thermoreception and temperature regulation. London: Academic Press, 1982, p. 320-321.

66. **Hessemer V and Bruck K.** Influence of menstrual cycle on shivering, skin blood flow, and sweating responses measured at night. *J Appl Physiol* 59: 1902-1910, 1985.

67. **Hessemer V and Bruck K.** Influence of menstrual cycle on thermoregulatory, metabolic, and heart rate responses to exercise at night. *J Appl Physiol* 59: 1911-1917, 1985.

68. **Holton P and Wood JB.** The effects of bilateral removal of the carotid bodies and denervation of the carotid sinuses in two human subjects. *J Physiol* 181: 365-378, 1965.

69. **Honda Y.** Role of carotid chemoreceptors in control of breathing at rest and in exercise: studies on human subjects with bilateral carotid body resection. *Jpn J Physiol* 35: 535-544, 1985.

70. **Hossman VG, Fitzgerald A, and Dollery CT.** Circadian rhythm of baroreflex activity and andrenergic vascular response. *Cardiovasc Res* 14: 125-129, 1980.

71. **Huang SY, Alexander JK, Grover RF, Maher JT, McCullough RE, McCullough RG, Moore LG, Sampson JB, Weil JV, and Reeves JT.** Hypocapnia and sustained hypoxia blunt ventilation on arrival at high altitude. *J Appl Physiol* 56: 602-606, 1984.

72. **Hughson RL and Morrissey M.** Delayed kinetics of respiratory gas exchange in the transition from prior exercise. *J Appl Physiol* 52: 921-929, 1982.

73. **Ingram DL.** Evaporative cooling in the pig. *Nature* 207: 415-416, 1965.

74. **Inomoto T, Mercer JB, and Simon E.** Interaction between hypothalamic and extrahypothalamic body temperatures in the control of panting in rabbits. *Pflugers Arch* 398: 142-146, 1983.

75. **Israel SL and Schneller O.** The thermogenic property of progesterone. *Fertil Steril* 1: 53-64, 1950.

76. **Jessen C.** Independent clamps of peripheral and central temperatures and their effects on heat production in the goat. *J Physiol (Lond)* 311: 11-22, 1981.

77. **Jessen C.** Temperature Regulation in Humans and Other Mammals. Germany: Springer-Verlag Berlin Heidelberg, 2001, p. 193-194.

78. **Kagawa S, Stafford MJ, Waggener TB, and Severinghaus JW.** No effect of naloxone on hypoxia-induced ventilatory depression in adults. *J Appl Physiol* 52: 1030-1034, 1982.

79. **Keller AD.** *Temperature: Its Measurement and Control in Science and Industry.Temperature regulation disturbances in dogs following hypothalamic ablations. In J. D. Hardy (Ed.),*. New York: Reinhold, 1963.

80. **Khan DA, Aslam M, and Khan ZU.** Changes in plasma electrolytes during acclimatization at high altitude. *J Pak Med Assoc* 46: 128-131, 1996.

81. **Klausen K, Robinson S, Micahel ED, and Myhre LG.** Effect of high altitude on maximal working capacity. *J Appl Physiol* 21: 1191-1194, 1966.

82. **Kleinbaum D, Kupper L, and Muller K.** *Applied regression analysis and other multivariable methods.* Boston: PWS-KENT Publishing Company, 1988.

83. **Kluger MJ.** Fever. New Jersey: Princeton University Press, 1975, p. 195-196.

84. **Kluger MJ.** Fever. *Pediatrics* 66: 720-724, 1980.

85. **Kozlowski S and Saltin B.** Effect of Sweat Loss on Body Fluids. *J Appl Physiol* 19: 1119-1124, 1964.

86. **Krieger DT.** Food and water restriction shifts corticosterone, temperature, activity and brain amine periodicity. *Endocrinology* 95: 1195-1201, 1974.

87. **Krogh A and Lindhard J.** The regulation of respiration and circulation during the initial stages of muscular work. *J Physiol (Lond)* 47: 112, 1913.

88. **Kronert H and Pleschka K.** Lingual blood flow and its hypothalamic control in the dog during panting. *Pflugers Arch* 367: 25-31, 1976.

89. **Kuhnen G and Jessen C.** The metabolic response to skin temperature. *Pflugers Arch* 412: 402-408, 1988.

90. **Lagneaux D and Lecomte J.** [Effects of the addition of carbon dioxide on manifestations of acute hypoxia in rats]. *C R Seances Soc Biol Fil* 181: 616-621, 1987.

91. **Lahiri S.** Physiological responses and adaptations to high altitude. *Int Rev Physiol* 15: 217-251, 1977.

92. **Lambertsen CJ.** Physical, chemical, and nervous interactions in respiratory control. In: *Medical Physiology* (14 ed.), edited by Mountcastle VB, 1980, p. 1873-1900.

93. **Lambertsen CJ.** Respiratory and cerebral circulatory control during exercise at 0.21 and 2.0 atmospheres of inspired PO_2. *Journal of Applied Physiology* 14: 966, 1959.

94. **Lin C, Chen S, Kou G, and Kuo C.** An enzymatic microassay for lactate concentration in blood and hemolymph. *Acta Zool Taiw* 10: 91-101, 1999.

95. **Lloyd BB.** The chemical stimulus to breathing. *Br Med Bull* 19: 10-14, 1963.

96. **Lopez M, Sessler DI, Walter K, Emerick T, and Ayyalapu A.** Reduced sweating threshold during exercise-induced hyperthermia. *Pflugers Arch* 430: 606-611, 1995.

97. **Lugliani R, Whipp BJ, and Wasserman K.** A role for the carotid body in cardiovascular control in man. *Chest* 63: 744-750, 1973.

98. **MacDougall JD, Reddan WG, Layton CR, and Dempsey JA.** Effects of metabolic hyperthermia on performance during heavy prolonged exercise. *J Appl Physiol* 36: 538-544, 1974.

99. **Maher JT, Cymerman A, Reeves JT, Cruz JC, Denniston JC, and Grover RF.** Acute mountain sickness: increased severity in eucapnic hypoxia. *Aviat Space Environ Med* 46: 826-829, 1975.

100. **Mariak Z, Lewko J, Luczaj J, Polocki B, and White MD.** The Relationship between directly measured human cerebral and tympanic temperatures during changes in brain temperatures. *Eur J Appl Physiol* 69: 545-549, 1994.

101. **Mariak Z, White MD, Lewko J, Lyson T, and Piekarski P.** Direct cooling of the human brain by heat loss from the upper respiratory tract. *J Appl Physiol* 87: 1609-1613, 1999.

102. **Martin BJ, Morgan EJ, Zwillich CW, and Weil JV.** Control of breathing during prolonged exercise. *J Appl Physiol* 50: 27-31, 1981.

103. **Martin BJ, Morgan EJ, Zwillich CW, and Weil JV.** Influence of exercise hyperthermia on exercise breathing pattern. *J Appl Physiol* 47: 1039-1042, 1979.

104. **Mateika JH and Duffin J.** A review of the control of breathing during exercise. *Eur J Appl Physiol Occup Physiol* 71: 1-27, 1995.

105. **Mateika JH and Duffin J.** The ventilation, lactate and electromyographic thresholds during incremental exercise tests in normoxia, hypoxia and hyperoxia. *Eur J Appl Physiol Occup Physiol* 69: 110-118, 1994.

106. **McEwen GN, Jr. and Heath JE.** Resting metabolism and thermoregulation in the unrestrained rabbit. *J Appl Physiol* 35: 884-886, 1973.

107. **McLellan TM.** Ventilatory and plasma lactate response with different exercise protocols: a comparison of methods. *Int J Sports Med* 6: 30-35, 1985.

108. **Medbo JI and Sejersted OM.** Plasma K+ changes during intense exercise in endurance-trained and sprint-trained subjects. *Acta Physiol Scand* 151: 363-371, 1994.

109. **Mekjavic IB and Bligh J.** The increased oxygen uptake upon immersion. The raised external pressure could be a causative factor. *Eur J Appl Physiol Occup Physiol* 58: 556-562, 1989.

110. **Mekjavic IB, Eiken O, LaPrairie A, and Banister EW.** The pattern of breathing during hypoxic exercise. *Eur J Appl Physiol Occup Physiol* 56: 619-622, 1987.

111. **Mekjavic IB and Rempel ME.** Determination of esophageal probe insertion length based on standing and sitting height. *J Appl Physiol* 69: 376-379, 1990.

112. **Mekjavic IB, Sunderberg CJ, and Linnarsson D.** Core temperature "null zone". *J Appl Physiol* 71: 1289-1295, 1991.

113. **Mitchell GS, Smith CA, and Dempsey JA.** Changes in the VI-VCO2 relationship during exercise in goats: role of carotid bodies. *J Appl Physiol* 57: 1894-1900, 1984.

114. **Mitchell GS, Smith CA, Vidruk EH, Jameson LC, and Dempsey JA.** Effects of p-chlorophenylalanine on ventilatory control in goats. *J Appl Physiol* 54: 277-283, 1983.

115. **Miyamura M, Ishida K, Kobayashi T, Ohkuwa T, and Itoh H.** Effects of acute hypoxia on ventilatory response at the onset of cycle exercise in man. *Jpn J Physiol* 42: 823-829, 1992.

116. **Nadel ER.** Circulatory and thermal regulations during exercise. *Fed Proc* 39: 1491-1497, 1980.

117. **Nagel A, Herold W, Roos U, and Jessen C.** Skin and core temperatures as determinants of heat production and heat loss in the goat. *Pflugers Arch* 406: 600-607, 1986.

118. **Natalino MR, Zwillich CW, and Weil JV.** Effects of hyperthermia on hypoxic ventilatory response in normal man. *J Lab Clin Med* 89: 564-572, 1977.

119. **Nielsen M.** Regulation der Korpertemperatur bei Muskelarbeit. *Skand Arch Physiol* 79: 197-217, 1938.

120. **Nybo L, Moller K, Volianitis S, Nielsen B, and Secher NH.** Effects of hyperthermia on cerebral blood flow and metabolism during prolonged exercise in humans. *J Appl Physiol* 93: 58-64, 2002.

121. **Nybo L and Nielsen B.** Middle cerebral artery blood velocity is reduced with hyperthermia during prolonged exercise in humans. *J Physiol* 534: 279-286, 2001.

122. **Oelberg DA, Evans AB, Hrovat MI, Pappagianopoulos PP, Patz S, and Systrom DM.** Skeletal muscle chemoreflex and pHi in exercise ventilatory control. *J Appl Physiol* 84: 676-682, 1998.

123. **Park YS, Pendergast DR, and Rennie DW.** Decrease in body insulation with exercise in cool water. *Undersea Biomed Res* 11: 159-168, 1984.

124. **Parsons KC.** *Human thermal environments*. London: Taylor and Francis, 2003.

125. **Paterson DJ.** Potassium and ventilation in exercise. *J Appl Physiol* 72: 811-820, 1992.

126. **Paterson DJ, Robbins PA, and Conway J.** Changes in arterial plasma potassium and ventilation during exercise in man. *Respir Physiol* 78: 323-330, 1989.

127. **Petersen ES and Vejby-Christensen H.** Effect of Body Temperature on Steady State Ventilation and Metabolism in Exercise. *Acta Physiol Scand* 89: 342-351, 1973.

128. **Petersen ES and Vejby-Christensen H.** Effects of body temperature on ventilatory response to hypoxia and breathing pattern in man. *J Appl Physiol* 42: 492-500, 1977.

129. **Prefaut C, Ramonatxo M, Boyer R, and Chardon G.** Human gas exchange during water immersion. *Respir Physiol* 34: 307-318, 1978.

130. **Pugh LG.** Man at high altitude: studies carried out in the Himalaya. *Sci Basis Med Annu Rev*: 32-54, 1964.

131. **Qayyum MS, Barlow CW, O'Connor DF, Paterson DJ, and Robbins PA.** Effect of raised potassium on ventilation in euoxia, hypoxia and hyperoxia at rest and during light exercise in man. *J Physiol (Lond)* 476: 365-372, 1994.

132. **Rapanos T and Duffin J.** The ventilatory response to hypoxia below the carbon dioxide threshold. *Can J Appl Physiol* 22: 23-36, 1997.

133. **Rasch W and Cabanac M.** Selective brain cooling is affected by wearing headgear during exercise. *J Appl Physiol* 74: 1229-1233, 1993.

134. **Rasch W, Samson P, Cote J, and Cabanac M.** Heat loss from the human head during exercise. *J Appl Physiol* 71: 590-595, 1991.

135. **Read DJ.** A clinical method for assessing the ventilatory response to carbon dioxide. *Australas Ann Med* 16: 20-32, 1967.

136. **Rebuck AS and Woodley WE.** Ventilatory effects of hypoxia and their dependence on PCO2. *J Appl Physiol* 38: 16-19, 1975.

137. **Rhind SG, Gannon GA, Shek PN, Brenner IK, Severs Y, Zamecnik J, Buguet A, Natale VM, Shephard RJ, and Radomski MW.** Contribution of exertional hyperthermia to sympathoadrenal-mediated lymphocyte subset redistribution. *J Appl Physiol* 87: 1178-1185, 1999.

138. **Rhoades R.** The regulation of body temperature. In: *Medical Physiology*, edited by Rhoades R and Tanner G. Boston: Little, Brown and Company, 1995.

139. **Rothchild I and Barnes C.** The effects of dosage, and or estrogen, androgen or salicylate administration on the degree of body temperature elevation induced by progesterone. *Enocrinology* 50: 485-496, 1952.

140. **Sancheti A and White MD.** Human minute ventilation responses to carbon dioxide levels prior to and following an exercise induced hyperthermia. *International Union of Physiological Sciences Thermal Physiology Symposium*, Wollongong, Australia. Australian Physiological and Pharmacological Society, 2001, p. 134P.

141. **Sancheti A and White MD.** Tidal volume and frequency of respiration: Relationships to esophageal temperature during exercise induced hyperthermia. *9th Int. Conf. Environ Ergonom IX*, edited by J W and M H, Dortmund, Germany. Shaker Verlag, 2000, p. 89-92.

142. **Satinoff E.** Behavioural thermoregulation in the cold. In: *Handbook of Physiology, sect 4: Environmental Physiology*, edited by Fregly MJ and Blatteis CM. New York: Oxford University Press, 1996, p. 481-505.

143. **Satinoff E.** A reevaluation of the concept of the homeostatic organization of temperature regulation. In: *Handbook of Behavioral Neurobiology*, edited by Teitelbaum P. New York: Plenum Press, 1983, p. 443-472.

144. **Sato F, Nishimura M, Igarashi T, Yamamoto M, Miyamoto K, and Kawakami Y.** Effects of exercise and CO2 inhalation on intersubject variability in ventilatory and heart rate responses to progressive hypoxia. *Eur Respir J* 9: 960-967, 1996.

145. **Savourey G, Besnard Y, Launay JC, Guinet A, Hanniquet AM, Caterini R, and Bittel J.** Short hypobaric hypoxia and breathing pattern: effect of positive end expiratory pressure. *Aviat Space Environ Med* 70: 863-866, 1999.

146. **Saxton C.** Effects of severe heat stress on respiration and metabolic rate in resting man. *Aviat Space Environ Med* 52: 281-286, 1981.

147. **Schmidt-Nielsen K, Schmidt-Nielsen B, Jarnum SA, and Houpt TR.** Body temperature of the camel and its relation to water economy. *Am J Physiol* 188: 103-112, 1957.

148. **Skinner JS and McLellan TH.** The transition from aerobic to anaerobic metabolism. *Res Q Exerc Sport* 51: 234-248, 1980.

149. **Somers VK, Mark AL, Zavala DC, and Abboud FM.** Influence of ventilation and hypocapnia on sympathetic nerve responses to hypoxia in normal humans. *J Appl Physiol* 67: 2095-2100, 1989.

150. **Sommer LZ, Iscoe S, Robicsek A, Kruger J, Silverman J, Rucker J, Dickstein J, Volgyesi GA, and Fisher JA.** A simple breathing circuit minimizing changes in alveolar ventilation during hyperpnoea. *Eur Respir J* 12: 698-701, 1998.

151. **Sorensen SC and Severinghaus JW.** Respiratory sensitivity to acute hypoxia in man born at sea level living at high altitude. *J Appl Physiol* 25: 211-216, 1968.

152. **Stadie WC, Austin JH, and Robinson HW.** The effect of temperature on the acid-base protein equilibrium and its influence on the CO_2 absorption curve of whole blood, true and separated serum. *J Biol Chem* 66: 901, 1925.

153. **Stanier MW, Mount LE, and Bligh J.** Body Temperature and its regulation. In: *Energy Balance and Temperature Regulation.* Cambridge: Cambridge University Press, 1985, p. 54-72.

154. **Stelzner JK and Hausfater G.** Posture, microclimate, and thermoregulation in yellow baboons. *Primates* 27: 449-463, 1986.

155. **Stephenson LA, Wenger CB, O'Donovan BH, and Nadel ER.** Circadian rhythm in sweating and cutaneous blood flow. *Am J Physiol* 246: R321-324, 1984.

156. **Strange S, Secher NH, Pawelczyk JA, Karpakka J, Christensen NJ, Mitchell JH, and Saltin B.** Neural control of cardiovascular responses and of ventilation during dynamic exercise in man. *J Physiol* 470: 693-704, 1993.

157. **Swanson GD, Whipp BJ, Kaufman RD, Aqleh KA, Winter B, and Bellville JW.** Effect of hypercapnia on hypoxic ventilatory drive in carotid body-resected man. *J Appl Physiol* 45: 871-877, 1978.

158. **Tenney SM, Remmers JE, and Mithoefer JC.** Interaction of CO2 and hypoxic stimuli on ventilation at high altitude. *Q J Exp Physiol Cogn Med Sci* 48: 192-201, 1963.

159. **Thauer R.** Warm regularization and fieberfahigkeit after operational intervened at the nervous system of homiothermic sucking animals. *Pflugers Archiv fur die Gesamte Physiologie* 236: 102-147, 1935.

160. **Timbal J, Colin J, and Boutelier C.** Circadian variations in the sweating mechanism. *J Appl Physiol* 39: 226-230, 1975.

161. **Tryba AK and Ramirez JM.** Response of the respiratory network of mice to hyperthermia. *J Neurophysiol* 89: 2975-2983, 2003.

162. **Veicsteinas A and Rennie DW.** Thermal insulation and shivering threshold in Greek sponge divers. *J Appl Physiol* 52: 845-850, 1982.

163. **Vejby-Christensen H and Petersen ES.** Effect of body temperature on ventilatory transients at start and end of exercise in man. *Respir Physiol* 17: 315-324, 1973.

164. **Vizek M, Pickett CK, and Weil JV.** Interindividual variation in hypoxic ventilatory response: potential role of carotid body. *J Appl Physiol* 63: 1884-1889, 1987.

165. **von Euler C.** The functional organization of the respiratory phase-switching mechanisms. *Fed Proc* 36: 2375-2380, 1977.

166. **Ward DS, Berkenbosch A, DeGoede J, and Olievier CN.** Dynamics of the ventilatory response to central hypoxia in cats. *J Appl Physiol* 68: 1107-1113, 1990.

167. **Ward SA, Blesovsky L, Russak S, Ashjian A, and Whipp BJ.** Chemoreflex modulation of ventilatory dynamics during exercise in humans. *J Appl Physiol* 63: 2001-2007, 1987.

168. **Ward SA, Whipp BJ, Koyal S, and Wasserman K.** Influence of body CO2 stores on ventilatory dynamics during exercise. *J Appl Physiol* 55: 742-749, 1983.

169. **Wasserman K.** Breathing during exercise. *N Engl J Med* 298: 780-785, 1978.

170. **Wasserman K.** Determinants and detection of anaerobic threshold and consequences of exercise above it. *Circulation* 76: VI29-39, 1987.

171. **Wasserman K, Van Kessel AL, and Burton GG.** Interaction of physiological mechanisms during exercise. *J Appl Physiol* 22: 71-85, 1967.

172. **Wasserman K, Whipp BJ, Casaburi R, and Beaver WL.** Carbon dioxide flow and exercise hyperpnea. Cause and effect. *Am Rev Respir Dis* 115: 225-237, 1977.

173. **Wasserman K, Whipp BJ, and Davis JA.** Respiratory physiology of exercise: metabolism, gas exchange, and ventilatory control. *Int Rev Physiol* 23: 149-211, 1981.

174. **Wasserman K, Whipp BJ, Koyal SN, and Cleary MG.** Effect of carotid body resection on ventilatory and acid-base control during exercise. *J Appl Physiol* 39: 354-358, 1975.

175. **Weil JV, Byrne-Quinn E, Sodal IE, Friesen WO, Underhill B, Filley GF, and Grover RF.** Hypoxic ventilatory drive in normal man. *J Clin Invest* 49: 1061-1072, 1970.

176. **Weil JV, Byrne-Quinn E, Sodal IE, Kline JS, McCullough RE, and Filley GF.** Augmentation of chemosensitivity during mild exercise in normal man. *J Appl Physiol* 33: 813-819, 1972.

177. **Weil JV and Zwillich CW.** Assessment of ventilatory response to hypoxia: methods and interpretation. *Chest* 70: 124-128, 1976.

178. **Welbergen E and Clijsen L.** The influence of body position on maximal performance in cycling. *Eur J Appl Physiol Occup Physiol* 61: 138-142, 1990.

179. **Wenger CB, Roberts MF, Stolwijk JA, and Nadel ER.** Nocturnal lowering of thresholds for sweating and vasodilation. *J Appl Physiol* 41: 15-19, 1976.

180. **Whelan RF and Young IM.** Effect of adrenaline and noradrenaline infusions on respiration in man. *Brit J Pharmacol* 8: 98-102, 1953.

181. **Whipp BJ.** Peripheral chemoreceptor control of exercise hyperpnea in humans. *Med Sci Sports Exerc* 26: 337-347, 1994.

182. **Whipp BJ.** Ventilatory control during exercise in humans. *Annu Rev Physiol* 45: 393-413, 1983.

183. **Whipp BJ, Ward SA, Lamarra N, Davis JA, and Wasserman K.** Parameters of ventilatory and gas exchange dynamics during exercise. *J Appl Physiol* 52: 1506-1513, 1982.

184. **Whipp BJ and Wasserman K.** Carotid bodies and ventilatory control dynamics in man. *Fed Proc* 39: 2668-2673, 1980.

185. **White MD and Cabanac M.** Exercise hyperpnea and hyperthermia in humans. *J Appl Physiol* 81: 1249-1254, 1996.

186. **Wyndham CH and Atkins AR.** A physiological scheme and mathematical model of temperature regulation in man. *Pflugers Arch* 303: 14-30, 1968.

187. **Wyss CR, Brengelmann GL, Johnson JM, Rowell LB, and Niederberger M.** Control of skin blood flow, sweating, and heart rate: role of skin vs. core temperature. *J Appl Physiol* 36: 726-733, 1974.

188. **Zwillich CW, Sahn SA, and Weil JV.** Effects of hypermetabolism on ventilation and chemosensitivity. *J Clin Invest* 60: 900-906, 1977.

APPENDIX A

Esophageal Probe Calibration Data

Each participant's esophageal thermocouple probe was calibrated in a regulated temperature hot water bath with a mercury thermometer (Cenco Instruments, Chicago, Ill., USA). Water temperature was increased to approximately 30, 34, 38 and 42°C and allowed to stabilize for at least 10 min before measurements were recorded. Each probe was immersed for 5 min at each temperature and values were then recorded over a 60 s period. Individual calibration curves were constructed for each esophageal probe versus the mercury thermometer. A linear regression was developed across the four calibration temperatures of ~30, 34, 38, 42°C. Table A.1 lists the mean temperature values over a 60 s period at each temperature condition for both the esophageal probe and the mercury thermometer. Table A.2 lists the calibration factor for each participant's esophageal thermocouple probe. Figure A.1 shows the esophageal probe values plotted against the mercury thermometer values for a typical participant. The correlation coefficient is given along with the regression equation.

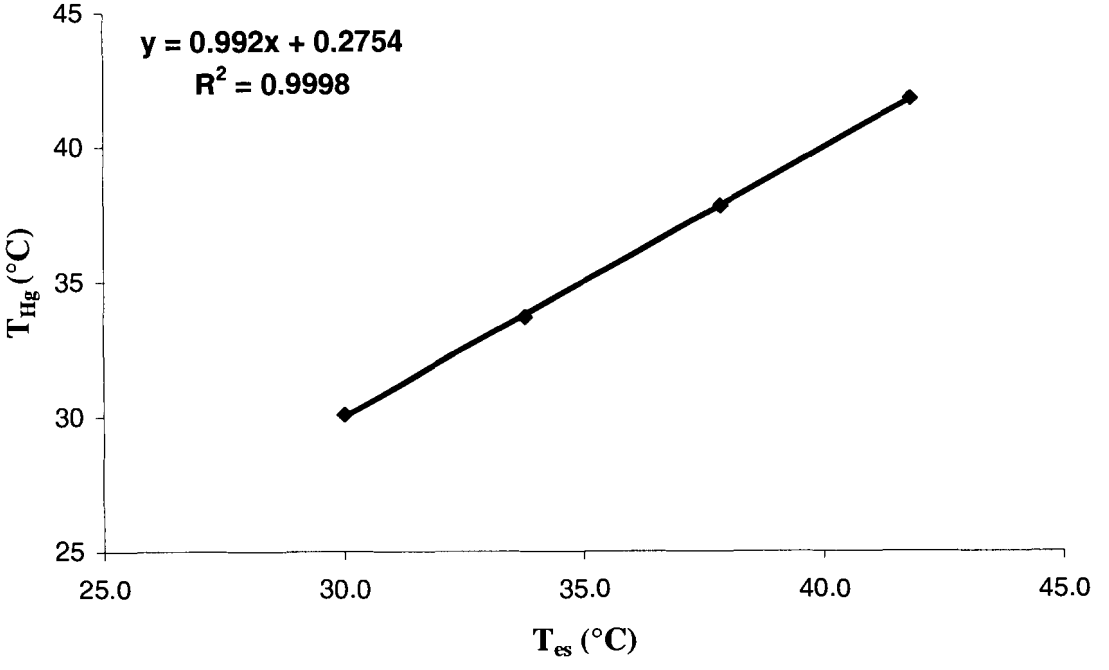
Table A.1 Calibration values for esophageal thermocouple probes for each participant compared against a mercury thermometer at 30, 34, 38 and 42°C.
T_{es} represents esophageal probes, T_{Hg} represents mercury thermometer

Subject	30 T_{Hg} (°C)	30 T_{es} (°C)	34 T_{Hg} (°C)	34 T_{es} (°C)	38 T_{Hg} (°C)	38 T_{es} (°C)	42 T_{Hg} (°C)	42 T_{es} (°C)
1	30.1	30.0	33.7	33.8	37.8	37.8	41.8	41.8
2	30.1	30.2	33.7	33.9	37.8	37.9	41.8	41.9
3	30.1	30.0	33.8	33.9	37.8	37.8	41.8	41.9
4	30.1	30.2	33.8	33.8	37.8	37.9	41.9	41.8
5	30.2	30.2	33.7	33.9	37.8	37.9	41.8	41.9
6	30.1	30.2	33.8	33.9	37.8	37.8	41.8	41.9
7	30.2	30.2	33.8	33.9	37.8	37.8	41.8	41.8
8	30.2	30.3	33.7	33.9	37.9	37.9	41.8	41.9
9	30.1	30.2	33.8	33.9	37.9	37.9	41.8	41.8
10	30.2	30.14	33.7	33.8	37.8	37.9	41.8	41.8
11	30.1	30.1	33.7	33.8	37.8	37.8	41.8	41.8
Mean	**30.1**	**30.2**	**33.7**	**33.9**	**37.8**	**37.9**	**41.8**	**41.8**
SD	0.05	0.09	0.05	0.05	0.04	0.05	0.03	0.05

Fig A.2 Calibration factors for values for esophageal thermocouple probes for each participant compared against a mercury thermometer at 30, 34, 38 and 42°C.

Subject	Correlation coefficient	Calibration equation for esophageal thermocouple probes
1	$R^2 = 0.9998$	y = 0.992x + 0.2754
2	$R^2 = 0.9998$	y = 1.005x - 0.299
3	$R^2 = 0.9999$	y = 0.9904x + 0.3084
4	$R^2 = 0.9998$	y = 1.0138x - 0.5536
5	$R^2 = 0.9996$	y = 1.0036x - 0.2341
6	$R^2 = 1.000$	y = 0.9999x - 0.0719
7	$R^2 = 0.9997$	y = 1.0057x - 0.291
8	$R^2 = 0.9999$	y = 0.9973x + 0.0642
9	$R^2 = 0.9999$	y = 1.0034x - 0.1553
10	$R^2 = 0.9997$	y = 0.9919x + 0.2397
11	$R^2 = 0.9999$	y = 1.003x - 0.1608

Fig A.1 **Esophageal thermocouple probe (T_{es}) values plotted against a mercury thermometer (T_{Hg}) values at 30, 34, 38 and 42°C for a typical esophageal probe (Esophageal probe for Participant 1).**
Data points are the means for a 60 s period of a typical probe.
The correlation coefficient is given along with the regression equation.



APPENDIX B

Preliminary Sub-maximal exercise test

This session served to acquaint the participants with the laboratory equipment and procedures to be used during the study as well as to establish their physical profile. Peak oxygen consumption ($\dot{V}O_{2peak}$) for underwater cycling on a recumbent hydraulic powered bicycle was estimated by a ramp cycle ergometer test while the subjects are immersed in thermally neutral water (~33°C). After a 2-minute warm-up period with no load, resistance was increased gradually to produce 4 steady-state heart rates (HR) between 60-140 beats·min^{-1}. Each work load was held for a minimum of 2 min or until the subjects HR did not vary by more than 5 beats·min^{-1} over a 30 s period. The participants $\dot{V}O_{2peak}$ was estimated by plotting a regression line to their $\dot{V}O_2$ against HR scatter plot for the sub-maximal exercise session. The age predicted maximum HR was used in the linear regression equation to give a predicted $\dot{V}O_{2peak}$ for each participant.

This experiment required the participants to exercise on a head-out underwater recumbent cycle ergometer. The load on the ergometer was provided by a hydraulic motor, which was used to apply backpressure to the flywheel as the participant pedalled

in a forward circular motion. Increasing or decreasing the hydraulic pump speed, which is measured in hertz, varied the resistance.

An important consideration when measuring ventilatory excursions on a recumbent cycle ergometer as opposed to a seated cycle ergometer is that recumbent ergometers have been shown to elicit much lower maximal power outputs due to the limb position and gravitational effects (2). Furthermore in a study by Diaz et al. (1) it has been shown that recumbent ergometers are found to produce lower $\dot{V}O_{2peak}$ by ~ 7.4 %. This would explain why the estimated $\dot{V}O_{2peak}$ values for the participants in the current study appeared to be slightly lower then the relative norm for their age group and fitness level.

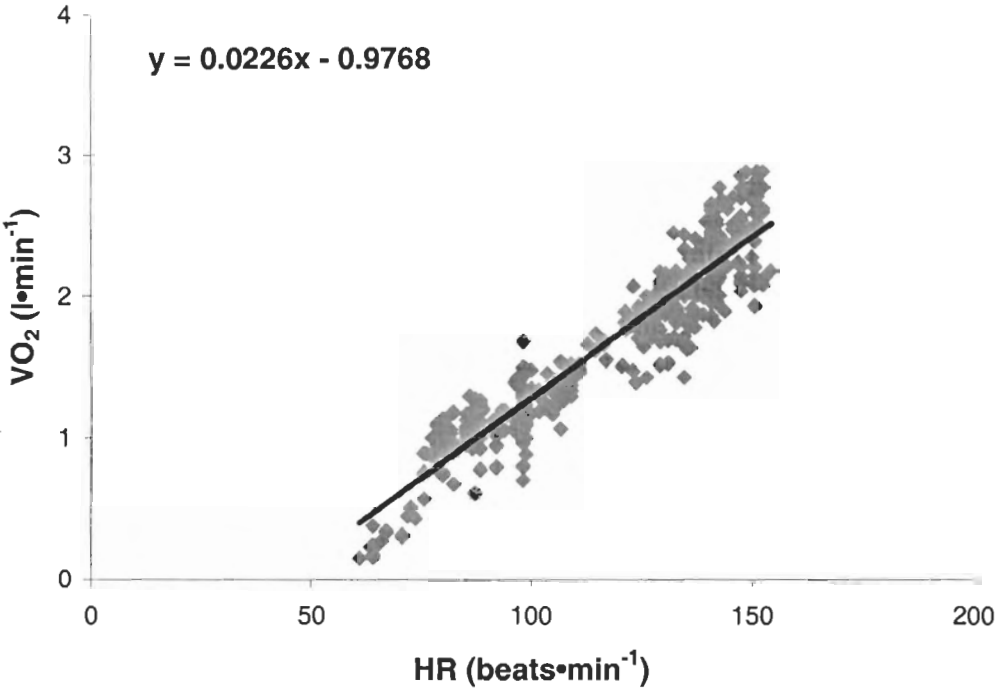
Table B.1 Sub-maximal exercise test values for age-predicted $\dot{V}O_{2peak}$ on an underwater recumbent hydraulic powered cycle ergometer.

Age-predicted max HR is determined by the equation: 220-age. Age-predicted $\dot{V}$O2peak* represents the predicted $\dot{V}$O2peak for cycling on an underwater recumbent hydraulic cycle ergometer

Subject	Age (yr)	Age-predicted max HR (beats·min^{-1})	Age-predicted $\dot{V}O_{2peak}$* (L·min^{-1})
1	27	193	3.15
2	21	199	2.69
3	22	198	3.50
4	22	198	3.67
5	22	198	2.72
6	29	191	2.96
7	21	199	4.24
8	34	186	3.99
9	22	198	3.41
10	22	198	2.92
11	19	201	3.30
Mean	**23.7**	**196.3**	**3.32**
SD	4.43	4.43	0.50

Fig B.1 Oxygen consumption ($\dot{V}O_2$) plotted against heart rate (HR) for a typical participant's (Participant 3) Sub-maximal exercise test.

The equation for the regression line is used to estimate the participants $\dot{V}O2peak$ on a underwater recumbent hydraulic powered cycle ergometer.



References

1. **Diaz FJ, Hagan RD, Wright JE, and Horvath SM.** Maximal and submaximal exercise in different positions. *Med Sci Sports Exerc* 10: 214-217, 1978.

2. **Welbergen E and Clijsen L.** The influence of body position on maximal performance in cycling. *Eur J Appl Physiol Occup Physiol* 61: 138-142, 1990.

APPENDIX C

Power calculations to determine sample size

A power analysis of comparisons for a detectable difference of ventilation at a similar level of hyperthermia as proposed in this study was done to justify sample size selection. Data from Cabanac and White's (1) study, during rest and passive hyperthermia (increase of T_{es} by ~2°C) was used for this calculation. The mean ventilation for subjects while at rest and a steady-state T_{es} of 36.6°C (SD 0.1) was 10.0 $L \cdot min^{-1}$ (SD 2.4). At the end of the hyperthermic period the mean T_{es} was 39.0°C (SD 0.2) and the ventilation was increased to 19.3 $L \cdot min^{-1}$ (SD 7.9). The effect size of 9.3 $L \cdot min^{-1}$ was then used for the power calculation. Using a sample size of $\eta = 10$, and an $\alpha = 0.05$, the power of replicating this finding would be 0.99.

Reference

1. **Cabanac M and White MD.** Core temperature thresholds for hyperpnea during passive hyperthermia in humans. *Eur J Appl Physiol* 71: 71-76, 1995.