Cerebrovascular and Respiratory Responses to Poikilocapnia and Eucapnia in Resting Normothermic and Hyperthermic Humans

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ABSTRACT

Human cerebrovascular responses in the middle cerebral artery (MCA), posterior cerebral artery (PCA), and basilar artery (BA) were assessed in two studies. In the first study, an index of cerebrovascular conductance (ICVC) in the MCA was decreased ($P<0.05$) in poikilocapnic, hyperthermic humans, while ICVC was maintained in the PCA and BA. Eucapnia during hyperthermia returned ICVC in the MCA, PCA, and BA to resting ICVC values. In the second study the effects of volitional hyperventilation on cerebral blood velocity (CBV) and ICVC responses in normothermic humans were assessed in the same three cerebral vessels. Results indicated that, unlike in hyperthermia, responses were uniform with CBV and ICVC decreases ($P<0.05$) in normothermic poikilocapnia in all three cerebral vessels with no differences ($P>0.05$) from normothermic resting values when $P_{ET}CO_2$ was restored to eucapnic partial pressures. In conclusion**,** evidence suggests there are regional differences of cerebrovascular responses in hyperthermic, but not normothermic humans.

Keywords: Cerebral blood velocity; control of breathing; eucapnia; hyperthermia; hyperventilation; poikilocapnia; transcranial Doppler; thermal hyperpnea

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF EQUATIONS

LIST OF DEFINITIONS

Cerebral Autoregulation[1] – Adjustment of cerebral arteriolar calibre, or cerebrovascular resistance, to match cerebral blood flow to metabolic needs. See dynamic and static cerebral autoregulation as well.

Cerebral Blood Velocity – The mathematical average of the velocities of red blood cells inside a blood vessel in the cerebrum.

Cerebrovascular Conductance[1] – The reciprocal of cerebrovascular resistance and proportional to the fourth power of vessel radius; $C = \dot{Q}/MAP$.

Cerebrovascular Reactivity[1] – Highly sensitive distribution of CBF in response to changes in arterial PO_2 and PCO_2.

Cerebral Perfusion Pressure[1] – The net pressure difference between intracranial pressure and blood pressure at Circle of Willis, which results in blood flow in the brain.

Cerebrovascular Resistance[1] – The degree to which the cerebral arterioles impede the flow of blood; $R = MAP/\dot{Q}$.

Chemosensitivity – The sensitivity of a physiological response to chemical a stimulus such as cerebral blood velocity responding to carbon dioxide partial pressures.

Core Temperature[2] – The mean temperature of the thermal core.

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[1] **Ainslie PN, and Duffin J**. *Am J Physiol Regul Integr Comp Physiol* 296: R1473-1495, 2009.
[2] **Mercer J, and Werner J**. *Jpn J Physiol* 51(2): 245-280, 2001.

Dynamic Autoregulation[1] – The rapid regulation of cerebral blood flow to changes in arterial blood pressure that occur in a few seconds.

Eccrine Sweating or Thermal Sweating[2] – Response of eccrine sweat glands to a thermal stimulus.

Eucapnia – Resting arterial partial pressure of carbon dioxide.

Hypocapnia – A reduced arterial partial pressure of carbon dioxide with respect to eucapnia.

Hypercapnia – An elevated arterial partial pressure of carbon dioxide with respect to eucapnia.

Hyperthermia[2] – A core temperature that is elevated above its resting value for individuals in a normal active state.

Hyperventilation – An increase in pulmonary ventilation rate that reduces P_aCO_2 below normal.

Respiratory Control Centre – Autonomic nuclei located in the reticular formations of the medulla oblongata and pons that control respiration.

Static Autoregulation[1] – The slow regulation of cerebral blood flow to gradual or progressive changes in cerebral perfusion pressure.

Thermal Hyperpnea – An increase in tidal volume and frequency of breathing occurring during severe heat stress, which is caused by a large increase in core temperature.

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[1] **Ainslie PN, and Duffin J**. *Am J Physiol Regul Integr Comp Physiol* 296: R1473-1495, 2009.
[2] **Mercer J, and Werner J**. *Jpn J Physiol* 51(2): 245-280, 2001.

Thermal Tachypnea[2] – A rapid respiratory frequency accompanied by an increase in respiratory minute volume, and commonly, a decrease in tidal volume to allow heat dissipation.

Transcranial Doppler[1] – An ultrasound device that allows for the measurement of lumenal flow velocities of red blood cells using the Doppler shift principle.

[1] **Ainslie PN, and Duffin J**. *Am J Physiol Regul Integr Comp Physiol* 296: R1473-1495, 2009.
[2] **Mercer J, and Werner J**. *Jpn J Physiol* 51(2): 245-280, 2001.

LIST OF ABBREVIATIONS

ACV	active cutaneous vasodilation
BA	basilar artery
BAv	basilar artery mean blood velocity
CA	cerebral autoregulation
CBF	cerebral blood flow
CBV	cerebral blood velocity
CPP	cerebral perfusion pressure
CSF	cerebral spinal fluid
CVC	cerebrovascular conductance
HT	hyperthermia (T_{CORE}~38ºC)
ICP	intracranial pressure
ICVC	index of cerebrovascular conductance
MAP	mean arterial pressure
MCA	middle cerebral artery
MCAv	middle cerebral artery mean blood velocity
NT	normothermia (T_{CORE}~37ºC)
P_aCO_2	arterial partial pressure of carbon dioxide
PCA	posterior cerebral artery
PCAv	posterior cerebral artery mean blood velocity

PEFR	peak expiratory flow rate
$P_{ET}CO_2$	end-tidal partial pressure of carbon dioxide
$P_{ET}O_2$	end-tidal partial pressure of oxygen
$\dot{Q}$	cardiac output
RCC	respiratory control centre
RH	relative humidity
SBC	selective brain cooling
T_{AMB}	ambient temperature
T_{CORE}	core temperature
TCD	transcranial Doppler
T_e	expiratory time
T_{ES}	esophageal temperature
T_i	inspiratory time
T_{RE}	rectal temperature
$\bar{T}_{SK}$	mean skin temperature
T_{TOT}	total time of one complete breath cycle
VA	vertebral artery
$\dot{V}_E$	expired pulmonary ventilation rate
V_T	tidal volume

CHAPTER ONE: LITERATURE REVIEW

1.1 Overview

Changes in vasomotor tone occur in the brain and allow for variance in cerebral blood flow (CBF). The cerebral vasculature is highly responsive to partial pressures of carbon dioxide (PCO_2) in the brain, and as a result CBF changes ~3.8% per mm Hg PCO_2 within the range of arterial partial pressures of carbon dioxide (P_aCO_2) of 35-55 mm Hg (41). This phenomenon is referred to as cerebrovascular CO_2 reactivity, or simply, CO_2 reactivity. The transient calibre of cerebral arterioles is critical to the maintenance of central pH as it allows for clearing or conservation of cerebrovascular CO_2.

In normal breathing, the end-tidal partial pressure of CO_2 ($P_{ET}CO_2$) is known to slightly underestimate P_aCO_2 at rest by less than 1 mm Hg (5). During hypocapnia $P_{ET}CO_2$ is equivalent to P_aCO_2 at rest (1, 35). The P_aCO_2, however, can be overestimated during hypercapnia, and exercise (1, 79). Based on this information $P_{ET}CO_2$ is best used as an indicator of P_aCO_2 in normal breathing at rest, or during hypocapnic breathing, which can occur during hyperthermia.

During hyperthermia in humans, significant decreases (13, 21, 35) in $P_{ET}CO_2$ are elicited by elevations in expired pulmonary ventilation rate ($\dot{V}_E$). During passive hyperthermia these drops in $P_{ET}CO_2$ can be greater than 5 mm Hg (105), and drop to values as low as 18.9 mm Hg (57, 104). This hypocapnia

appears to result in cerebral vasoconstriction, eliciting decreases in cerebral blood velocity (CBV), which is an index of CBF (1) obtained using transcranial Doppler ultrasonography (TCD). Furthermore, respiratory drive is partly dependent on concentrations of PCO_2 and/or $[H^+]$ in the brainstem. The elevation in $\dot{V}_E$ despite a drop in $P_{ET}CO_2$ during hyperthermia is contrary to the view that lower $P_{ET}CO_2$ will elicit a weaker respiratory drive. Therefore, it appears (9) that either there is/are an additional respiratory drive(s), or an increase in chemosensitivity of pulmonary ventilation due to elevations in body temperature. It remains to be discovered where this additional drive originates, or if the hyperventilation during hyperthermia is due to increased chemosensitivity (105). If it comes from a resultant increase in chemosensitivity, then CBF/CBV might be expected to remain constant or increase in the brainstem during a hyperthermic condition.

In hyperthermia (13, 35, 36, 73) CBV is decreased in the middle cerebral artery (MCA). Furthermore, large decreases in $P_{ET}CO_2$ reduce the drive to breathe, but this does not occur during hyperthermia when there is hyperventilation (13, 35, 36, 73). This suggests that the PCO_2 in the brain is not wholly responsible for changes in $\dot{V}_E$ and CBV during exercise or passively induced hyperthermia (13, 36, 73). Since the respiratory control centres (RCC) located in the brainstem are the main central nervous system loci responsible for respiratory drive, then changes in MCA CBV would appear to be of lesser consequence than perfusion changes in the medulla oblongata and pons with respect to control of breathing.

It is therefore important – during hyperthermia in humans – to determine the changes in CBV and cerebral perfusion in the basilar artery (BA), which supplies blood to the midbrain, pons, and upper lateral medulla oblongata. The BA vascularizes the pons and, therefore, the pontine respiratory centres including the pneumotaxic respiratory centre and apneustic respiratory centre, which provide impulses to the ventral and dorsal respiratory groups of the upper medulla oblongata (42, 60, 61, 63). Furthermore, the BA vascularizes tissues adjacent to the 4th ventricle, which include chemosensitive tissues (42, 60, 61, 63). The posterior cerebral artery (PCA) can also be investigated, it is supplied primarily by the BA, and provides vascularization of the choroid body of the 4th ventricle, which produces the CSF near the brainstem and central chemoreceptors (42, 60, 61, 63).

For studies of cerebral perfusion, the quotient of CBV and mean arterial blood pressure (MAP) is often employed to give an index of cerebrovascular conductance (ICVC). This is to account for changes in perfusion pressure arising from variations in blood pressure (13).

The goal of the first study in this thesis was to measure ICVC in resting volunteers in the MCA, PCA, and BA during poikilocapnic normothermic rest, poikilocapnic hyperthermia, and eucapnic hyperthermia. Furthermore, a second study investigated CBV and ICVC in resting volunteers in the MCA, PCA, and BA during normothermic poikilocapnic rest, poikilocapnic normothermic hyperventilation, and eucapnic normothermic hyperventilation. This was done to determine if temperature is responsible for regional variations in CBV and ICVC

evident during hyperthermia. This literature review culminates in a rationale that allows for the statement of the experimental hypotheses for Study 1 and Study 2. The outcomes of these studies contribute to the explanation of unresolved mechanisms of breathing control in hyperthermic humans.

1.2 Literature Review

This literature review begins with an overview on measurements of respiratory drive, and is followed by a description of what is known about breathing in hyperthermia. Next, there is an exploration of the literature as it pertains to hypocapnia and hypercapnia, especially as a result of hyperthermia and how it relates to CBV and cerebrovascular conductance. Furthermore, there is a review of peripheral vascular and thermoregulatory responses to hyperthermia including eccrine sweating, cutaneous vasodilation, and selective brain cooling as well as a description of the effects of these homeostatic responses on CBV. This literature review also contains three sections on cerebral hemodynamics along with an integration of the previous sections to discuss the limitations of the existing literature, thus creating the foundation for a statement of the rationale of the two studies in this thesis.

1.2.1 Indices of Resting Respiratory Drive and Timing

Breathing patterns in humans are a result of the integration of several different inputs including a central pattern generator in the medulla oblongata, and peripheral inputs such as temperature, which give information to feedforward and feedback systems that allow for normal control of breathing (29). There are

different indices of respiratory drive and timing in humans that are employed (11, 66) including: expiratory time (T_e, s), peak expiratory flow rate (PEFR, L/min), mean inspiratory flow rate (Tidal Volume (V_T)/Inspiratory time (T_i) or V_T/T_i, (L/s) and airway occlusion pressure ($P_{0.1,}$ mm Hg).

For humans of different body sizes, it is apparent that the ratio of inspiratory and expiratory time with respect to total breath time is the same (10). The primary method of decreasing breathing frequency is the prolongation of expiration duration, which delays the onset of inspiration (11, 66). Mean inspiratory flow rate is equal to the tidal volume divided by inspiration time and is an index of inspiratory drive that can be obtained from breath-by-breath measures of pulmonary ventilation (11, 66). Another index of respiratory drive is airway occlusion pressure. While the airway is occluded for 0.1 s the pressure produced from the inspiratory effort is used as an index of inspiratory drive (11, 66). Furthermore, the inspiratory duty cycle, T_i/T_{TOT}, is used as an index of inspiratory timing as it relates to the duration of the inspiratory phase with respect to the entire ventilatory cycle (66).

The above indices are useful measures of inspiratory flow and absolute breathing pattern assessments at rest (11, 66). In studies examining active expiration, these indices cannot act as accurate indicators of total respiratory drive as they only examine the inspiratory portion of the respiratory cycle (11, 66). Therefore, studies using these indices must be cognizant of this limitation.

1.2.2 Hyperthermic Breathing: Panting and Non-Panting Responses

Hyperthermia occurs when T_{CORE} is raised to temperatures above resting by ~1^{o}C (7, 65). Hyperthermia in humans has been shown to increase $\dot{V}_E$. This is known as thermal hyperpnea, and it is similar to a second phase thermoregulatory panting response (43, 105, 106). Thermal hyperpnea is also known as hyperthermia-induced hyperventilation (36, 38). The onset of this response is generally considered to be evident at a T_{CORE} of ~38^{o}C in resting humans (21).

Some mammals such as dogs, sheep, and cats display a biphasic thermoregulatory panting response to hyperthermia. Thermal tachypnea, also known as first phase panting, is where breathing frequency is elevated, often 200-300 breaths/min or greater, with a concurrent decrease in tidal volume (V_T). During thermal tachypnea there is an elevated functional residual capacity (59, 84, 86), and this breathing pattern does not alter $P_{ET}CO_2$. Thermal tachypnea generally occurs after increases in surface or skin temperature of the body. Panting animals switch from thermal tachypnea to second phase thermal hyperpnea, which reduces $P_{ET}CO_2$, after increases in T_{CORE} (87). These mammals have an enhanced respiratory drive during hyperthermia and many of them have no thermoregulatory eccrine sweating (8, 9, 33). In thermal hyperpnea, or second phase panting, breathing frequency is elevated and V_T is normal or slightly elevated (87). This increase in $\dot{V}_E$, that produces a decrease in $P_{ET}CO_2$, translates to reductions in P_aCO_2 (105). Humans, in the absense of heat stress, could start to become apnoeic at low $P_{ET}CO_2$ values, which can drop

below 20 mm Hg (9, 39, 57). However, they are able to maintain rhythmic breathing when hyperthermic with these low $P_{ET}CO_2$ values (9, 39, 57). This suggests that a supplementary respiratory drive exists that is able to sustain breathing at very low P_aCO_2 concentrations, and it may come from the preoptic anterior hypothalamus (8). Another possibility is that hyperthermia increases chemosensitivity (30).

Humans and rats as well as many other animals, including the horse, do not use the ventilatory system as a primary heat loss mechanism. Non-panting increases in $\dot{V}_E$ during hyperthermia are nonetheless observed in both rats and humans (8, 21, 105, 106). Rats also display a continuation of respiratory drive at apnoeic P_aCO_2 values during hyperthermia. There is, therefore, evidence of a secondary respiratory drive during hyperthermia (8). In the rat, when the hypothalamus was isolated from the RCC in the brainstem, there was an elimination of the additional respiratory drive present during hyperthermia (8). This is a clear indication that the hypothalamus provides an additional drive to breathing during hyperthermia. It appears that the same may be possible for the human RCC in response to hyperthermia. This, however, has never been directly demonstrated in humans.

During normothermia the central chemoreceptors in the brainstem elicit increases in $\dot{V}_E$ in response to increases in PCO_2 (2, 72). If the hypothalamus is important in modulating respiratory drive during hyperthermia, and that respiratory drive is dependent on P_aCO_2, it is not clear how decreases in CBV (13, 35, 36) are coupled with increased respiratory drive if the brainstem is less

perfused and receives less PCO_2 and/or $[H^+]$. The PCO_2 and/or $[H^+]$ in the brainstem, however, is determined by a balance of the rate of production and removal of CO_2.

During hyperthermia, the increased respiratory drive decreases PCO_2 in the brain yet there is still an increase in $\dot{V}_E$ even though there is an apparent decrease in CBV. Therefore, hyperthermia appears to decrease CBV via vasoconstriction of the cerebral arterioles as a result of decreased PCO_2 and/or $[H^+]$ in the cerebral spinal fluid (CSF). This assumes that all cerebral vessels respond in the same way as the MCA to increases in temperature and P_aCO_2. It has yet to be resolved during hyperthermia what changes occur to CBV in other cerebral blood vessels besides the MCA, though one study has examined the PCA in hyperthermic conditions (71).

1.2.3 Hypercapnia and Hypocapnia

To resolve how breathing is controlled in hyperthermic humans, changes in P_aCO_2 must be considered. Hypercapnia is a physiological state by which the blood, and tissues have an elevated PCO_2. The cerebral vessels are very sensitive to partial pressures of CO_2. Elevated concentrations of CO_2 in the cerebral blood cause dilation of arterioles, while decreases in blood PCO_2 during hypocapnia cause constriction of the cerebral arterioles (1, 78, 100). Cerebral perfusion is affected by changes in CO_2 because the cerebral perfusion pressure (CPP) is affected by constriction of the cerebral arterioles. Furthermore, CPP is equivalent to the difference between intracranial pressure (ICP), and MAP in the Circle of Willis (34). For a constant MAP, constriction of the cerebral arterioles

results in reduced CBF and, in effect, decreases ICP by decreasing cerebral blood volume (12, 97). A decrease in ICP would increase cerebral perfusion pressure by increasing the difference between MAP and ICP.

During normothermia with hypercapnia, hyperventilation is evident because of increased input from both peripheral and central chemoreceptors to the RCC in the brainstem (24, 79). In steady-state conditions, if there is an increase in CSF PCO_2 and/or $[H^+]$, this will stimulate the central chemoreceptors. In acute hypercapnia, the peripheral chemoreceptors act first to increase ventilatory drive (103). Hypercapnia could potentially impair cerebral autoregulation (CA), as the cerebral vasculature is more sensitive to hypercapnia than to hypocapnia (1). Therefore, hypercapnic induced elevations in MAP caused by catecholamine release, tachycardia and hyperventilation (93, 96) may further increase CBF and inhibit a true interpretation of cerebrovascular responses. Hyperthermic hyperventilation causes hypocapnia, or decreases in $P_aCO_2/P_{ET}CO_2$ (105).

Decreases in P_aCO_2 reduce CBF by ~3.8%/mm Hg within the P_aCO_2 range of 35-55 mm Hg (1). Furthermore, diastolic CBV is decreased during hypocapnia due to increases in cerebrovascular resistance from arteriolar vasoconstriction (55, 74). It could also stand to reason that induction of eucapnia can result in increases in diastolic blood flow that could be due to either an increase in arteriolar calibre, which would reduce cerebrovascular resistance, or an increase in heart rate (44). It is therefore important, for experiments with TCD, to strictly control P_aCO_2 by regulating $P_{ET}CO_2$ (1) so that it does not act as

a confounding influence when studying the cerebrovascular and respiratory responses to hyperthermia. This is possible with an end-tidal forcing system (56).

1.2.4 Eccrine Sweating

Heat loss to the environment from the human body can be accomplished via radiation, convection, conduction, and evaporation. The major physiological mechanism for heat loss in humans is evaporative heat loss from sweat. During hyperthermia, physiological responses include an increase in the secretion of sweat onto the surface of the skin by eccrine sweat glands. The eccrine sweat glands are cholinergic glands innervated by the sympathetic nervous system (83). During bouts of hyperthermia, increased sympathetic cholinergic activity is evident and this releases acetylcholine that acts on muscarinic-3 receptors, which stimulate secretion from eccrine sweat glands (91). The eccrine sweat glands serve two functions: to secrete sweat to the surface of the skin in response to the release of acetylcholine and to reabsorb sodium before secretion to produce sweat that is hypotonic with respect to body fluids. The secretion of sweat to the skin surface functions as a mechanism for heat loss to the environment via the high heat of vaporization of water; water is the primary component of human sweat (91). The sweat that is secreted also contains ions and compounds such as sodium, potassium, lactate, urea, ammonia, amino acids, protein macromolecules, polysaccharides, and histamines (15, 40, 76, 91). These all act to increase the boiling point of water and the amount of heat it will dissipate (68, 95). The duct of the eccrine sweat gland is composed of a secretory coil and a duct (91). The distribution of these glands on the surface of

the skin is highly variable depending on the location on the body (98, 102). The forehead has the largest concentration of eccrine sweat glands, followed by the arms, the back, and finally the legs (110).

Heat loss from the human head can reach values of 200-250 W via convection and, primarily, from the evaporation of sweat (84). This can account for between two fifths and one half of the total heat exchange of the body during heat stress (84). This illustrates the notion that the head is a powerful heat sink capable of assuaging increases in body temperature (84).

1.2.5 Cutaneous Vasodilation

Thermoregulatory control of skin blood flow in humans is under sympathetic neural control, and includes the noradrenergic vasoconstrictor system and a sympathetic active vasodilator system (25). With whole body warming, first there is a release of noradrenergic vasoconstriction, followed by active cutaneous vasodilation (ACV) that is partially controlled by the sympathetic cholinergic system along with unknown co-transmitters (53, 54). During hyperthermia, ACV increases blood flow to the skin and compliments evaporative heat loss from eccrine sweating (52). Skin blood flow is approximately 250 mL/min in normothermia, and dissipates heat at approximately 80-90 kcal/h, which is about equal to the heat generated by basal metabolic processes (49). Thermoregulatory vasodilation can increase skin blood flow to between 6 and 8 L/min (99). Control of ACV during heat stress by the thermoregulatory centres of the hypothalamus is affected by changes in body core and skin temperature (70). Core temperature is the more potent modulator of cutaneous blood flow (111).

Changes in skin temperature influence cutaneous sympathetic vasomotor tone, but also influence ACV (80). The skin blood flow of the hand displays a different response than forearm skin to whole body heating (88). The increase in blood flow in the hand, and other acral surfaces, is a one-phased response, while the forearm displays a two-phased response (88). The first phase of the response in the forearm is thought to be due to a withdrawal of sympathetic vasoconstrictor tone. The second phase response, in the forearm and other non-acral surfaces, is thought to be due to ACV (88). These phasic response differences indicate that these limb components may be under different mechanisms of thermoregulatory control (88).

During dynamic exercise in hyperthermia, an increase in skin temperature will increase cutaneous blood flow (80). Conversely, the same changes in skin temperature in normothermia only acted to decreased noradrenergic vasoconstriction, and did not increase ACV (80). However, ACV appears to increase proportionately with core temperature for a given skin temperature (19). This increased cutaneous blood flow serves to increase convective heat transfer from the core to the skin (25).

Furthermore, these increases in cutaneous blood flow require an increase in cardiac output ($\dot{Q}$) so as to continue to supply oxygen to organs such as the heart, and the brain (50). Centrally, the heart must increase $\dot{Q}$ to sustain the increased cutaneous blood flow (50) and this accomplished by proportionate increases in heart rate as a result of elevated sympathetic drive (69). However, it appears as though during heat stress, the heart is not fully capable of supplying

the necessary $\dot{Q}$ and there is a decrease in MAP that can potentially lead to syncope due to decreases in cerebrovascular blood conduction (50, 73).

1.2.6 Cerebral Blood Flow and Autoregulation

Cerebral blood flow estimates can be accomplished with CBV measurements from large cerebral vessels recorded with TCD ultrasonography. Using a waveform envelope, the mean CBV is calculated by the TCD, which gives an index of CBF. This relationship is valid as long as the diameter of the vessel in question remains constant (26). Although cerebral arterioles are highly transient in calibre (1), they are not directly assessed by TCD ultrasonography.

Cerebral autoregulation refers to the adjustment of cerebral arteriolar calibre to maintain values of CBF that are sufficient to accommodate metabolic need (1). Cerebral autoregulation has two response components: static CA and dynamic CA. Static CA maintains CBF during slow changes in cerebral perfusion pressure (78). Dynamic CA is an immediate regulation of CBF to rapid changes in arterial blood pressure (BP), such as that which occurs within 30 – 60 s in skeletal muscle (51, 112). It is believed that the underlying mechanisms by which CA is controlled differ between static and dynamic CA (32) and that the cerebral circulation may be regulated more effectively under dynamic than static CA (112). The range of BP in which CBF is maintained varies between individuals, but it is generally believed that CBF is constant between cerebral perfusion pressures of 50-150 mm Hg (58). Cerebral blood flow can also be affected by cerebral metabolism, systemic factors such as $\dot{Q}$, and sympathetic

nerve activity (1). The relative impact of these factors is minor and can be controlled (1). The effects of sympathetic nerve activity are controversial, though any potential effect seems to be masked by autoregulation, CO_2 reactivity, and changes in $\dot{Q}$ (1, 101). Furthermore, despite $\dot{Q}$ being significantly increased during hyperthermia, MAP falls due to the profound peripheral vasodilation, which elicits a decrease in CBV (35).

It is not evident then, how or why there are maintained decreases in CBV in the MCA when $P_{ET}CO_2$ is restored during eucapnic hyperthermia (13, 35, 73). The time constant for the CBV response to changes in $P_{ET}CO_2$ has been shown to be ~7 s (82). Therefore, CA should be effective unless there is an increase in metabolic demand or changes in P_aCO_2 (1). However, it is assumed that there should be no change in P_aCO_2 during eucapnic hyperthermia (1). Another possibility could be that there is a dilation of the major vessels (82, 108), which would give an apparent reduction in flow velocity measurements obtained using TCD from vessels such as the MCA, PCA, and BA.

1.2.7 Cerebral Blood Velocity and Conductance in Hyperthermia

For observed increases in core temperature of ~ 1ºC and poikilocapnic breathing, MCA CBV is decreased by ~25% from normothermic rest (13, 35, 36, 73). When $P_{ET}CO_2$ is clamped at eucapnic partial pressures, CBV in the MCA is still significantly reduced (13, 35, 36, 46, 73). This would suggest that there is an effect of temperature that decreases conduction in this cerebral vessel (13, 35, 36, 73). It is assumed that the PCA and BA respond in a similar way as the MCA to most stimuli including CO_2, and O_2 (75, 77); however one recent study showed

evidence of regional differences in hypocapnic reactivity between cerebral arteries (109). Though the MCA has been well investigated in hyperthermia, the PCA has yet to be extensively assessed in these conditions (71). Only one study has examined the MCA and PCA in eucapnic hyperthermia, and increases in CBV were found in both these vessels (71). These results for the MCA CBV differ from those found in previous studies during eucapnic hyperthermia (13, 35, 36, 73). Finally, there is an apparent lack of investigation of the BA in hyperthermic conditions.

It is possible that increases in temperature result in increased CO_2 production by the cellular metabolic processes, i.e. the Q10 effect (92). As well, it is unclear if the CO_2 production from the RCC due to increased ventilatory drive in hyperthermia results an increased flow in the BA. The increase in CO_2 may also be negligible due to the small mass of the RCC; although, the whole body would be affected by the Q10 effect. However, during hyperthermia, the resultant hyperpnea could more than nullify the marginal increase in CO_2 production caused by the Q10 effect (21).

One of the major assumptions of TCD is that there is no constriction or dilation of the major cerebral arteries in response to various stimuli such as O_2 and CO_2 (94). A dilation of the MCA (108), for example, could account for the additional decreases in CBV during hyperthermia that have been documented (13, 35, 36, 73). It has also been observed that hydration level does not significantly affect CBV in the MCA during hyperthermia (35, 37). One thing that could affect CBV during hyperthermia is that there may be an increase in ICP,

though this was documented in comatose brain injury patients with fever (89). Though some studies argue against this relationship (28, 47), an increase in ICP during hyperthermia for a constant MAP could, nevertheless, result in a decreased CPP and therefore CBV, due to a reduced ICP - arterial pressure gradient (1). It remains to be determined how ICP changes in healthy hyperthermic relative to healthy normothermic humans.

It is unclear as to how changes in MAP and total peripheral resistance in hyperthermia influence CBV in the cerebral circulation. It is for this reason that ICVC is calculated (13), as it is a quotient of CBV and MAP. The circulatory system evidently plays a major role in thermoregulation, functioning peripherally to dissipate heat during bouts of hyperthermia to protect vital tissues from overheating.

1.2.8 Selective Brain Cooling: Vascular and Respiratory Mechanisms

The circulatory system is especially important for cranial thermoregulation where selective brain cooling (SBC) is thought to occur. This SBC is the maintenance brain temperature below that of core temperature in the thorax during hyperthermia (16). The mechanisms of SBC may act as another possible influence on CBF during hyperthermia.

There are three groups of veins that are pertinent to SBC during hyperthermia in humans, they are: the emissary veins, the facial veins, and the ophthalmic veins. The direction of flow in these veins is related to skin and brain temperatures. The emissary veins are primarily constricted during hypothermia,

but dilated during hyperthermia (17). This dilation allows blood draining from the scalp to flow through the cranium and into the brain during hyperthermia. Therefore, increases in temperature cause an increase in flow in the emissary veins, which provide a passage for cooled blood from the scalp to pass into the intra-cranial cavity (17). Cooled blood from the scalp contributes to SBC in humans via this venous drainage. The facial veins also allow cooled blood from the face to flow inwards during hyperthermia, such as during running when there is increased heat loss via convection from the face (17, 22). The flow of blood in the facial veins is also increased in hyperthermia, with cooled blood from the surface of the face flowing back towards the cranium (18). The flow of blood in this artery is generally directed from brain to face, but in hyperthermia the direction is reversed and flow is increased (23). The ophthalmic veins are interesting because they are also able to change the direction of blood flow; during hyperthermia blood courses inwards to cool the brain, and in hypothermia they flow outwards to heat extracranial structures (17, 22, 23). These responses to hyperthermia in the extra-cranial vessels highlight the variety of the vascular adaptations to hyperthermia.

In addition to the circulatory mechanisms mentioned above by which SBC is achieved, there are also contributions of pulmonary ventilation to SBC in hyperthermic humans. When humans become hyperthermic they demonstrate a thermal hyperpnea, or hyperthermic hyperventilation (105). Hyperthermic hyperventilation results in cooling of the upper airway via evaporative heat loss. This heat loss within the upper airway cools the blood in the internal carotid

artery flowing towards the brain (20, 105). Heat loss during hyperthermia can also be accomplished through the upper airway as a result of dilatation of the nasal mucosa. During hyperthermia there is a three-fold increase in mucosal blood flow that, when coupled with elevated rates of respiratory heat exchange, contributes to SBC in humans during passively-induced hyperthermia (107).

Selective brain cooling has been shown to be effective in humans for maintaining brain temperature below T_{CORE} (16, 20, 108). It is not clear, however, if and how SBC affects CBV in major vessels such as the MCA, PCA, and BA. Existing literature (13, 35, 36, 73) suggests that hyperthermia results in decreases in MCA CBV. However, one study (71) has shown that eucapnic hyperthermia results in increases in CBV in the MCA and PCA. It is thought that MCA CBV is indicative of CBF changes in other cerebral vessels (1, 108), but this assumption has yet to be validated in the BA during hyperthermia.

1.2.9 Mean Arterial Pressure During Hyperthermia

During hyperthermia, increases in heart rate, drops in stroke volume and a fall in total peripheral resistance (35), result in decreases in MAP in humans (27, 35, 45). These views are not universal, and in some studies of hyperthermia (13, 36), however, MAP stays the same or rises for the similar increases in T_{CORE}. It is not clear why the MAP response to hyperthermia is varied from study to study. During exercise, however, MAP is regulated as a result of a resetting, or increase, of the baroreflex set-point (81, 85). This allows for the baroreflex to operate at the prevalent MAP during exercise (81, 85). In hyperthermia, the

baroreflex set-point is functional, however peripheral autoregulation is apparently impaired (27), which might explain why there is a drop in MAP.

During normothermic hyperventilation, MAP either increases or remains constant (41, 55), though one review indicates a fall in MAP in most hyperventilation studies (14). These differing results are curious. The respiratory muscles are more active during hyperventilation and this would cause an increase in venous return (67). This, combined with the peripheral vasoconstriction that occurs due to the drop in $P_{ET}CO_2$ (3, 48) should lead to an increase in central blood volume and MAP. Furthermore, pulmonary reflexes initiate sympathetic and parasympathetic activity during pulmonary ventilation (4). A decrease in lung volume results in sympathetic peripheral vasoconstriction, while inflation results in a withdrawal of sympathetic activity (4). During inflation of the lung there is a reduction of arterial baroreflex sensitivity and activity (6). If the lungs were ventilated during hyperventilation at a higher breathing frequency, but a lower tidal volume, then there would be less stretching of the lungs. This could contribute to the sympathetic peripheral vasoconstriction and increased cardiac output that would result in an increase in MAP that is sometimes observed (41, 55).

According to Ainslie and Duffin (1), a complete study of cerebrovascular responses should include an assessment of cerebrovascular conductance (CVC). This is the inverse of cerebrovascular resistance (1), and can be assessed by calculating the quotient of CBV and MAP (13) to give ICVC, an important indicator of cerebrovascular perfusion that accounts for changes in

CBV due to changes in MAP. The ICVC does not entirely reflect cerebrovascular conductance because it is the quotient of CBF and CPP (1). Furthermore, CPP is composed of MAP minus the sum of ICP and sagittal sinus pressure (1). Under normal conditions, ICP and sagittal sinus pressure are negligible (31). Therefore, ICVC is a good indicator of cerebrovascular conductance. In hyperthermia, aside from the cerebrovascular responses in the MCA (13, 35, 36, 73) and one study of hyperthermic responses in the PCA (71), there is an absence of knowledge regarding the BA, and a complete study is warranted.

1.3 Rationale

The existing information regarding hyperthermia and its effects on CBF in cerebral vessels other than the MCA remains incomplete (13, 35, 36, 73), although there is one such study in the PCA (71). An investigation of the effects of hyperthermia, while controlling $P_{ET}CO_2$, on the ICVC in the BA has yet to be assessed in humans. The BA provides blood for the brainstem, including the midbrain, pons, pontine respiratory centres, and the upper lateral medulla oblongata (60, 61, 90). Knowing how ICVC in the brainstem changes will help resolve the mechanisms by which respiratory control, pulmonary ventilation, and cerebral vasculature respond to hyperthermia and hyperventilation. Changes to $\dot{V}_E$ are modulated from the broad collection of neurons of the pons and lateral medulla oblongata that compose the RCC (60, 61). The apparent paradox is that pulmonary ventilation increases despite assumed decreases in perfusion of the RCC in the brainstem during hypocapnia (1, 108). During hyperthermia there are increases in core temperature that could potentially increase local CO_2

production at the cellular level, which could lead to the increased $\dot{V}_E$ that is observed (13, 35, 36, 105). It is therefore important to understand the effects of hyperventilation on ICVC in the MCA, PCA, and BA in hyperthermia and on CBV and ICVC normothermia in order to understand the effects of hyperthermia and hyperventilation on the control of breathing.

Understanding the effects of hyperthermia and hyperventilation in the BA and PCA would be a valuable addition to the existing literature (13, 35, 36, 71, 73) so as to help understand the nature of the perfusion to the brainstem and RCC during hyperthermia. Autonomic drives including that for human pulmonary ventilation originate in the pons and lateral medulla oblongata (62), and it is therefore essential to understand the blood supply to these structures during hyperthermia and hyperventilation in order to aid in the understanding of the mechanisms by which increases in body temperature elicit thermal hyperpnea.

A study of ICVC in hyperthermia is needed so as to properly assess the existence, or non-existence, of regional differences in cerebrovascular responses to heat stress. The respiratory control centre is located in the pons and medulla oblongata of the brainstem and is sensitive to PCO_2 and/or $[H^+]$ in the CSF (79). The apparent paradox is that there is an assumed decrease in cerebral perfusion and a known hypocapnia, which should elicit a decrease in $\dot{V}_E$. The opposite is observed (13, 35, 73, 105); humans hyperventilate during hyperthermia. Many possibilities have been discussed as to how increased ventilatory drive is elicited in hyperthermic humans. Knowing what is occurring with respect to blood flow and conductance near the brainstem is an important contribution to the

understanding of how pulmonary ventilation is controlled in hyperthermic humans.

My previous work in my undergraduate thesis (64) allowed me to develop the skills and knowledge to complete my master's studies. My undergraduate thesis included a study that was conducted to learn the challenging TCD methodology and to assess if there were regional differences in cerebral blood velocity in normothermic and hyperthermic humans. Six male volunteers were measured for MCAv, PCAv and BAv at rest during normothermia and during eucapnic hyperthermia. The study revealed regional differences in CBV at these 3 sites, with no effect of eucapnic hyperthermia on these outcome measures. However, the study in my undergraduate thesis did not examine ICVC or MAP, nor was there a hyperthermic poilkilocapnic condition. A measure of ICVC is needed to adequately assess the perfusion of the cerebral vessels being observed in hyperthermia and it is included in the following studies of this thesis.

1.4 Hypotheses

Study 1: Thermal Hyperpnea and Temperature-Dependent Regional Differences in Cerebrovascular Responses in Humans

1. The ICVC in the MCA will be maintained during poikilocapnic and eucapnic hyperthermia.
2. During hyperthermia ICVC in the PCA and BA will not change or will increase.

Study 2: Effects of Poikilocapnic and Eucapnic Voluntary Hyperventilation on Cerebrovascular Responses in Normothermic Humans

1. During normothermia CBV and ICVC in the MCA, PCA, and BA will decrease during voluntary hyperventilation and hypocapnia.
2. During normothermia, while controlling $P_{ET}CO_2$ at a eucapnic partial pressure and maintaining voluntary hyperventilation, CBV and ICVC in the MCA, PCA, and BA will return to normal resting values.

1.5 Testable Questions

Study 1: Thermal Hyperpnea and Temperature-Dependent Regional Differences in Cerebrovascular Responses in Humans

1. Does passive poikilocapnic hyperthermia result in maintenance of MCA cerebral conductance? Is this MCA ICVC restored to resting values during eucapnic hyperthermia?
2. Does passive poikilocapnic and eucapnic hyperthermia result in changes in PCA and BA ICVC that are parallel to changes in the MCA?

Study 2: Effects of Poikilocapnic and Eucapnic Voluntary Hyperventilation on Cerebrovascular Responses in Normothermic Humans

1. Does normothermic voluntary hyperventilation decrease CBV and ICVC in the MCA, PCA, and BA?
2. Does normothermic voluntary hyperventilation with eucapnic $P_{ET}CO_2$ result in a full restoration of CBV and ICVC in the MCA, PCA, and BA to normothermic resting values?

1.6 References

1. **Ainslie PN, and Duffin J**. Integration of Cerebrovascular CO_2 Reactivity and Chemoreflex Control of Breathing: Mechanisms of Regulation, Measurement, and Interpretation. *Am J Physiol Regul Integr Comp Physiol* 296: 1473-1495, 2009.

2. **Asmussen E, and Nielsen M**. Ventilatory Response to CO_2 During Work at Normal and at Low Oxygen Tensions. *Acta Physiol Scand* 39: 27-35, 1957.

3. **Barker SJ, Hyatt J, Clarke C, and Tremper KK**. Hyperventilation Reduces Transcutaneous Oxygen Tension and Skin Blood Flow. *Anesthesiology* 75: 619-624, 1991.

4. **Berne RM**. The Cardiovascular System. In: *Principles of Physiology*, edited by Berne RM, Levy MN, Stanton BA, and Koeppen BM. St. Louis, MO: Mosby Inc., 1990, p. 454.

5. **Bjurstedt H, Hesser CM, Liljestrand G, and Matell G**. Effects of Posture on Alveolar-Arterial CO_2 and O_2 Differences and on Alveolar Dead Space in Man. *Acta Physiol Scand* 54: 65-82, 1962.

6. **Blaber A, and Hughson R**. Cardiorespiratory Interactions During Fixed-Pace Resistive Breathing. *J Appl Physiol* 80: 1618-1626, 1996.

7. **Bligh J, and Johnson KG**. Glossary of Terms for Thermal Physiology. *J Appl Physiol* 35: 941-961, 1973.

8. **Boden AG, Harris MC, and Parkes MJ**. The Preoptic Area in the Hypothalamus Is the Source of the Additional Respiratory Drive at Raised Body Temperature in Anaesthetised Rats. *Exp Physiol* 85: 527-537, 2000.

9. **Boden AG, Harris MC, and Parkes MJ**. A Respiratory Drive in Addition to the Increase in CO_2 Production at Raised Body Temperature in Rats. *Exp Physiol* 85: 309-319, 2000.

10. **Boggs D, and Tenney S**. Scaling Respiratory Pattern and Respiratory Drive. *Respir Physiol* 58: 245-251, 1984.

11. **Boggs DF**. Comparative Control of Respiration. In: *Treatise on Pulmonary Toxicology: Comparative Biology of the Normal Lung*, edited by Parent RA. Boca Raton, FL: CRC Press, Inc., 1992, p. 309-349.

12. **Brian JE**. Carbon Dioxide and the Cerebral Circulation. *Anesthesiology* 88: 1365-1386, 1998.

13. **Brothers RM, Wingo JE, Hubing KA, and Crandall CG**. The Effects of Reduced End-Tidal Carbon Dioxide Tension on Cerebral Blood Flow During Heat Stress. *J Physiol (Lond)* 587: 3921-3927, 2009.

14. **Brown E**. Physiological Effects of Hyperventilation. *Physiol Rev* 33: 445-471, 1953.

15. **Brusilow SW, and Gordes EH**. Ammonia Secretion in Sweat. *Am J Physiol* 214: 513-517, 1968.

16. **Cabanac M**. Selective Brain Cooling in Humans: "Fancy" or Fact? *FASEB J* 7: 1143-1147, 1993.

17. **Cabanac M, and Brinnel H**. Blood Flow in the Emissary Veins of the Human Head During Hyperthermia. *Eur J Appl Physiol* 54: 172-176, 1985.

18. **Cabanac M, and Caputa M**. Natural Selective Cooling of the Human Brain: Evidence of Its Occurrence and Magnitude. *J Physiol* 286: 255-264, 1979.

19. **Cabanac M, and Massonnet B**. Thermoregulatory Responses as a Function of Core Temperature in Humans. *J Physiol (Lond)* 265: 587-596, 1977.

20. **Cabanac M, and White M**. Heat Loss from the Upper Airways and Selective Brain Cooling in Humans. *Ann N Y Acad Sci* 813: 613-616, 1997.

21. **Cabanac M, and White MD**. Core Temperature Thresholds for Hyperpnea During Passive Hyperthermia in Humans. *Eur J Appl Physiol Occup Physiol* 71: 71-76, 1995.

22. **Caputa M**. Selective Brain Cooling: A Multiple Regulatory Mechanism. *J Therm Biol* 29: 691-702, 2004.

23. **Caputa M, Perrin G, and Cabanac M**. [Reversal of Human Ophthalmic Vein Blood Flow : Selective Cooling of the Brain]. *C R Acad Sci Hebd Seances Acad Sci D* 287: 1011-1014, 1978.

24. **Chambers WW, Seigel MS, Liu JC, and Liu CN**. Thermoregulatory Responses of Decerebrate and Spinal Cats. *Exp Neurol* 42: 282-299, 1974.

25. **Charkoudian N**. Skin Blood Flow in Adult Human Thermoregulation: How It Works, When It Does Not, and Why. In: *Mayo Clinic*2003, p. 603-612.

26. **Clyde BL, Resnick DK, Yonas H, Smith HA, and Kaufmann AM**. The Relationship of Blood Velocity as Measured by Transcranial Doppler Ultrasonography to Cerebral Blood Flow as Determined by Stable Xenon Computed Tomographic Studies after Aneurysmal Subarachnoid Hemorrhage. *Neurosurgery* 38: 896-896, 1996.

27. **Crandall CG, Cui J, and Wilson TE**. Effects of Heat Stress on Baroreflex Function in Humans. *Acta Physiol Scand* 177: 321-328, 2003.

28. **Cremer OL, and Kalkman CJ**. Cerebral Pathophysiology and Clinical Neurology of Hyperthermia in Humans. *Prog Brain Res* 162: 153-169, 2007.

29. **Cunningham D, Howson M, Metias E, and Petersen E**. Patterns of Breathing in Response to Alternating Patterns of Alveolar Carbon Dioxide Pressures in Man. *J Physiol (Lond)* 376: 31-45, 1986.

30. **Curtis AN, Walsh ML, and White MD**. Influence of Passive Hyperthermia on Human Ventilation During Rest and Isocapnic Hypoxia. *Appl Physiol Nutr Me* 32: 721-732, 2007.

31. **Czosnyka M, and Pickard J**. Monitoring and Interpretation of Intracranial Pressure. *J Neurol Neurosur Ps* 75: 813-821, 2004.

32. **Dawson SL, Blake MJ, Panerai RB, and Potter JF**. Dynamic but Not Static Cerebral Autoregulation Is Impaired in Acute Ischaemic Stroke. *Cerebrovasc Dis* 10: 126-132, 2000.

33. **Dempsey JA**. Crossing the Apnoeic Threshold: Causes and Consequences. *Exp Physiol* 90: 13-24, 2005.

34. **Edvinsonn L KD**. *Cerebral Blood Flow and Metabolism*. Philadelphia: Lippincott, Williams & Wilkins, 2002, p. 510.

35. **Fan JL, Cotter JD, Lucas RA, Thomas K, Wilson L, and Ainslie PN**. Human Cardiorespiratory and Cerebrovascular Function During Severe Passive Hyperthermia: Effects of Mild Hypohydration. *J Appl Physiol* 105: 433-445, 2008.

36. **Fujii N, Honda Y, Hayashi K, Kondo N, Koga S, and Nishiyasu T**. Effects of Chemoreflexes on Hyperthermic Hyperventilation and Cerebral Blood Velocity in Resting Heated Humans. *Exp Physiol* 93: 994-1001, 2008.

37. **Fujii N, Honda Y, Hayashi K, Kondo N, and Nishiyasu T**. Effect of Hypohydration on Hyperthermic Hyperpnea and Cutaneous Vasodilation During Exercise in Men. *J Appl Physiol* 105: 1509-1518, 2008.

38. **Fujii N, Honda Y, Hayashi K, Soya H, Kondo N, and Nishiyasu T**. Comparison of Hyperthermic Hyperpnea Elicited During Rest and Submaximal, Moderate-Intensity Exercise. *J Appl Physiol* 104: 998-1005, 2008.

39. **Gaudio R, Jr., and Abramson N**. Heat-Induced Hyperventilation. *J Appl Physiol* 25: 742-746, 1968.

40. **Gitlitz PH, Sunderman Jr FW, and Hohnadel DC**. Ion-Exchange Chromatography of Amino Acids in Sweat Collected from Healthy Subjects During Sauna Bathing. *Clin Chem* 20: 1305-1312, 1974.

41. **Grubb RL, Jr., Raichle ME, Eichling JO, and Ter-Pogossian MM**. The Effects of Changes in P_aCO_2 on Cerebral Blood Volume, Blood Flow, and Vascular Mean Transit Time. *Stroke* 5: 630-639, 1974.

42. **Haines DE**. *Neuroanatomy: An Atlas of Structures, Sections, and Systems*. Philadelphia, PA: Lippincott Williams & Wilkins, 2000, p. 256.

43. **Haldane JS, and Priestley JG**. The Regulation of the Lung-Ventilation. *J Physiol (Lond)* 32: 225-266, 1905.

44. **Harrison MR, Clifton GD, Penneil AT, and DeMaria AN**. Effect of Heart Rate on Left Ventricular Diastolic Transmitral Flow Velocity Patterns Assessed by Doppler Echocardiography in Normal Subjects. *Am J Card* 67: 622-627, 1991.

45. **Havenith G, Luttikholt VGM, and Vrijkotte TGM**. The Relative Influence of Body Characteristics on Humid Heat Stress Response. *Eur J Appl Physiol* 70: 270-279, 1995.

46. **Hayashi K, Honda Y, Miyakawa N, Fujii N, Ichinose M, Koga S, Kondo N, and Nishiyasu T**. Effect of CO_2 on the Ventilatory Sensitivity to Rising Body Temperature During Exercise. *J Appl Physiol* 110: 1334-1341, 2011.

47. **Huschak G, Hoell T, Wiegel M, Hohaus C, Stuttmann R, Meisel HJ, and Mast H**. Does Brain Temperature Correlate with Intracranial Pressure? *Journal of Neurosurgical Anesthesiology* 20: 105-109, 2008.

48. **Ito T, Moore JI, and Koss MC**. Topical Application of CO_2 Increases Skin Blood Flow. *J Invest Dermatol* 93: 259-262, 1989.

49. **Johnson JM, Brengelmann GL, Hales JR, Vanhoutte PM, and Wenger CB**. Regulation of the Cutaneous Circulation. *Fed Proc* 45: 2841-2850, 1986.

50. **Johnson JM, and Proppe DW**. Cardiovascular Adjustments to Heat Stress. In: *Handbook of Physiology*, edited by Fregly MJ, and Blatteis CM. New York, NY: Oxford University Press, 1996, p. 215-243.

51. **Jones R, and Berne R**. Local Regulation of Blood Flow in Skeletal Muscle. *Circ Res* 15: 126-138, 1964.

52. **Kamijo YI, Lee K, and Mack GW**. Active Cutaneous Vasodilation in Resting Humans During Mild Heat Stress. *J Appl Physiol* 98: 829-837, 2005.

53. **Kellogg D**. In Vivo Mechanisms of Cutaneous Vasodilation and Vasoconstriction in Humans During Thermoregulatory Challenges. *J Appl Physiol* 100: 1709-1718, 2006.

54. **Kellogg Jr DL, Pergola PE, Piest KL, Kosiba WA, Crandall CG, Grossmann M, and Johnson JM**. Cutaneous Active Vasodilation in Humans Is Mediated by Cholinergic Nerve Cotransmission. *Circ Res* 77: 1222-1228, 1995.

55. **Kety SS, and Schmidt CF**. The Effects of Active and Passive Hyperventilation on Cerebral Blood Flow, Cerebral Oxygen Consumption, Cardiac Output, and Blood Pressure of Normal Young Men. *J Clin Invest* 25: 107-119, 1946.

56. **Koehle MS, Giles LV, Curtis AN, Walsh ML, and White MD**. Performance of a Compact End-Tidal Forcing System. *Respir Physiol Neurobiol* 167: 155-161, 2009.

57. **Landis E, Long W, Dunn J, Jackson C, and Meyer U**. Studies on the Effects of Baths on Man: III. Effects of Hot Baths on Respiration, Blood and Urine. *American Journal of Physiology--Legacy Content* 76: 35-48, 1926.

58. **Lassen NA**. Cerebral Blood Flow and Oxygen Consumption in Man. *Physiol Rev* 39: 183-238, 1959.

59. **Lim PK, and Grodins FS**. Control of Thermal Panting. *Am J Physiol* 180: 445-449, 1955.

60. **Marieb EN, and Hoehn K**. *Human Anatomy & Physiology*. San Fransisco, CA: Pearson Education, 2010, p. 1156.

61. **Martini FH**. Blood Vessels and Circulation. In: *Fundamentals of Anatomy and Physiology*. San Fransisco, CA: Benjamin Cummings, 2006, p. 708-757.

62. **Martini FH**. The Brain and Cranial Nerves. In: *Fundamentals of Anatomy and Physiology*. San Fransisco, CA: Benjamin Cummings, 2006, p. 452-478.

63. **Martini FH**. The Respiratory System. In: *Fundamentals of Anatomy and Physiology*. San Fransisco, CA: Benjamin Cummings, 2006, p. 813-856.

64. **McDonald PLL**. *Effects of Hyperthermia on Human Middle Cerebral, Posterior Cerebral, and Basilar Artery Blood Velocities During Eucapnia*. Undergraduate Thesis. In: Biomedical Physiology and Kinesiology. Burnaby, BC.: Simon Fraser University, 2011, p. 80.

65. **Mercer J, and Werner J**. Glossary of Terms for Thermal Physiology. *Jpn J Physiol* 51: 245-280, 2001.

66. **Milic-Emili J, Whitelaw W, and Grassino A**. Measurement and Testing of Respiratory Drive. In: *Lung Biology in Health and Disease Regulation of Breathing*, edited by Hozbein T. NY, New York: Marcel Dekker, 1981, p. 675-743.

67. **Miller JD, Pegelow DF, Jacques AJ, and Dempsey JA**. Skeletal Muscle Pump Versus Respiratory Muscle Pump: Modulation of Venous Return from the Locomotor Limb in Humans. *J Physiol (Lond)* 563: 925-943, 2005.

68. **Mitchell D, Wyndham C, Atkins A, Vermeulen A, Hofmeyr H, Strydom N, and Hodgson T**. Direct Measurement of the Thermal Responses of Nude Resting Men in Dry Environments. *Pflugers Archiv: Eur J Physiol* 303: 324-343, 1968.

69. **Moran DS, Shitzer A, and Pandolf KB**. A Physiological Strain Index to Evaluate Heat Stress. *Am J Physiol-Reg I* 275: 129-134, 1998.

70. **Nadel ER, Bullard RW, and Stolwijk JA**. Importance of Skin Temperature in the Regulation of Sweating. *J Appl Physiol* 31: 80-87, 1971.

71. **Nelson MD, Haykowsky MJ, Stickland MK, Altamirano-Diaz LA, Willie CK, Smith KJ, Petersen SR, and Ainslie PN**. Reductions in Cerebral Blood Flow During Passive Heat Stress in Humans: Partitioning the Mechanisms. *J Physiol* 589: 4053-4064, 2011.

72. **Nielsen M, and Smith H**. Studies on the Regulation of Respiration in Acute Hypoxia; with a Appendix on Respiratory Control During Prolonged Hypoxia. *Acta Physiol Scand* 24: 293-313, 1952.

73. **Nybo L, and Nielsen B**. Middle Cerebral Artery Blood Velocity Is Reduced with Hyperthermia During Prolonged Exercise in Humans. *J Physiol (Lond)* 534: 279-286, 2001.

74. **Ogawa S, Handa N, Matsumoto M, Etani H, Yoneda S, Kimura K, and Kamada T**. Carbondioxide Reactivity of the Blood Flow in Human Basilar Artery Estimated by the Transcranial Doppler Method in Normal Men: A Comparison with That of the Middle Cerebral Artery. *Ultrasound Med Biol* 14: 479-483, 1988.

75. **Ogoh S, Nakahara H, Ainslie PN, and Miyamoto T**. The Effect of Oxygen on Dynamic Cerebral Autoregulation: Critical Role of Hypocapnia. *J Appl Physiol* 108: 538-543, 2010.

76. **Pallavicini JC, Gabriel O, Sant'Agnese PA, and Buskirk ER**. Isolation and Characterization of Carbohydrate Protein Complexes from Human Sweat. *Ann N Y Acad Sci* 106: 330-338, 1963.

77. **Park CW, Sturzenegger M, Douville CM, Aaslid R, and Newell DW**. Autoregulatory Response and CO_2 Reactivity of the Basilar Artery. *Stroke* 34: 34-39, 2003.

78. **Paulson OB, Strandgaard S, and Edvinsson L**. Cerebral Autoregulation. *Cerebrovasc Brain Metab Rev* 2: 161-192, 1990.

79. **Peebles K, Celi L, McGrattan K, Murrell C, Thomas K, and Ainslie PN**. Human Cerebrovascular and Ventilatory CO_2 Reactivity to End-Tidal, Arterial and Internal Jugular Vein PCO_2. *J Physiol (Lond)* 584: 347-357, 2007.

80. **Pergola PE, Kellogg DL, Jr., Johnson JM, and Kosiba WA**. Reflex Control of Active Cutaneous Vasodilation by Skin Temperature in Humans. *Am J Physiol* 266: H1979-1984, 1994.

81. **Potts JT, Shi XR, and Raven PB**. Carotid Baroreflex Responsiveness During Dynamic Exercise in Humans. *Am J Physiol-Heart C* 265: 1928-1938, 1993.

82. **Poulin MJ, Liang PJ, and Robbins PA**. Fast and Slow Components of Cerebral Blood Flow Response to Step Decreases in End-Tidal in Humans. *J Appl Physiol* 85: 388-397, 1998.

83. **Randall WC, and Kimura KK**. The Pharmacology of Sweating. *Pharmacol Rev* 7: 365-397, 1955.

84. **Rasch W, Samson P, Cote J, and Cabanac M**. Heat Loss from the Human Head During Exercise. *J Appl Physiol* 71: 590-595, 1991.

85. **Raven PB, Fadel PJ, and Ogoh S**. Arterial Baroreflex Resetting During Exercise: A Current Perspective. *Exp Physiol* 91: 37-49, 2006.

86. **Richards SA**. The Biology and Comparative Physiology of Thermal Panting. *Biol Rev Camb Philos Soc* 45: 223-264, 1970.

87. **Robertshaw D**. Mechanisms for the Control of Respiratory Evaporative Heat Loss in Panting Animals. *J Appl Physiol* 101: 664-668, 2006.

88. **Roddie IC, Shepherd JT, and Whelan RF**. The Contribution of Constrictor and Dilator Nerves to the Skin Vasodilatation During Body Heating. *J Physiol* 136: 489-497, 1957.

89. **Rossi S, Zanier ER, Mauri I, Columbo A, and Stocchetti N**. Brain Temperature, Body Core Temperature, and Intracranial Pressure in Acute Cerebral Damage. *J Neurol Neurosurg Psychiatry* 71: 448-454, 2001.

90. **Salamon G, and Huang YP**. *Radiologic Anatomy of the Brain*. New York: Springer-Verlag, 1976, p. 404.

91. **Sato K**. The Physiology, Pharmacology, and Biochemistry of the Eccrine Sweat Gland. *Rev Physiol Biochem Pharmacol* 79: 51-131, 1977.

92. **Saxton C**. Effects of Severe Heat Stress on Respiration and Metabolic Rate in Resting Man. *Aviat Space Envir Md* 52: 281-286, 1981.

93. **Sechzer P, Egbert L, Linde H, Cooper D, Dripps R, and Price H**. Effect of CO_2 Inhalation on Arterial Pressure, ECG and Plasma Catecholamines and 17-OH Corticosteroids in Normal Man. *J Appl Physiol* 15: 454-458, 1960.

94. **Serrador JM, Picot PA, Rutt BK, Shoemaker JK, and Bondar RL**. Mri Measures of Middle Cerebral Artery Diameter in Conscious Humans During Simulated Orthostasis. *Stroke* 31: 1672-1678, 2000.

95. **Snellen J, Mitchell D, and Wyndham C**. Heat of Evaporation of Sweat. *J Appl Physiol* 29: 40-44, 1970.

96. **Somers VK, Mark AL, and Abboud FM**. Sympathetic Activation by Hypoxia and Hypercapnia-Implications for Sleep Apnea. *Clin Exp Hypertens* 10: 413-422, 1988.

97. **Strandgaard S, and Paulson OB**. Cerebral Autoregulation. *Stroke* 15: 413-416, 1984.

98. **Szabo G**. The Number of Eccrine Sweat Glands in Human Skin. *Adv Biol Skin* 3: 1-5, 1962.

99. **Taylor WF, Johnson JM, O'Leary D, and Park MK**. Effect of High Local Temperature on Reflex Cutaneous Vasodilation. *J Appl Physiol* 57: 191-196, 1984.

100. **Toda N, and Okamura T**. Cerebral Vasodilators. *Jpn J Pharmacol* 76: 349-367, 1998.

101. **Van Lieshout JJ, and Secher NH**. Point: Counterpoint: Sympathetic Activity Does/Does Not Influence Cerebral Blood Flow. *J Appl Physiol* 105: 1364-1366, 2008.

102. **Weiner J**. The Regional Distribution of Sweating. *J Physiol (Lond)* 104: 32-40, 1945.

103. **West JB**. Control of Ventilation - How Gas Exchange Is Regulated. In: *Respiratory Physiology: The Essentials*. Philadelphia, PA.: Lippincott Williams & Wilkins, 2008, p. 123-138.

104. **Whipp BJ, and Pardy RL**. Breathing During Exercise. In: *Comprehensive Physiology*, edited by Terjung R. San Fransisco, CA: John Wiley & Sons, Inc., 2008, p. 605-629.

105. **White MD**. Components and Mechanisms of Thermal Hyperpnea. *J Appl Physiol* 101: 655-663, 2006.

106. **White MD, and Cabanac M**. Exercise Hyperpnea and Hyperthermia in Humans. *J Appl Physiol* 81: 1249-1254, 1996.

107. **White MD, and Cabanac M**. Nasal Mucosal Vasodilatation in Response to Passive Hyperthermia in Humans. *Eur J Appl Physiol Occup Physiol* 70: 207-212, 1995.

108. **White MD, Greiner JG, and McDonald PLL**. Point: Counterpoint "Humans Do / Do Not Demonstrate Selective Brain Cooling During Hyperthermia.". *J Appl Physiol* 110: 569-574, 2011.

109. **Willie CK, Macleod DB, Shaw AD, Smith KJ, Tzeng YC, Eves ND, Ikeda K, Graham J, Lewis NC, and Day TA**. Regional Brain Blood Flow in Man During Acute Changes in Arterial Blood Gases. *J Physiol (Lond)* 2012.

110. **Willis I, Harris DR, and Moretz W**. Normal and Abnormal Variations in Eccrine Sweat Gland Distribution. *J Invest Dermatol* 60: 98-103, 1973.

111. **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.

112. **Zhang R, Zuckerman JH, Iwasaki K, Wilson TE, Crandall CG, and Levine BD**. Autonomic Neural Control of Dynamic Cerebral Autoregulation in Humans. *Circulation* 106: 1814-1820, 2002.

CHAPTER TWO: STUDY 1

Thermal Hyperpnea and Temperature-Dependent Regional Differences in Cerebrovascular Responses in Humans

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2.1 Introduction

Our previous research illustrated regional differences in cerebral blood velocities irrespective of changes in body temperature (15). This led us to believe that we had not adequately assessed cerebral perfusion. Consequently, in the current study we assessed mean arterial blood pressure (MAP) to index cerebral perfusion pressure as well as cerebral blood velocity (CBV) to give an index of cerebral blood flow (CBF). The quotient of CBV and MAP (Eqn. 2.2) was used as an index of cerebrovascular conductance (ICVC).

Hyperthermia increases pulmonary ventilation ($\dot{V}_E$) in humans (2, 3, 6-8) causing a decrease in end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$). This thermal hyperpnea or hyperthermia-induced hyperventilation in resting humans (25) and associated hypocapnia appear to result in a global cerebral arteriolar vasoconstriction. As well, there appears to be reductions in both CBV and ICVC in the middle cerebral artery (MCA) during hyperthermia (2, 6, 7). Brothers et al. (2), for the MCA, showed a ~30% decrease in ICVC in poikilocapnic hyperthermia and a ~14% decrease of ICVC in eucapnic hyperthermia. Furthermore, Fan et al. (6) showed, for the MCA, an ~8% increase in cerebrovascular resistance at a ~1.0ºC hyperthermia, and a ~25% increase in cerebrovascular resistance at a ~2.0ºC hyperthermia. Fujii et al. (7) showed a reduction of MCA ICVC for a 0.4ºC increase in T_{ES}. They concluded that cerebral CO_2 reactivity was unaffected by increases in body temperature, though there was an unexplained ~20% decrease in eucapnic MCA CBV even though MAP

was constant (7). Interestingly, Fan et al. (6) showed no change in the MCA cerebrovascular resistance sensitivity to $P_{ET}CO_2$ during passive hyperthermia.

It remains to be established if the basilar artery (BA) responds similarly to the MCA during hyperthermia (2, 6, 7, 22). However, one study has observed an increase in MCA and posterior cerebral artery (PCA) CBV during eucapnic hyperthermia (18). According to the existing model for the control of resting pulmonary ventilation (20), respiratory drive is largely dependent on the partial pressure of carbon dioxide (PCO_2) or [H^+] sensed by both the central and peripheral chemoreceptors (1, 17, 20). If PCO_2 and/or [H^+] values drop, it follows that there should be a reduction in $\dot{V}_E$. Very low $P_{ET}CO_2$ values can elicit reductions in CBF that can lead to syncope (4, 21). It is unclear what is driving the persisting increase in pulmonary ventilation in poikilocapnic hyperthermia (2, 6-8, 22, 25).

During hyperthermia, returning $P_{ET}CO_2$ to eucapnic partial pressures only partially restores MCA CBV to a normothermic rate (2, 7, 22). Thermal hyperpnea continues during apparently reduced cerebrovascular perfusion (2, 6, 22). The BA supplies blood to the midbrain, pons, and upper lateral medulla oblongata. Respiratory centres in the pons, including the apneustic and pneumotaxic have a blood supply from the pontine arteries that branch directly from the BA (13, 14). Furthermore, the PCA vascularizes the body of the 4th ventricle, which has chemosensitive tissues located at its floor (13, 14). Blood flow in the BA and PCA need to be assessed to help resolve the mechanism of

the control of breathing in hyperthermia. This study was conducted to measure ICVC in the MCA as well as caudally in the PCA and BA.

Mean arterial pressure (MAP) decreases in hyperthermia (6) but some studies show no change (2, 7). Since MAP can decline in hyperthermia (6, 12), ICVC was employed to assess cerebrovascular perfusion changes that might be explained by changes in MAP during these conditions.

The goal of this study was to assess the effects of passive hyperthermia on ICVC in resting volunteers during poikilocapnia and eucapnia. It was hypothesized that ICVC in the PCA and BA would not respond in the same way to passively induced hyperthermia as ICVC in the MCA (2, 6, 22). With a projected decrease in MAP during hyperthermia (6, 12), and a reduced MCA CBV (2, 6, 7, 22), it was hypothesized that $ICVC_{MCA}$ would remain constant. Furthermore, to account for thermal hyperpnea, it was hypothesized ICVC would be maintained or increased in the PCA and BA.

2.2 Methods

2.2.1 Participants

Power calculations were performed to determine the sample sizes required to detect a significant difference in both middle cerebral artery mean blood velocity (MCAv) and $\dot{V}_E$. During resting hyperthermia, when core temperature is increased by 1ºC (9), there is a decrease in MCAv from 69 ± 10 cm/s to 60 ± 14 cm/s (mean ± SD). Hyperthermia has also been shown to elicit increases in $\dot{V}_E$ from 9.5 ± 1.1 L/min in resting normothermia to 26.7 ± 21.0

L/min in resting hyperthermia (3, 7). Power calculations from data presented by Fan et al. (6) for MCAv show that a sample size of 7 volunteers is required to detect a significant difference at a ß = 0.90 and an α = 0.05. With the same parameters, based on the $\dot{V}_E$ data (3, 7), a sample size of 8 volunteers is required to detect significant differences in this variable at α = 0.05.

This study was conducted with 8 male participants. Each participant was college aged, was a non-smoker and had no acute or chronic pulmonary deficiencies (Table 2.1). Each potential volunteer, prior to accepting to participate in the study, was given a walk-through of the laboratory so as to explain potential risks and protocols of the study. Following an introduction to the laboratory and a 24-hour reflection period, each study participant was asked to fill out a Physical Activity Readiness Questionnaire (PAR-Q), a Laboratory for Exercise and Environmental Physiology Confidential Health Screen Questionnaire, and an informed consent form. Each participant was asked to abstain from alcohol, caffeine, and exercise in the 24 h prior to data collection. They were also asked to abstain from consuming a large meal 3-4 h prior. Each volunteer was asked to drink a litre of water in the morning and water was made available *ab libitum* to the volunteers over the duration of each trial.

2.2.2 Instrumentation

2.2.2.1 Ventilatory/Metabolic Variables

The volunteer wore a nose clip and mouthpiece during measurement of pulmonary ventilation and its components. The mouthpiece was connected to a two-way flow sensor measuring pulmonary ventilation and a two-way non-

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

The inspired air, during clamping of end-tidal gases, was composed of a mixture of compressed air, CO_2 and N_2. A LabVIEW software program (National Instruments, Austin, TX, USA, Version 7.1) and end-tidal forcing system (11) controlled the opening time of electronic solenoid valves attached to the three gas cylinders. Based on the measured values from the expired air of the breath immediately preceding it, LabVIEW altered the time each valve is open so as to stabilize end tidal concentrations of various gases. In this way, it was assured that $P_{ET}CO_2$ and end-tidal partial pressure of O_2 ($P_{ET}O_2$) remained constant at the desired values over the course of the prescribed thermoregulatory stresses. The breathing apparatus was also connected to a humidifier via 250 cm of 3.8 cm

diameter corrugated Collins tubing. The humidifier-moistened air was delivered to the participant from the cylinders of compressed gas.

2.2.2.2 Cardiovascular Variables

Heart rate (HR) and mean arterial pressure (MAP) were recorded using a beat-by-beat Finopres blood pressure monitor (Model 1, Amsterdam, Netherlands). Using a waveform envelope, the mean CBV is calculated by the TCD, and cerebrovascular mean blood velocities in the MCA (MCAv), PCA (PCAv), and BA (BAv) were collected using three Spencer transcranial Doppler (TCD) probes (Model PMD 150, Seattle, WA, USA). Haemoglobin oxygen saturation and HR will also be monitors using a MasimoSET radical signal extraction pulse oximeter (Model RDS1, Irvine, CA, USA). A urinometer was used to measure the specific gravity of urine obtained pre and post hyperthermia.

2.2.2.3 Body Temperatures

Skin temperature and core temperature (T_{CORE}) were continuously recorded throughout each test. Core temperatures were measured in the rectum and esophagus, while skin temperatures were averaged over 6 surface locations and expressed as their un-weighted mean value ($\overline{T}_{SK}$). These 6 locations included forehead (T_{FH}), chest (T_{CH}), scapula (T_{SC}), forearm (T_{FA}), front thigh (T_{FT}), and back calf (T_{BC}). Esophageal temperatures (T_{ES}) were sampled with a pediatric sized nasopharyngeal esophageal temperature thermocouple (9 FR, Mallinckrodt Medical Inc., St. Louis, MO, USA) placed at the T8/T9 level. The depth (L) was found with Mekjavic and Rempel's standing height equation (16).

$L = 0.228 \bullet (\text{standing height (cm)}) - 0.194$ ……..……...(2.1)

Rectal temperatures (T_{RE}) were sampled from a sheathed thermocouple inserted 15 cm into the rectum (12 FR, Mallinckrodt Medical Inc., St. Louis, MO, USA). Skin temperatures were recorded by T-type, copper/constantan thermocouples (Omega Engineering Inc., Stanford, CT, USA) secured on the right side of the participant's body with waterproof, hypoallergenic tape. Calibrations of esophageal, rectal, and skin thermocouple probes were completed in a regulated temperature water bath (VWR International, Model 1196 West Chester, Pennsylvania, USA) over the range of expected physiological values. Reference temperatures were recorded using a Fisher Scientific platinum thermometer (Traceable Calibration Control Company, Pt-100Ω, Friendswood, TX, USA).

2.2.2.4 Climate Chamber

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

2.2.2.5 Data Acquisition

Ventilatory data were sampled and recorded on a breath-by-breath basis with a metabolic cart. The flow signal from the metabolic cart for each breath was used to trigger LabVIEW to sample and record all temperature and physiological measurements (National Instruments, Austin, TX, USA, Version 7.1).

2.2.3 Protocol

Each volunteer was asked to participate in a study that consists of three different measurement periods (Fig. 2.1). Each experimental trial began with the collection of a urine sample and instrumentation of the volunteer for monitoring of cardiorespiratory responses, CBV, beat-by-beat blood pressure, and body temperatures. Next there was a 10 min monitoring of resting data at room temperature during poikilocapnic normothermic breathing. This was followed by a resting poikilocapnic normothermia data collection period (NT-REST), poikilocapnic body-warming period, poikilocapnic hyperthermia (HT-PC), and eucapnic hyperthermia data collection (HT-EC), sequentially.

Each volunteer was then seated in the climate chamber at 50^{o}C/25%RH while wearing a rain suit, and T_{CORE} was elevated to 1ºC above resting temperature or to at least 38 ºC. $P_{ET}CO_2$ was controlled at eucapnic partial pressures during the eucapnic hyperthermic core temperature condition with the ETF (11). Oxygen consumption, $\dot{V}_E$, T_{ES}, T_{RE}, and $\overline{T}_{SK}$ were collected by the data acquisition system across all conditions.

The MAP and HR were continuously collected on a beat-by-beat basis with a Finopres blood pressure monitor. During these experimental conditions outcome variables included MCAv, PCAv, and BAv. These variables were monitored using transcranial Doppler sonography via the temporal and foraminal insonation windows. During steady state conditions, the MCAv and PCAv were collected simultaneously over 5 min and then collection of BAv was conducted in the following 5 min. Cerebral blood vessel validation was performed for the MCA

by comparing NT-REST velocities to typical values, looking for the aortic valve notch in the waveform, and ipsilateral occlusion of the internal carotid artery to decrease CBV. The PCA was validated by comparing NT-REST velocities to typical velocities after finding the bifurcation for the PCA, ipsilateral occlusion of the internal carotid artery, and removal of visual stimulation to decrease CBV. The BA was obtained by not deviating the Doppler probe from the central sagittal plane and a comparison of NT-REST velocities to typical velocities. After completion of the hyperthermic trial another urine sample was collected.

2.2.4 Statistical Analyses

Data on MCAv, PCAv, BAv, $\dot{V}_E$, MAP, T_{CORE}, $\overline{T}_{SK}$, $P_{ET}O_2$, and $P_{ET}CO_2$ were averaged individually during each of the steady state NT-REST, HT-PC, and HT-EC periods. Then the same was done for all participants, and standard deviations were reported. A one-way ANOVA (Levels: NT-REST, HT-PC, HT-EC) was conducted across all conditions for each outcome variable. A paired two-tailed t-test was performed between the average of the means of NT-REST, HT-PC, and HT-EC if there was a main effect in the one-way ANOVA. The level of significance was set at an $\alpha = 0.05$.

The blood pressure and CBV data were used to calculate (Eq. 2.2) an index of cerebrovascular conductance (ICVC) (19). Equation 2.2, as employed by Brothers et al. (2), was used to calculate ICVC below where ICVC is the index of cerebrovascular conductance, CBV is cerebral blood velocity, and MAP is mean arterial pressure.

ICVC = CBV/MAP……..……..……(2.2)

The coefficient of variation was calculated for MCAv, PCAv, and BAv in NT-REST.

2.3 Results

Passively induced hyperthermia significantly increased T_{ES} ($P<0.001$) from 36.7 ± 0.3 ºC in NT-REST to 37.9 ± 0.1 ºC in HT-PC, and 38.1 ± 0.2 ºC in HT-EC (Fig. 2.2A). Similarly, $\bar{T}_{SK}$ increased ($P<0.001$) from 32.8 ± 0.8 ºC in NT-REST to 39.0 ± 0.7 ºC in HT-PC and 39.7 ºC in HT-EC (Fig. 2.2B). Urine specific gravity was not significantly different ($P=0.50$) and remained at ~1.013 during the course of the hyperthermic trial.

During NT-REST, $\dot{V}_E$ (Fig. 2.3A) was 11.3 ± 2.3 L/min and showed a trend to increase to 20.4 ± 11.5 L/min during HT-PC ($P=0.06$). During HT-EC, however, $\dot{V}_E$ (Fig. 2.3A) significantly increased ($P<0.05$) to 32.1 ± 13.6 L/min with respect to both NT-REST and HT-PC. The NT-REST $P_{ET}CO_2$ (Fig. 2.3B) was 40.7 ± 4.5 mm Hg and in HT-PC it was decreased ($P<0.05$) to 30.8 ± 8.4 mm Hg, while in HT-EC $P_{ET}CO_2$ was clamped ($P=0.43$) at 41.8 ± 3.2 mm Hg. Across all conditions, $P_{ET}O_2$ remained at ~107 mm Hg.

Mean arterial blood pressure (Table 2.1) decreased ($P<0.05$) from 106.6 ± 7.2 mm Hg in NT-REST to 87.5 ± 7.0 mm Hg in HT-PC and 89.8 ± 5.6 in HT-EC. As well, MAP between HT-PC and HT-EC was not significantly different ($P>0.05$).

There was a significant decrease ($P<0.001$) in MCAv during HT-PC to 71.3 ± 7.2 % of NT-REST. During HT-EC MCAv was significantly increased ($P<0.05$) with respect to HT-PC to 87.1 ± 9.2 % of NT-REST, but still significantly decreased ($P<0.05$) with respect to NT-REST (Fig. 2.4A). There were no

significant changes in PCAv with respect to the NT-REST values or between HT-PC and HT-EC. The BAv, however, significantly decreased ($P<0.05$) during HT-PC to 82.0 ± 10.2 % of NT-REST. During HT-EC, BAv showed a trend ($P=0.07$) to be significantly decreased to 87.6 ± 9.3 % of NT-REST, but was significantly increased ($P=0.05$) from HT-PC.

The $ICVC_{MCA}$ (Fig. 2.5A) was significantly decreased ($P<0.05$) during HT-PC to 87.1 ± 10.3 % of NT-REST. During HT-EC, $ICVC_{MCA}$ significantly returned to values that were not significantly different ($P>0.05$) than NT-REST, but were significantly increased ($P<0.05$) with respect to HT-PC. There were no significant differences ($P>0.05$) from NT-REST or between HT-PC and HT-EC for $ICVC_{PCA}$ and $ICVC_{BA}$.

The coefficient of variation during NT-REST for MCAv was 18.4%, and for BAv was 16.2%. Whereas, for PCAv during NT-REST with one outlier removed that was approximately 6 SD above the mean, the coefficient of variation was 20.3%.

2.4 Discussion

Significant regional differences in CBV and ICVC responses were observed during passively induced hyperthermia. The $ICVC_{MCA}$ was only decreased during HT-PC, while $ICVC_{PCA}$ and $ICVC_{BA}$ did not display any changes from NT-REST during HT-PC or HT-EC (Fig. 2.5). The MCAv and BAv decreased relative to NT-REST during poikilocapnic passive hyperthermia and partially recovered during eucapnic passive hyperthermia, but PCAv was not significantly different from NT-REST during both hyperthermic conditions (Fig 2.4). These results indicate that CBV and ICVC exhibit different responses to passively induced hyperthermia, and emphasize the need to include estimates of perfusion pressure when assessing cerebral perfusion (15).

There are a few mechanisms that could elicit such responses. One possibility that could explain the decrease in CBV in the MCA and BA is that there is a constriction of the cerebral arterioles due to the decreased PCO_2 downstream of the MCA and BA, which would result in an increased resistance to CBV in the poikilocapnic condition. When $P_{ET}CO_2$ was restored in HT-EC, CBV in the MCA and BA recovered partially towards but still remained or tended to remain lower than the NT-REST values. This decrease in CBV in the MCA and BA when $P_{ET}CO_2$ is restored could be due to a persistent hypotension and decrease in perfusion pressure between the internal carotid and cerebral arterioles downstream of the MCA as well as between the vertebral arteries and the cerebral arterioles downstream from the BA as a result of the passively induced hyperthermia. The MAP decreased during hyperthermia, which resulted

in a further decrease in the driving force for CBV on the opposite side of the major vessels as arterioles. Interestingly, the decrease in BAv during HT-PC was not as pronounced as that of MCAv. This could be due to a relatively greater physiological demand for blood due to the activity of the RCC, and other homeostatic nuclei of the brainstem.

Furthermore, the concomitant decrease in CBV and MAP results in an overall maintenance of ICVC in the PCA and BA, whereas there was a decrease of $ICVC_{MCA}$ during HT-PC (Fig. 2.5A). The increase in MCAv between HT-PC and HT-EC would indicate an increase in the conductance in the MCA between those two conditions.

Anatomically, there are differences between the MCA, PCA, and BA with respect to their function to supply different structures of the brain with blood. The internal carotid artery directly feeds the MCA, while the vertebral arteries supply the BA. The BA, however, supplies the PCA with blood, while the PCA also receives some blood from the internal carotid artery via the Circle of Willis. It could be that this maintains PCAv, through a combination of upstream and downstream modulations, because it can receive blood from two sources that could maintain blood flow through the vessel by sustaining the input pressure while there is an increase in output resistance due to the downstream hypocapnia-induced vasoconstriction of the arterioles. Much like a shunt, the PCA would receive the extra blood that is not able to pass through the MCA or BA due to the increased resistance downstream of those vessels.

These results are comparable to those of other studies (2, 6, 7, 10, 22) that have only examined the response of the MCA in actively or passively induced hyperthermia. Collectively, these studies demonstrate that in poikilocapnic hyperthermia MCAv is significantly reduced and restoring the partial pressure of CO_2 to eucapnic values results in an incomplete recovery relative to normothermic cerebral blood velocities (2, 6, 7, 10, 22). One study (18), however, found that CBV was increased in both the MCA and PCA during eucapnic hyperthermia. The results of this study are consistent with investigations into the behaviour of the BA during decreased periods of $P_{ET}CO_2$ (23, 24), though the drop in BAv during HT-PC was not a great as that in the MCA (Fig 2.4A&C). Overall, the results of this study support that there are regional differences in cerebrovascular responses to passively induced hyperthermia in the brain.

Limitations

The T_{ES} increased by a small amount from HT-PC to HT-EC. This latter limitation is not of concern since the $P_{ET}CO_2$ was maintained between HT-PC and HT-EC. Furthermore, it is assumed that major vessel diameters are unchanged.

There was some concern that the lack of randomization of the eucapnic and poikilocapnic conditions would confound the results. For this reason, a pilot study of the effect of time of hyperthermia was conducted. There were no evident differences in the results between the poikilocapnic conditions for hyperthermia, as shown in Appendix 5.1.

Future Directions

In the future, studies during hyperthermia that utilize transcranial Doppler ultrasonography should also include an investigation of the vertebral arteries and BA in addition to the more frequent assessments of the MCA. The exact mechanism by which regional differences in cerebrovascular responses occur is still unclear, and further research into the phenomenon is warranted. Of particular concern as well, is the differences in the MAP responses to hyperthermia that exist in the literature (2, 5-7, 9, 10, 22). Some studies showed a decrease (5, 6, 9) in MAP, while others observed a maintenance or an increase (2, 7).

Furthermore, the opportunity to collect diastolic, systolic, and peak blood velocity data from the Doppler system would present an attractive addition to the existing literature. The investigation on the effects of hyperthermia on diastolic, systolic, and peak blood velocity would seem to be of particular interest especially with our use of an ETF. This could be an area of potential investigation in the future.

Conclusions

This study has effectively demonstrated and confirmed that there are regional differences in cerebrovascular responses during passively induced hyperthermia. As hypothesized, it was evident that ICVC in the PCA and BA did not respond in the same way to passively induced hyperthermia as ICVC in the MCA. As well, the responses of ICVC in the PCA and BA appear to be equivalent in nature, while the conductance in the MCA showed evidence of a

different response. These results are consistent with the hypothesis that cerebrovascular conductance of blood in caudal cerebral blood vessels is maintained during hyperthermia.

2.5 References

1. **Ainslie PN, and Duffin J**. Integration of Cerebrovascular CO_2 Reactivity and Chemoreflex Control of Breathing: Mechanisms of Regulation, Measurement, and Interpretation. *Am J Physiol Regul Integr Comp Physiol* 296: 1473-1495, 2009.

2. **Brothers RM, Wingo JE, Hubing KA, and Crandall CG**. The Effects of Reduced End-Tidal Carbon Dioxide Tension on Cerebral Blood Flow During Heat Stress. *J Physiol (Lond)* 587: 3921-3927, 2009.

3. **Cabanac M, and White MD**. Core Temperature Thresholds for Hyperpnea During Passive Hyperthermia in Humans. *Eur J Appl Physiol Occup Physiol* 71: 71-76, 1995.

4. **Carey BJ, Eames PJ, Panerai RB, and Potter JF**. Carbon Dioxide, Critical Closing Pressure and Cerebral Haemodynamics Prior to Vasovagal Syncope in Humans. *Clin Sci* 101: 351-358, 2001.

5. **Crandall CG, Cui J, and Wilson TE**. Effects of Heat Stress on Baroreflex Function in Humans. *Acta Physiol Scand* 177: 321-328, 2003.

6. **Fan JL, Cotter JD, Lucas RA, Thomas K, Wilson L, and Ainslie PN**. Human Cardiorespiratory and Cerebrovascular Function During Severe Passive Hyperthermia: Effects of Mild Hypohydration. *J Appl Physiol* 105: 433-445, 2008.

7. **Fujii N, Honda Y, Hayashi K, Kondo N, Koga S, and Nishiyasu T**. Effects of Chemoreflexes on Hyperthermic Hyperventilation and Cerebral Blood Velocity in Resting Heated Humans. *Exp Physiol* 93: 994-1001, 2008.

8. **Haldane JS**. The Influence of High Air Temperatures: No. 1. *J Hyg (Lond)* 5: 494-513, 1905.

9. **Havenith G, Luttikholt VGM, and Vrijkotte TGM**. The Relative Influence of Body Characteristics on Humid Heat Stress Response. *Eur J Appl Physiol* 70: 270-279, 1995.

10. **Hayashi K, Honda Y, Miyakawa N, Fujii N, Ichinose M, Koga S, Kondo N, and Nishiyasu T**. Effect of CO_2 on the Ventilatory Sensitivity to Rising Body Temperature During Exercise. *J Appl Physiol* 110: 1334-1341, 2011.

11. **Koehle MS, Giles LV, Curtis AN, Walsh ML, and White MD**. Performance of a Compact End-Tidal Forcing System. *Respir Physiol Neurobiol* 167: 155-161, 2009.

12. **Koroxenidis GT, Shepherd JT, and Marshall RJ**. Cardiovascular Response to Acute Heat Stress. *J Appl Physiol* 16: 869-872, 1961.

13. **Marieb EN, and Hoehn K**. *Human Anatomy & Physiology*. San Fransisco, CA: Pearson Education, 2010, p. 1156.

14. **Martini FH**. The Brain and Cranial Nerves. In: *Fundamentals of Anatomy and Physiology*. San Fransisco, CA: Benjamin Cummings, 2006, p. 452-478.

15. **McDonald PLL**. *Effects of Hyperthermia on Human Middle Cerebral, Posterior Cerebral, and Basilar Artery Blood Velocities During Eucapnia*. Undergraduate Thesis. In: Biomedical Physiology and Kinesiology. Burnaby, BC.: Simon Fraser University, 2011, p. 80.

16. **Mekjavic IB, and Rempel ME**. Determination of Esophageal Probe Insertion Length Based on Standing and Sitting Height. *J Appl Physiol* 69: 376-379, 1990.

17. **Nattie E**. Julius H. Comroe, Jr., Distinguished Lecture: Central Chemoreception: Then ... And Now. *J Appl Physiol* 110: 1-8, 2011.

18. **Nelson MD, Haykowsky MJ, Stickland MK, Altamirano-Diaz LA, Willie CK, Smith KJ, Petersen SR, and Ainslie PN**. Reductions in Cerebral Blood Flow During Passive Heat Stress in Humans: Partitioning the Mechanisms. *J Physiol* 589: 4053-4064, 2011.

19. **Nichols WW, and O'Rourke MF**. Ultrasonic Blood Flow and Velocitometry. In: *Mcdonald's Blood Flow in Arteries*. London: Hodder Arnold, 2005, p. 151-163.

20. **Nielsen M, and Smith H**. Studies on the Regulation of Respiration in Acute Hypoxia; with a Appendix on Respiratory Control During Prolonged Hypoxia. *Acta Physiol Scand* 24: 293-313, 1952.

21. **Novak V, Spies JM, Novak P, McPhee BR, Rummans TA, and Low PA**. Hypocapnia and Cerebral Hypoperfusion in Orthostatic Intolerance. *Stroke* 29: 1876-1881, 1998.

22. **Nybo L, and Nielsen B**. Middle Cerebral Artery Blood Velocity Is Reduced with Hyperthermia During Prolonged Exercise in Humans. *J Physiol (Lond)* 534: 279-286, 2001.

23. **Ogoh S, Nakahara H, Ainslie PN, and Miyamoto T**. The Effect of Oxygen on Dynamic Cerebral Autoregulation: Critical Role of Hypocapnia. *J Appl Physiol* 108: 538-543, 2010.

24. **Park CW, Sturzenegger M, Douville CM, Aaslid R, and Newell DW**. Autoregulatory Response and CO_2 Reactivity of the Basilar Artery. *Stroke* 34: 34-39, 2003.

25. **White MD**. Components and Mechanisms of Thermal Hyperpnea. *J Appl Physiol* 101: 655-663, 2006.

2.6 Tables

Table 2.1: Participants' (n=8) individual sex, age, height, and weight as well as corresponding group means and standard deviations for each given physical characteristic.

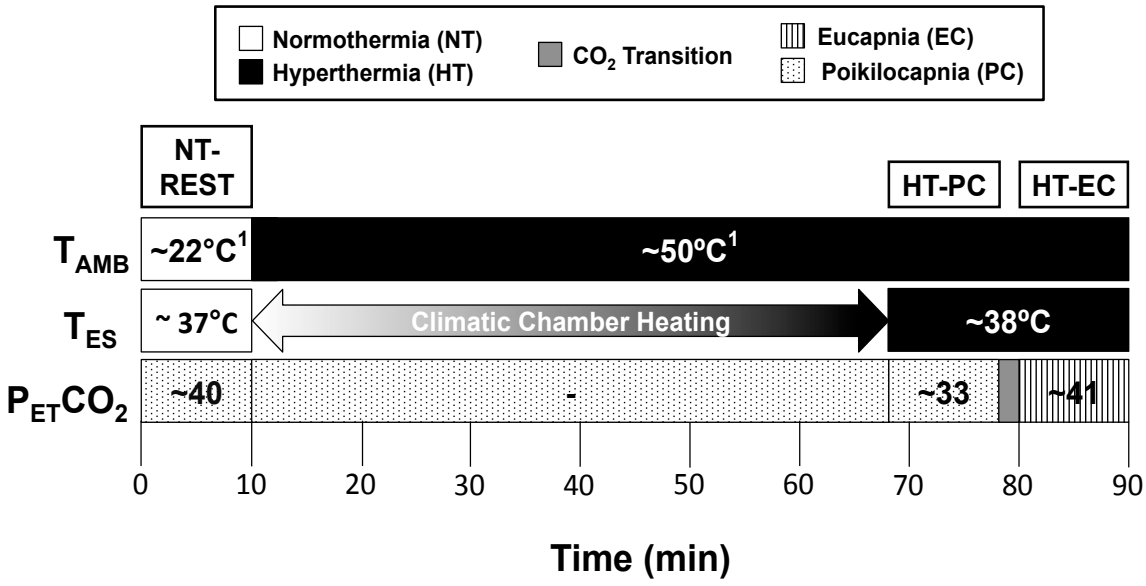
Participant	Sex	Age (y)	Height (m)	Weight (kg)
1	M	27	1.85	81
2	M	24	1.83	85
3	M	23	1.83	86
4	M	20	1.88	100
5	M	21	1.76	79
6	M	22	1.90	90
7	M	23	1.75	74
8	M	20	1.69	73
Mean		23	1.81	84
SD		2	0.07	9

Table 2.2: Participants' (n=8) mean arterial pressure (MAP, mm Hg) responses in normothermic rest (NT-REST), hyperthermic poikilocapnia (HT-PC), and hyperthermic eucapnia (HT-EC). † = P < 0.001, * = P < 0.05, NS = P > 0.05.

Participant	MAP NT-REST	MAP HT-PC	MAP HT-EC
1	102.3	91.7	90.2
2	102.5	84.2	87.4
3	101.8	93.0	89.3
4	111.1	85.5	87.2
5	106.7	82.5	82.6
6	96.6	86.0	88.5
7	117.8	77.2	90.7
8	114.1	99.5	88.5
Mean	106.6	87.5	89.8
S.D.	7.2	7.0	5.6
		*	NS
		†	

2.7 Figures

Figure 2.1: Study 1 Protocol; experimental trial conditions with ambient temperature (T_{AMB}), esophageal temperature (T_{ES}), and the end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$; mm Hg). Time periods are provided when cerebrovascular responses were assessed including normothermic rest (NT-REST), hyperthermic poikilocapnia (HT-PC), and hyperthermic eucapnia (HT-EC).



[1]25% Relative huminidity

Figure 2.2: Mean values of esophageal temperature (T_{ES}; A) and mean skin temperature ($\bar{T}_{SK}$; B) for all participants (n=8) in normothermic rest (NT-REST), hyperthermic poikilocapnic (HT-PC) and hyperthermic eucapnic (HT-EC).
† = P < 0.001, * = P < 0.05. For all figures, error bars indicate 1 SD.

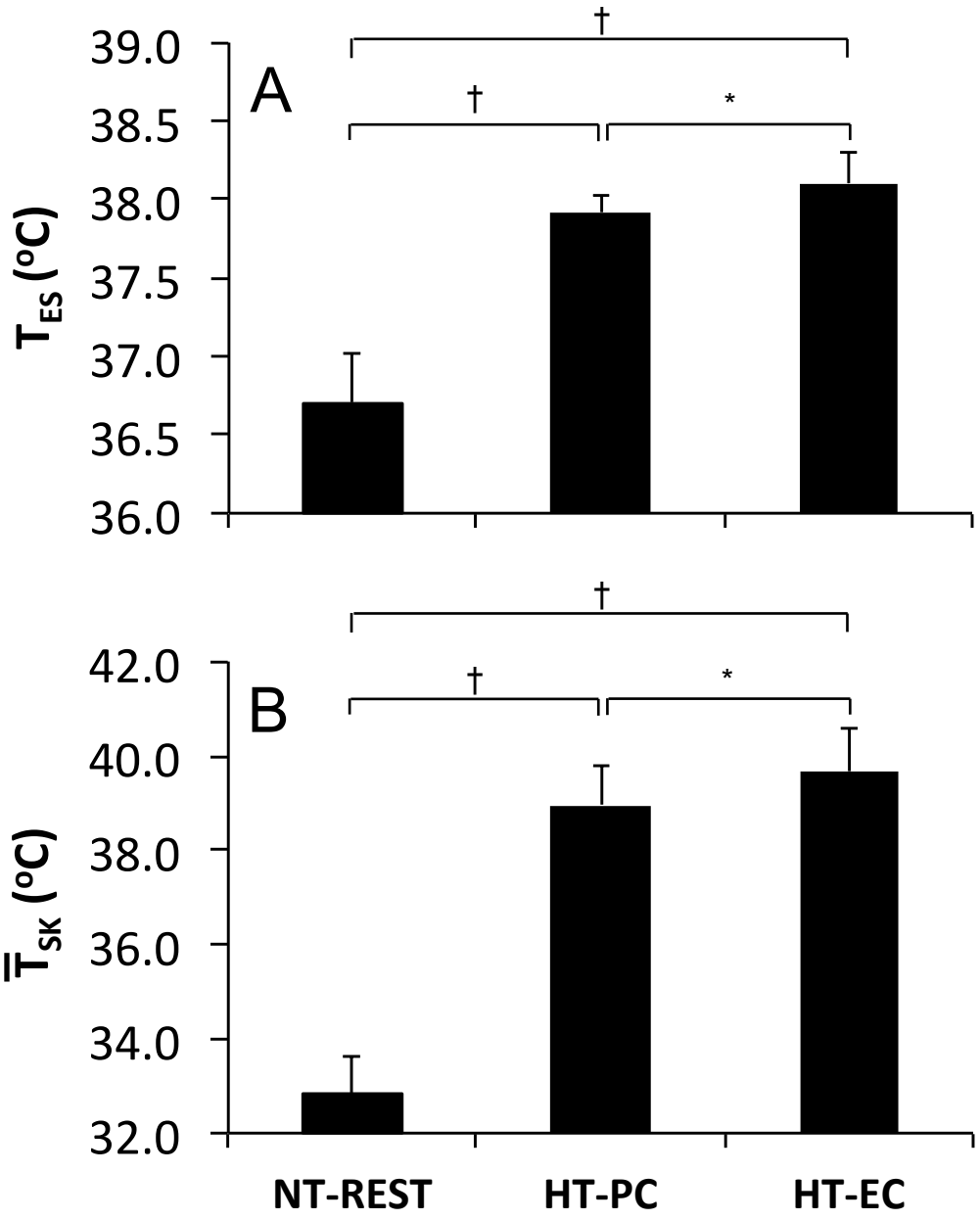


Figure 2.3: Mean values of pulmonary ventilation ($\dot{V}_E$; A), end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$; B), and end-tidal partial pressure of oxygen ($P_{ET}O_2$; C) for all participants (n=8) in normothermic rest (NT-REST) along with hyperthermic poikilocapnic (HT-PC) and hyperthermic eucapnic (HT-EC).
* = P < 0.05, NS = P > 0.05.

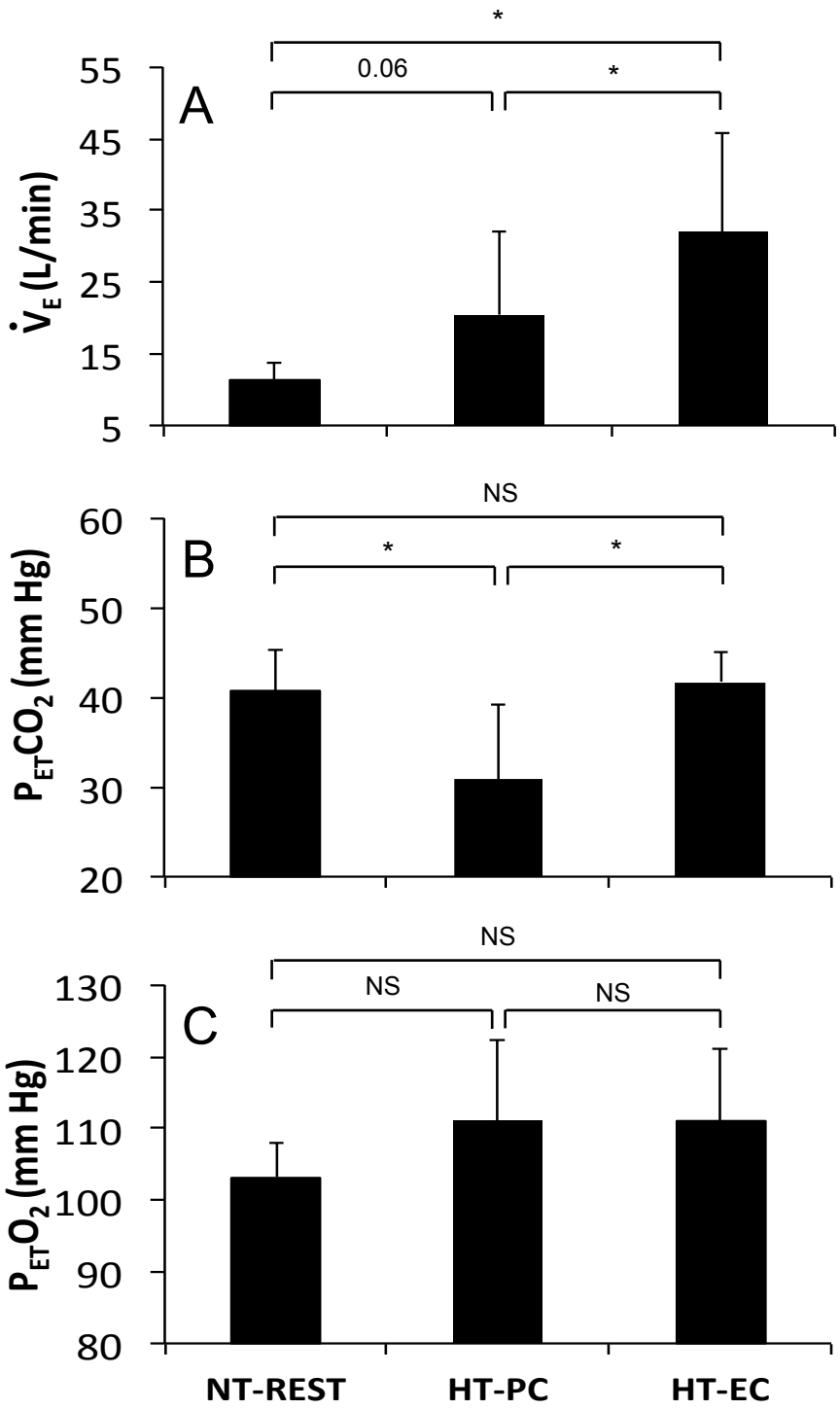


Figure 2.4: Mean percentage values of normothermic rest (NT-REST) cerebral blood velocities in the middle cerebral artery (MCAv; A), posterior cerebral artery (PCAv; B), and basilar artery (BAv; C) for all participants (n=8) during hyperthermic poikilocapnia (HT-PC) and hyperthermic eucapnia (HT-EC).
† = P <0.001, * = P < 0.05, NS = P > 0.05.

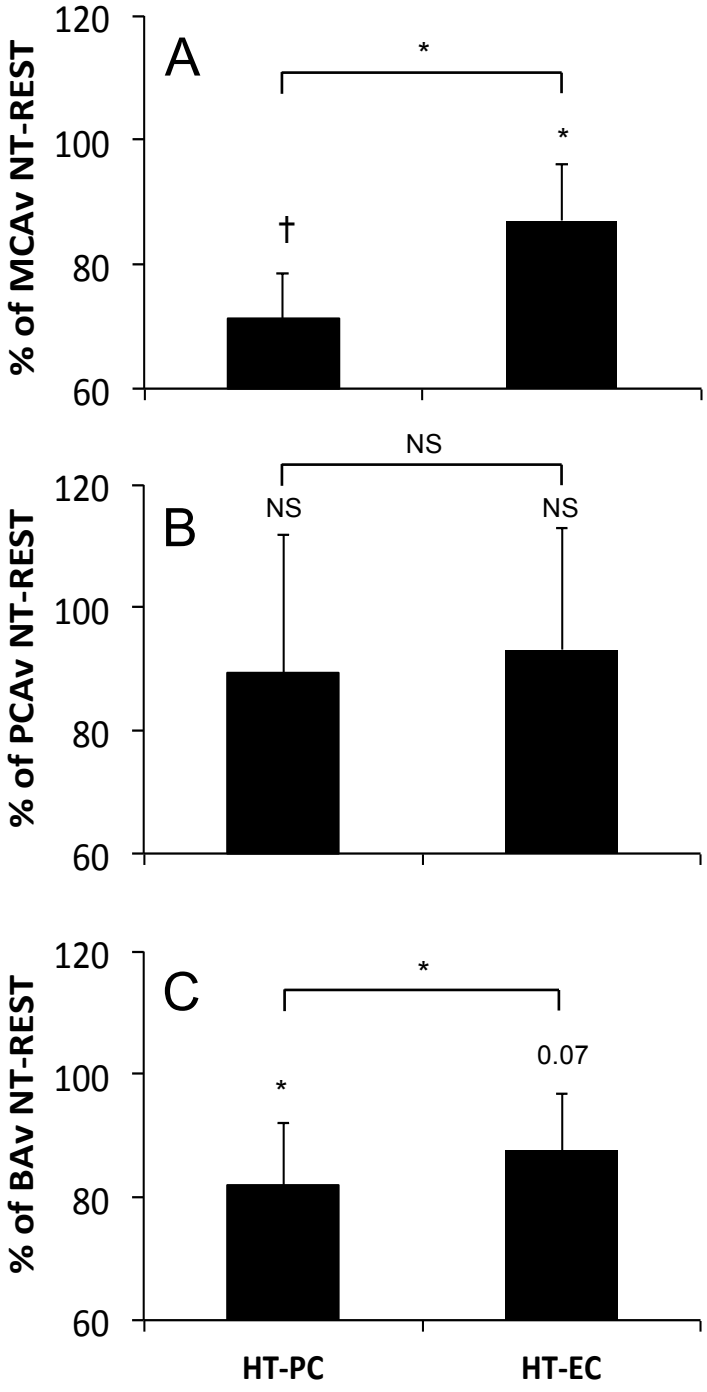
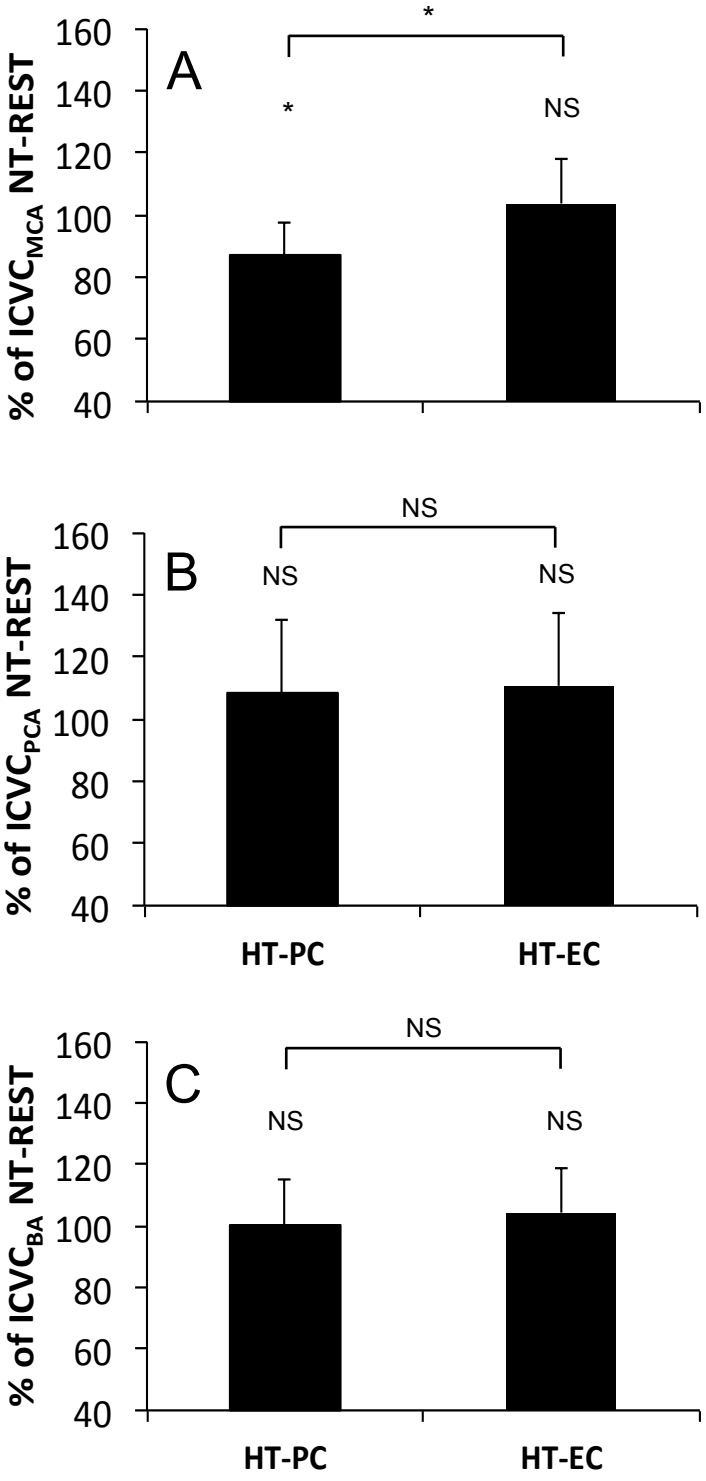


Figure 2.5: Indices of cerebrovascular conductance (ICVC, cm•s^{-1}•mm Hg^{-1}) expressed as a percentage of normothermic rest (NT-REST) in the middle cerebral artery (MCA; A), posterior cerebral artery (PCA; B), and basilar artery (BA; C) for all participants (n=8) during hyperthermic poikilocapnia (HT-PC) and hyperthermic eucapnia (HT-EC). * = P < 0.05, NS = P > 0.05.



CHAPTER THREE: STUDY 2

Effects of Poikilocapnic and Eucapnic Voluntary Hyperventilation on Cerebrovascular Responses in Normothermic Humans

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3.1 Introduction

Hyperventilation during hyperthermia (5, 7, 9, 10, 12) in humans causes a decrease in end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$). This hypocapnia results in cerebral arteriolar vasoconstriction (3, 4, 14, 23), which decreases cerebral blood velocity (CBV) and the index of cerebrovascular conductance (ICVC) in humans (1). It is not known how cerebrovascular responses during hypocapnic hyperventilation in normothermia compare to those that occur as a result of thermal hyperpnea in humans.

During normothermia, involuntary respiratory drive is largely dependent on the partial pressures of carbon dioxide (PCO_2) or [H^+] in the cerebrospinal fluid sensed by the central and peripheral chemoreceptors (24). In mammals, as PCO_2 and/or [H^+] values drop there is a proportional drop in the drive to breathe (8, 24). The drop in $P_{ET}CO_2$ during voluntary hyperventilation should elicit a drop in CBV in the middle cerebral artery (MCA), posterior cerebral artery (PCA), and basilar artery (BA). It remains to be established how voluntary increases in resting pulmonary ventilation rate ($\dot{V}_E$) during poikilocapnic and eucapnic normothermia affect CBV and ICVC in the MCA, PCA, and BA.

Human CBV, during thermal hyperpnea, appears to decrease in the middle cerebral artery (MCA) in poikilocapnic and eucapnic hyperthermia (5, 9, 10, 19), however, one study has shown an increase in MCA and PCA CBV in eucapnic hyperthermia (17). These studies, however, have not assessed the BA and the PCA has only been examined once in these conditions (17). These studies have also not compared normothermic relative to hyperthermic

cerebrovascualar responses during similar rates of pulmonary ventilation in poikilocapnia and eucapnia. It is therefore imperative to determine the changes in CBV in the basilar artery (BA), which supplies blood to posterior cerebral tissues including the midbrain, pons, and upper lateral medulla oblongata, to help resolve the mechanism of the control of breathing and the role of hyperventilation on cerebrovascular responses in these regions of the brain.

The goal of this study was to assess CBV and ICVC in resting volunteers in the MCA, PCA, and BA in poikilocapnic normothermic rest (NT-REST), poikilocapnic normothermic voluntary hyperventilation (NT-PC), and eucapnic normothermic voluntary hyperventilation (NT-EC). The voluntary $\dot{V}_E$ was set at the rate seen in Study 1. It was hypothesized that a decrease CBV and ICVC in the MCA, PCA, and BA will be observed in poikilocapnic normothermic hyperventilation. A second hypothesis was that there would be a complete restoration of CBV and ICVC observed in the MCA, PCA, and BA during eucapnic normothermic hyperventilation.

3.2 Methods

3.2.1 Participants

Power calculations were performed to determine the sample sizes required to detect a significant difference in both middle cerebral artery mean blood velocity (MCAv) and $\dot{V}_E$ in normothermic humans. Hyperthermic ventilatory and cerebrovascular data were used because $\dot{V}_E$ was matched in this study to hyperthermic values. During resting hyperthermia, when core temperature is

increased by 1ºC (9), there is a decrease in MCAv from 69 ± 10 cm/s to 60 ± 14 cm/s (mean ± SD). Hyperthermia has also been shown to elicit increases in $\dot{V}_E$ from 9.5 ± 1.1 L/min in resting normothermia to 26.7 ± 21.0 L/min in resting hyperthermia (7, 10). Power calculations from data presented by Fan et al. (9) for MCAv show that a sample size of 7 volunteers will be required to detect a significant difference at a ß = 0.90 and an α = 0.05. With the same parameters, based on the $\dot{V}_E$ data (7, 10), a sample size of 8 volunteers will be required to detect significant differences in this variable at α = 0.05.

This study was conducted with the same 8 male participants as study 1. Each participant was a college-aged non-smoker with no acute or chronic pulmonary deficiencies (Table 3.1). Each potential volunteer, prior to accepting to participate in the study, was given a walk-through of the laboratory so as to explain potential risks and protocols of the study. Following an introduction to the laboratory and a 24-hour reflection period, each study participant was asked to fill out a Physical Activity Readiness Questionnaire (PAR-Q), a Laboratory for Exercise and Environmental Physiology Confidential Health Screen Questionnaire, and an informed consent form. Each participant was asked to abstain from alcohol, caffeine, and exercise in the 24 h prior to data collection. Each volunteer was asked to abstain from consuming a large meal 3-4 h prior to the experimental trial.

3.2.2 Instrumentation

3.2.2.1 Ventilatory/Metabolic Variables

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

The inspired air, during clamping of end-tidal gases, was composed of a mixture of compressed air, CO_2 and N_2. A LabVIEW software program (National Instruments, Austin, TX, USA, Version 7.1) and end-tidal forcing system (15) controlled the opening time of electronic solenoid valves attached to the three gas cylinders. Based on the measured values from the expired air of the breath immediately preceding it, LabVIEW altered the time each valve is open so as to

stabilize end tidal concentrations of various gases. In this way, it was assured that $P_{ET}CO_2$ and end-tidal partial pressure of O_2 ($P_{ET}O_2$) remained constant at the desired values over the course of the prescribed ventilatory stresses. The breathing apparatus was also connected to a humidifier via 250 cm of 3.8 cm diameter corrugated Collins tubing. The humidifier-moistened air was delivered to the participant from the cylinders of compressed gas.

3.2.2.2 Cardiovascular Variables

Heart rate (HR) and mean arterial pressure (MAP) were recorded using a beat-by-beat Finopres blood pressure monitor (Model 1, Amsterdam, Netherlands). Using a waveform envelope, the mean CBV is calculated by the TCD, and cerebrovascular mean blood velocities in the MCA (MCAv), PCA (PCAv), and BA (BAv) were collected using a Spencer transcranial Doppler (TCD) (Model PMD 150, Seattle, WA, USA). Haemoglobin oxygen saturation and HR was monitored using a MasimoSET radical signal extraction pulse oximeter (Model RDS1, Irvine, CA, USA).

3.2.2.3 Body Temperatures

Skin temperature and core temperature (T_{CORE}) were continuously recorded throughout each test. Core temperatures were measured in the rectum and esophagus, while skin temperatures were averaged over 6 surface locations and expressed as their un-weighted mean value ($\overline{T}_{SK}$). These 6 locations included forehead (T_{FH}), chest (T_{CH}), scapula (T_{SC}), forearm (T_{FA}), front thigh (T_{FT}), and back calf (T_{BC}). Esophageal temperatures (T_{ES}) were sampled with a pediatric sized nasopharyngeal esophageal temperature thermocouple (9 FR,

Mallinckrodt Medical Inc., St. Louis, MO, USA) placed at the T8/T9 level. This depth (L) was found using Mekjavic and Rempel's equation (Eqn. 2.1) for standing height (16).

Rectal temperatures (T_{RE}) were sampled from a sheathed thermocouple inserted 15 cm into the rectum (12 FR, Mallinckrodt Medical Inc., St. Louis, MO, USA). Skin temperatures were recorded by T-type, copper/constantan thermocouples (Omega Engineering Inc., Stanford, CT, USA) secured on the right side of the participant's body with waterproof, hypoallergenic tape. Calibrations of esophageal, rectal, and skin thermocouple probes were completed in a regulated temperature water bath (VWR International, Model 1196 West Chester, Pennsylvania, USA) over the range of expected values. Reference temperatures were measured using a Fisher Scientific platinum thermometer (Traceable Calibration Control Company, Pt-100Ω, Friendswood, TX, USA).

3.2.2.4 Data Acquisition

Ventilatory data were sampled and recorded on a breath-by-breath basis with a metabolic cart. The flow signal from the metabolic cart for each breath was used to trigger LabVIEW to sample and record all temperature and physiological measurements (National Instruments, Austin, TX, USA, Version 7.1).

3.2.3 Protocol

Each volunteer was asked to participate in a study that consists of three different measurement periods (Fig. 3.1). Each experimental trial began with instrumentation of the volunteer for monitoring of cardiorespiratory responses, CBV, beat-by-beat blood pressure, and body temperatures. Next there was a collection of 10 min of resting data at room temperature during NT-REST.

This was followed by a poikilocapnic hyperventilation (NT-PC), and a eucapnic hyperventilation (NT-EC), sequentially. Volunteers were asked to hyperventilate at their mean $\dot{V}_E$ from eucapnic hyperthermia in study 1 by watching the tracing of their current pulmonary ventilation and $P_{ET}CO_2$ on a monitor of the metabolic cart. Each participant was given a target value for each of $\dot{V}_E$ and $P_{ET}CO_2$, and, to change the values, they were coached to change their tidal volume or breathing frequency accordingly.

Each volunteer was seated in the laboratory at ~24^{o}C/~25% RH. $P_{ET}CO_2$ will be controlled at eucapnic partial pressures during the eucapnic hyperventilation condition with the ETF (15). Oxygen consumption, $\dot{V}_E$, T_{ES}, T_{RE}, and $\overline{T}_{SK}$ were collected by the data acquisition system across all conditions. MAP and HR were continuously collected on a beat-by-beat basis with a Finopres blood pressure monitor. During these experimental conditions outcome variables included MCAv, PCAv, and BAv. These variables were monitored using transcranial Doppler sonography via the temporal and foraminal insonation windows. The MCAv and PCAv were collected simultaneously over 5 min and then collection of BAv was conducted in the following 5 min.

Cerebral blood vessel validation was performed for the MCA by comparing NT-REST velocities to typical velocities, looking for the aortic valve notch in the waveform, and using ipsilateral occlusion of the internal carotid artery to decrease CBV. The PCA was validated by comparing NT-REST velocities to typical velocities after finding the bifurcation for the PCA, ipsilateral occlusion of the internal carotid, and removal of visual stimulation to reduce CBV. The BA was obtained by not deviating the Doppler probe from the central sagittal plane and a comparison of NT-REST velocities to typical velocities.

3.2.4 Statistical Analyses

Data on MCAv, PCAv, BAv, $\dot{V}_E$, MAP, T_{CORE}, $\overline{T}_{SK}$, $P_{ET}O_2$, and $P_{ET}CO_2$ were averaged individually in each of NT-REST, NT-PC, and NT-EC, then for all participants, and standard deviations of the means were reported for each condition. A one-way ANOVA (Levels: NT-REST, NT-PC, and NT-EC) was conducted across all conditions for each outcome variable. A paired two-tailed t-test was employed to compare data collected between each of NT-REST, NT-PC, and NT-EC when significant main effects were found with the one-way ANOVA. The level of significance was set at an $\alpha = 0.05$.

The MAP and CBV data were used to calculate an index of cerebrovascular conductance (ICVC) (18). Equation 2.2, as employed by Brothers et al. (5), was used to calculate ICVC.

A coefficient of variation was calculated for MCAv, PCAv, and BAv in NT-REST.

3.3 Results

Voluntary hyperventilation did not alter T_{ES} (P>0.05) from ~37.0 ºC during NT-REST (Fig. 3.2A). Similarly, $\bar{T}_{SK}$ was unchanged (P>0.05) from ~33.1 ºC in NT-REST during voluntary hyperventilation (Fig. 3.2B). During NT-REST, $\dot{V}_E$ (Fig. 3.3A) was 10.0 ± 0.9 L/min and significantly increased to 24.0 ± 8.9 L/min during NT-PC (P<0.05). During NT-EC, $\dot{V}_E$ significantly increased (P<0.001) to 23.1 ± 6.7 L/min, but was not significantly different (P>0.05) from NT-PC. The NT-REST $P_{ET}CO_2$ (Fig. 3.3B) was 40.6 ± 2.1 mm Hg and in HT-PC it was decreased (P<0.001) to 29.9 ± 5.6 mm Hg, while in HT-EC $P_{ET}CO_2$ was clamped (P<0.001) at 40.5 ± 1.6 mm Hg. During NT-REST, $P_{ET}O_2$ was 101.0 ± 2.7 mm Hg and significantly increased (P<0.001) to 120.5 ± 6.6 mm Hg in NT-PC. During NT-EC $P_{ET}O_2$ was 113.9 ± 8.3 mm Hg, which is significantly decreased (P<0.05) with respect to NT-PC, but significantly increased (P<0.05) with respect to NT-REST.

Mean arterial blood pressure (Table 2.1) decreased (P<0.05) from 106.6 ± 7.2 mm Hg in NT-REST to 87.5 ± 7.0 mm Hg in HT-PC and 89.8 ± 5.6 in HT-EC. As well, MAP in HT-PC and HT-EC was not significantly different (P>0.05).

There was a significant decrease (P<0.05) in MCAv during NT-PC to 77.1 ± 10.6 % of NT-REST. During NT-EC MCAv was significantly increased (P<0.001) with respect to NT-PC to 102.2 ± 5.9 % of NT-REST, and was not significantly different (P>0.05) with respect to NT-REST (Fig. 4A).

During NT-PC, PCAv was significantly decreased ($P<0.001$) to 82.8 ± 11.7 % of NT-REST, then PCAv significantly increased ($P<0.05$) to 101.5 ± 6.8 % of NT-REST in NT-EC, which was not significantly different ($P>0.05$) than NT-REST values.

The BAv significantly decreased ($P<0.001$) during NT-PC to 80.3 ± 5.5 % of NT-REST. During NT-EC, BAv was significantly ($P<0.001$) increased from NT-PC to 101.1 ± 7.4 % of NT-REST, which was not significantly different ($P>0.05$) from NT-REST values.

The $ICVC_{MCA}$ was significantly decreased ($P<0.001$) during NT-PC to 74.1 ± 10.0 % of NT-REST. During NT-EC, $ICVC_{MCA}$ returned to 96.6 ± 8.2 % of NT-REST, which was not significantly different ($P>0.05$) with respect to NT-REST, and was significantly increased ($P<0.001$) with respect to HT-PC.

The $ICVC_{PCA}$ was significantly decreased ($P<0.001$) during NT-PC to 79.5 ± 9.8 % of NT-REST. During NT-EC, $ICVC_{PCA}$ returned to 96.0 ± 9.5 % of NT-REST, which was not significantly different ($P>0.05$) with respect to NT-REST, and was significantly increased ($P<0.001$) with respect to HT-PC.

The $ICVC_{BA}$ was significantly decreased ($P<0.001$) during NT-PC to 77.2 ± 4.6 % of NT-REST. During NT-EC, $ICVC_{BA}$ returned to 95.8 ± 12.0 % of NT-REST, which was not significantly different ($P>0.05$) with respect to NT-REST, and was significantly increased ($P<0.05$) with respect to HT-PC.

The coefficient of variation during NT-REST for MCAv was 14.1%, PCAv was 16.4% and BAv was 7.5%.

3.4 Discussion

The main findings of this study were that there were no significant differences in cerebrovascular responses between cerebral vessels during voluntary hyperventilation, and that the regional differences of the CBV responses found in study 1 are not elicited during volitional normothermic hyperventilation. Firstly, MCAv, PCAv, and BAv exhibited similar responses to normothermic poikilocapnic and normothermic eucapnic voluntary hyperventilation. Secondly, the $ICVC_{MCA}$, $ICVC_{PCA}$, $ICVC_{BA}$ did not exhibit stark differences in their responses to normothermic poikilocapnic and normothermic eucapnic voluntary hyperventilation.

These results indicate that CBV and ICVC exhibit the same responses to voluntary normothermic hyperventilation at the rate evident during hyperthermia (Study 1). The principal mechanism that could explain the decrease in CBV in the MCA, PCA, and BA in NT-PC is that there is a constriction of the cerebral arterioles downstream of the vessels as a result of the decreased P_aCO_2, which would result in an increased resistance to CBV. This is most likely a result of the decreased P_aCO_2 due to the decreased $P_{ET}CO_2$ in NT-PC, and when $P_{ET}CO_2$ was restored in NT-EC, CBV in the MCA, PCA, and BA completely recovered (Fig 3.5). The same responses were also observed in ICVC values of the MCA, PCA, and BA. That being said, MAP increased during voluntary hyperventilation, which would have resulted in an increase in the driving force for CBV on the opposite side of the major vessels as the arterioles.

It could be that, if these results were to be compared with study 1, that there is a decrease in sensitivity of cerebral blood vessels to CO_2 during hyperthermia. These results are comparable to those of other studies (1, 2, 20, 21) that have examined various forms of hyperventilation, though we are not aware of any that attempted to mimic thermal hyperpnea. The results are also consistent with investigations into the behaviour of the BA (Fig 3.4A&C) being consistent with the behaviour of the MCA during periods of decreased $P_{ET}CO_2$ (20, 21).

This study has helped to characterize cerebrovascular responses in the MCA, PCA, and BA in similar conditions to hyperthermia save for the increase in core temperature. Furthermore, the response of MAP to hyperventilation is poorly understood with some observations showing an increase or maintenance (11, 13), while another group reports a decrease (6). The MAP assessment in this study was used along with CBV to calculate ICVC.

Limitations

The TCD only measures CBV, which is an index of CBF. Furthermore, it is assumed that major vessel diameters are unchanged and evidence supports that large cerebral blood vessels do not dilate or constrict during PCO_2 manipulations (22). There was some concern that the lack of randomization of the eucapnic and poikilocapnic conditions would confound the results. Hence, a study of the effect of time of hyperventilation was conducted. There were no evident differences in the results between the poikilocapnic conditions for hyperventilation, as shown in Appendix 5.2.

Future Directions

In the future, studies during normothermic hyperventilation that utilize transcranial Doppler ultrasonography should also include an investigation of the PCA and BA in addition to the commonplace assessments of the MCA. The exact mechanism by which regional differences in cerebrovascular responses occur during hyperthermia is still unclear, although body temperature appears to be central to this mechanism. As well, the variety of MAP responses to hyperventilation that exist in the literature are of particular concern (6, 11, 13). An investigation leading to a more complete understanding of the effects of voluntary hyperventilation on MAP are warranted.

Furthermore, collection of diastolic, systolic, and peak blood velocity data from the TCD would be a valuable study when using the ETF. The effects of eucapnic $P_{ET}CO_2$ clamping with the ETF and diastolic velocity, for example, would represent an interesting study of increased CO_2 on CBV. This could be an area of potential investigation in the future.

Conclusions

This study has demonstrated that there are similar regional differences in cerebrovascular responses during voluntary hyperventilation in normothermia at a $\dot{V}_E$ similar to that seen in hyperthermia. It was hypothesized that CBV and ICVC in the MCA, PCA, and BA would respond in the same way to voluntary hyperventilation. The results of this study suggest that the % changes in CBV were similar in the MCA, PCA, and BA during normothermic voluntary hyperventilation in poikilocapnic and eucapnic conditions. The responses of

ICVC in the MCA, PCA, and BA also appear to be equivalent in nature in these conditions. These results are consistent with the hypothesis that ICVC would be maintained during normothermic eucapnic voluntary hyperventilation in major vessels of the brain.

3.5 References

1. **Ainslie PN, and Duffin J**. Integration of Cerebrovascular CO_2 Reactivity and Chemoreflex Control of Breathing: Mechanisms of Regulation, Measurement, and Interpretation. *Am J Physiol Regul Integr Comp Physiol* 296: 1473-1495, 2009.
2. **Bellapart J, and Fraser JF**. Transcranial Doppler Assessment of Cerebral Autoregulation. *Ultrasound Med Biol* 35: 883-893, 2009.
3. **Brian JE**. Carbon Dioxide and the Cerebral Circulation. *Anesthesiology* 88: 1365-1386, 1998.
4. **Brian JE, Jr., Faraci FM, and Heistad DD**. Recent Insights into the Regulation of Cerebral Circulation. *Clin Exp Pharmacol Physiol* 23: 449-457, 1996.
5. **Brothers RM, Wingo JE, Hubing KA, and Crandall CG**. The Effects of Reduced End-Tidal Carbon Dioxide Tension on Cerebral Blood Flow During Heat Stress. *J Physiol (Lond)* 587: 3921-3927, 2009.
6. **Brown E**. Physiological Effects of Hyperventilation. *Physiol Rev* 33: 445-471, 1953.
7. **Cabanac M, and White MD**. Core Temperature Thresholds for Hyperpnea During Passive Hyperthermia in Humans. *Eur J Appl Physiol Occup Physiol* 71: 71-76, 1995.
8. **Dempsey JA**. Crossing the Apnoeic Threshold: Causes and Consequences. *Exp Physiol* 90: 13-24, 2005.

9. **Fan JL, Cotter JD, Lucas RA, Thomas K, Wilson L, and Ainslie PN**. Human Cardiorespiratory and Cerebrovascular Function During Severe Passive Hyperthermia: Effects of Mild Hypohydration. *J Appl Physiol* 105: 433-445, 2008.

10. **Fujii N, Honda Y, Hayashi K, Kondo N, Koga S, and Nishiyasu T**. Effects of Chemoreflexes on Hyperthermic Hyperventilation and Cerebral Blood Velocity in Resting Heated Humans. *Exp Physiol* 93: 994-1001, 2008.

11. **Grubb RL, Jr., Raichle ME, Eichling JO, and Ter-Pogossian MM**. The Effects of Changes in P_aCO_2 on Cerebral Blood Volume, Blood Flow, and Vascular Mean Transit Time. *Stroke* 5: 630-639, 1974.

12. **Haldane JS**. The Influence of High Air Temperatures: No. 1. *J Hyg (Lond)* 5: 494-513, 1905.

13. **Kety SS, and Schmidt CF**. The Effects of Active and Passive Hyperventilation on Cerebral Blood Flow, Cerebral Oxygen Consumption, Cardiac Output, and Blood Pressure of Normal Young Men. *J Clin Invest* 25: 107-119, 1946.

14. **Kety SS, and Schmidt CF**. The Effects of Altered Arterial Tensions of Carbon Dioxide and Oxygen on Cerebral Blood Flow and Cerebral Oxygen Consumption of Normal Young Men. *J Clin Invest* 27: 484-492, 1948.

15. **Koehle MS, Giles LV, Curtis AN, Walsh ML, and White MD**. Performance of a Compact End-Tidal Forcing System. *Respir Physiol Neurobiol* 167: 155-161, 2009.

16. **Mekjavic IB, and Rempel ME**. Determination of Esophageal Probe Insertion Length Based on Standing and Sitting Height. *J Appl Physiol* 69: 376-379, 1990.

17. **Nelson MD, Haykowsky MJ, Stickland MK, Altamirano-Diaz LA, Willie CK, Smith KJ, Petersen SR, and Ainslie PN**. Reductions in Cerebral Blood Flow During Passive Heat Stress in Humans: Partitioning the Mechanisms. *J Physiol* 589: 4053-4064, 2011.

18. **Nichols WW, and O'Rourke MF**. Ultrasonic Blood Flow and Velocitometry. In: *Mcdonald's Blood Flow in Arteries*. London: Hodder Arnold, 2005, p. 151-163.

19. **Nybo L, and Nielsen B**. Middle Cerebral Artery Blood Velocity Is Reduced with Hyperthermia During Prolonged Exercise in Humans. *J Physiol (Lond)* 534: 279-286, 2001.

20. **Ogoh S, Nakahara H, Ainslie PN, and Miyamoto T**. The Effect of Oxygen on Dynamic Cerebral Autoregulation: Critical Role of Hypocapnia. *J Appl Physiol* 108: 538-543, 2010.

21. **Park CW, Sturzenegger M, Douville CM, Aaslid R, and Newell DW**. Autoregulatory Response and CO_2 Reactivity of the Basilar Artery. *Stroke* 34: 34-39, 2003.

22. **Serrador JM, Picot PA, Rutt BK, Shoemaker JK, and Bondar RL**. Mri Measures of Middle Cerebral Artery Diameter in Conscious Humans During Simulated Orthostasis. *Stroke* 31: 1672-1678, 2000.

23. **Wasserman AJ, and Patterson JL, Jr.** The Cerebral Vascular Response to Reduction in Arterial Carbon Dioxide Tension. *J Clin Invest* 40: 1297-1303, 1961.

24. **West JB**. Control of Ventilation - How Gas Exchange Is Regulated. In: *Respiratory Physiology: The Essentials*. Philadelphia, PA.: Lippincott Williams & Wilkins, 2008, p. 123-138.

3.6 Tables

Table 3.1: Participants' (n=8) individual sex, age, height, and weight as well as corresponding group means and standard deviations for each given physical characteristic.

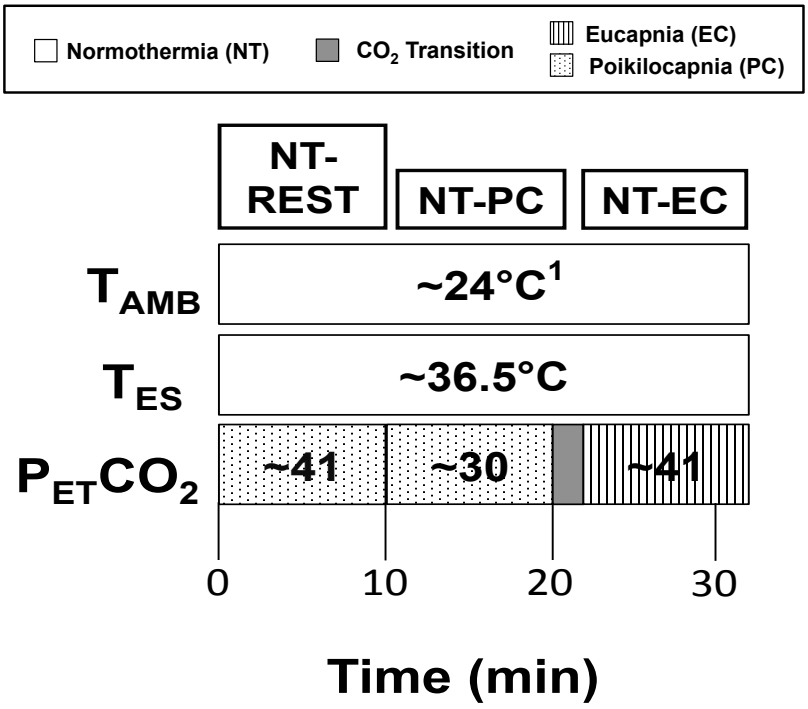
Participant	Sex	Age (y)	Height (m)	Weight (kg)
1	M	27	1.85	81
2	M	24	1.83	85
3	M	23	1.83	86
4	M	20	1.88	100
5	M	21	1.76	79
6	M	22	1.90	90
7	M	23	1.75	74
8	M	20	1.69	73
Mean		23	1.81	84
SD		2	0.07	9

Table 3.2: Participants' (n=8) mean arterial pressure (MAP, mm Hg) responses in normothermic rest (NT-REST), normothermic poikilocapnia (NT-PC), and normothermic eucapnia (NT-EC). † = P < 0.001, * = P < 0.05, NS = P > 0.05.

Participant	MAP NT-REST	MAP NT-PC	MAP NT-EC
1	99.9	102.6	107.6
2	104.9	109.6	115.6
3	106.7	111.1	117.1
4	102.4	100.6	104.9
5	107.0	112.7	107.1
6	105.0	109.4	118.7
7	119.4	121.4	116.3
8	107.6	116.5	116.6
Mean	106.6	110.5	113.0
S.D.	5.8	6.8	5.5
	†	NS	
	*		

3.7 Figures

Figure 3.1: Study 2 Protocol; experimental trial conditions with ambient temperature (T_{AMB}), esophageal temperature (T_{ES}), and the end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$). Time periods are provided when cerebrovascular responses were assessed including normothermic rest (NT-REST), normothermic poikilocapnia (NT-PC), and normothermic eucapnia (NT-EC).



[1]25% Relative huminidity

Figure 3.2: Mean values of esophageal temperature (T_{ES}; A) and mean skin temperature ($\bar{T}_{SK}$; B) for all participants (n=8) in normothermic rest (NT-REST), normothermic poikilocapnic (NT-PC) and normothermic eucapnic (NT-EC). NS = P > 0.05. For all figures, error bars indicate 1 SD.

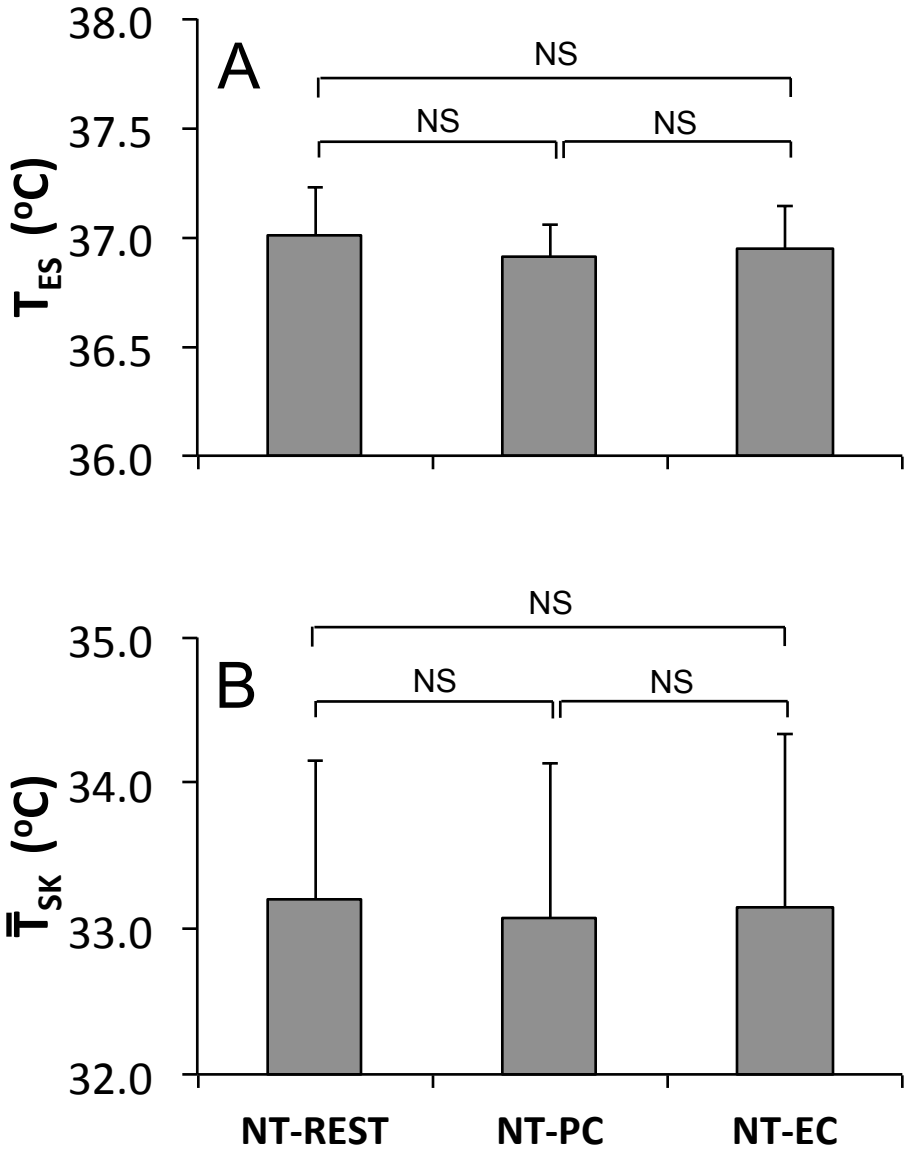


Figure 3.3: Mean values of pulmonary ventilation ($\dot{V}_E$; A), end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$; B), and end-tidal partial pressure of oxygen ($P_{ET}O_2$; C) for all participants (n=8) during normothermic rest (NT-REST), normothermic poikilocapnia (NT-PC) and normothermic eucapnia (NT-EC).
† = P < 0.001, * = P < 0.05, NS = P > 0.05.

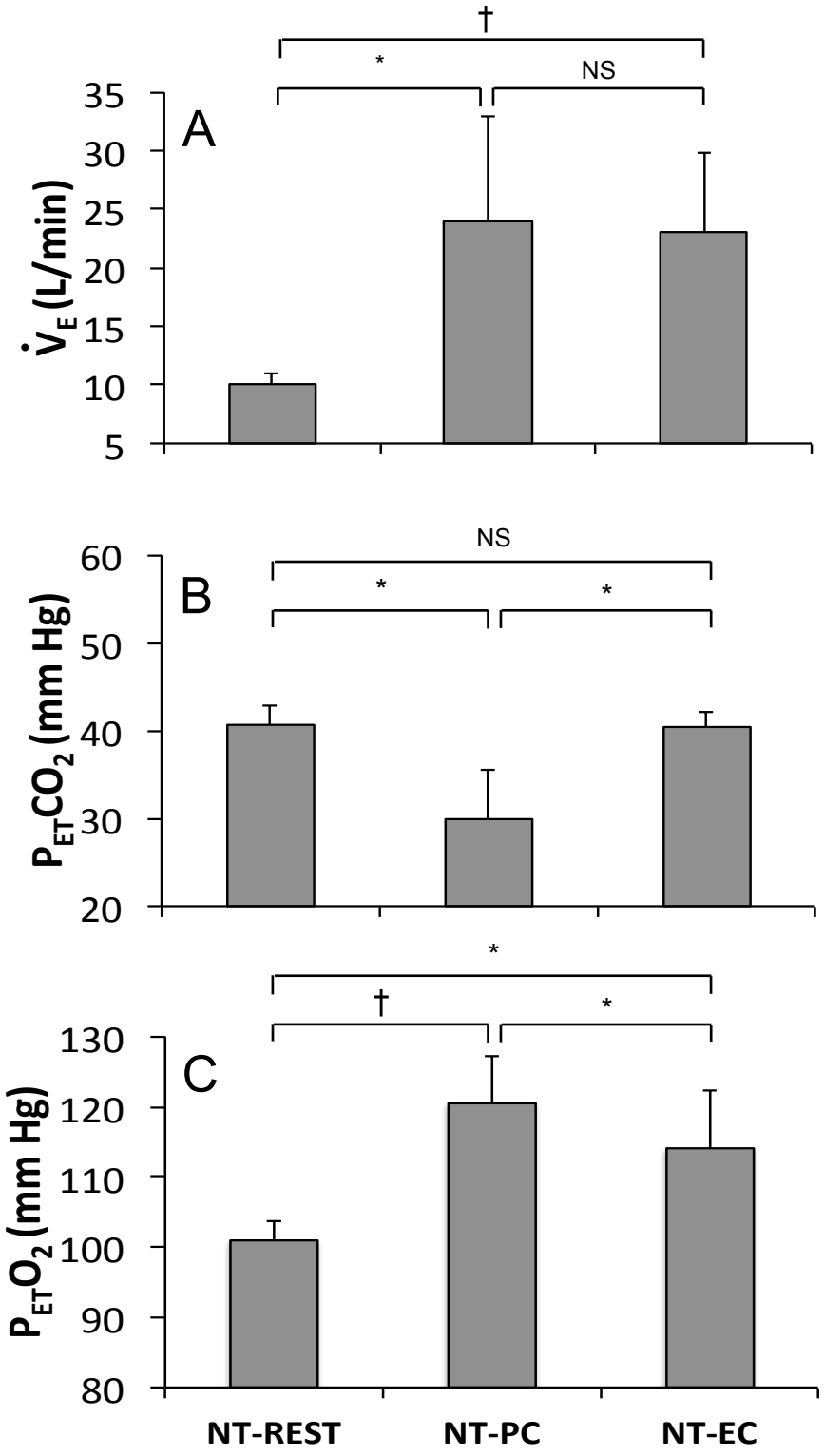


Figure 3.4: Mean percentage values of normothermic rest (NT-REST) of the middle cerebral artery mean blood velocity (MCAv; A), posterior cerebral artery mean blood velocity (PCAv; B), and basilar artery mean blood velocity (BAv; C) for all participants (n=8) during normothermic poikilocapnia (NT-PC) and normothermic eucapnia (NT-EC). † = P <0.001, NS = P > 0.05.

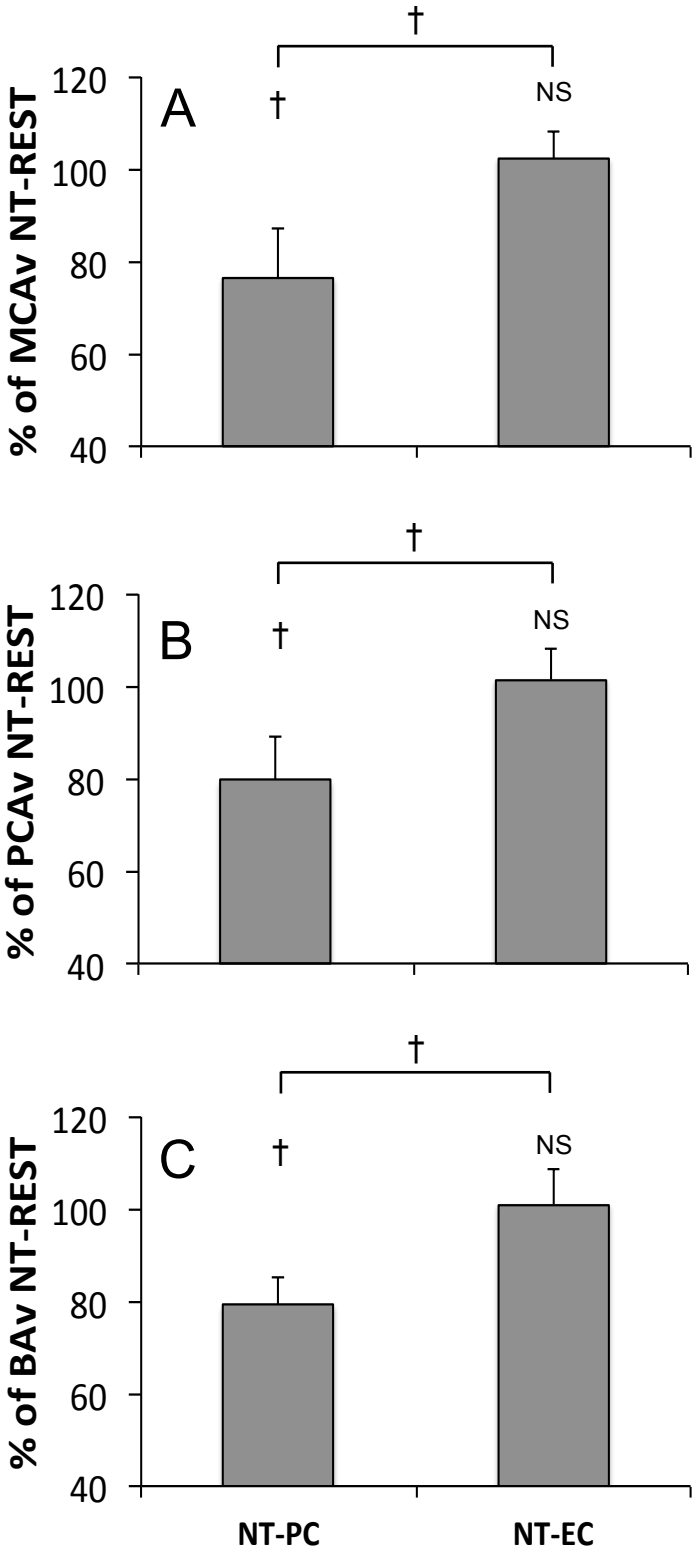
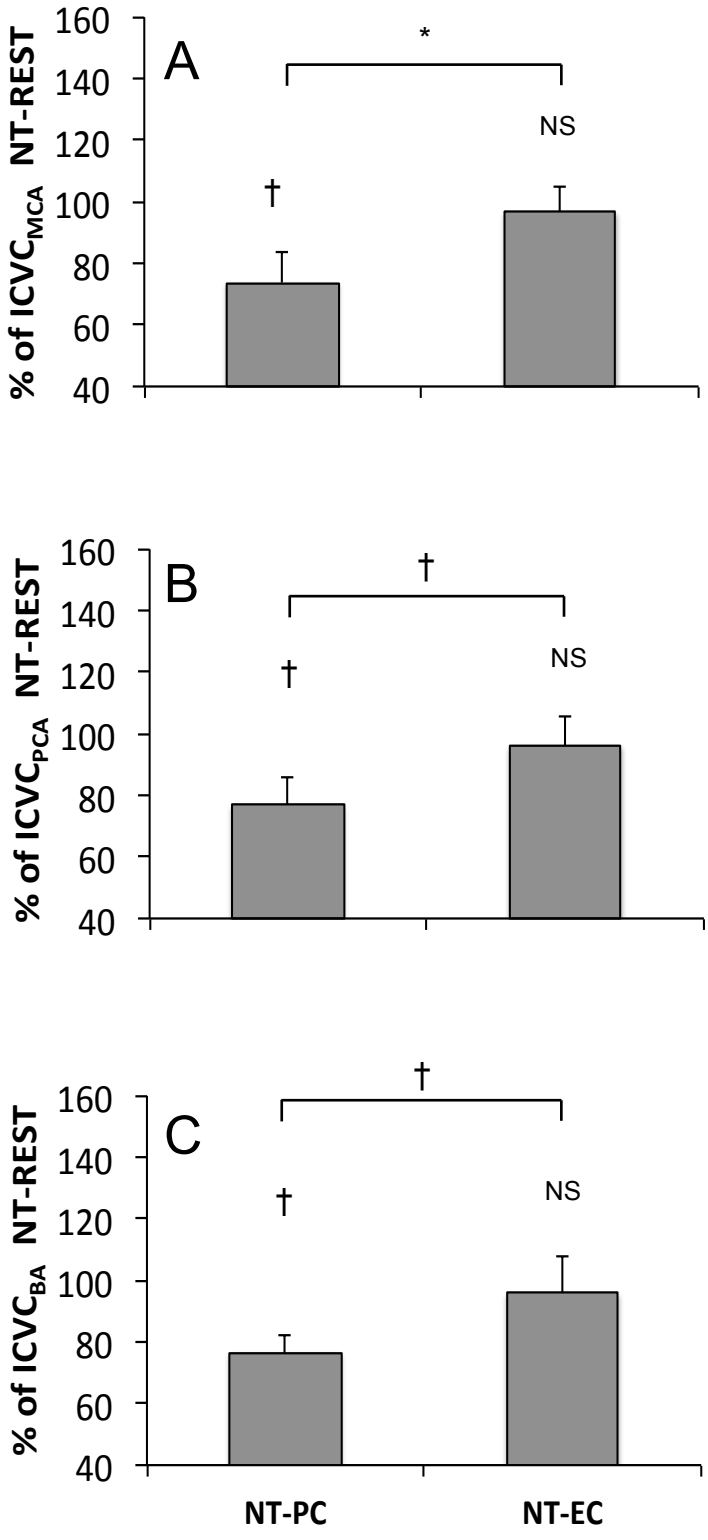


Figure 3.5: Indices of cerebrovascular conductance (ICVC, cm•s^{-1}•mm Hg^{-1}) expressed as a percentage of normothermic rest (NT-REST) in the middle cerebral artery (MCA; A), posterior cerebral artery (PCA; B), and basilar artery (BA; C) for all participants (n=8) during normothermic poikilocapnia (NT-PC) and hyperthermic eucapnia (NT-EC). † = P <0.001, * = P < 0.05, NS = P > 0.05.



CHAPTER FOUR: RESPONSES TO RESEARCH HYPOTHESES AND TESTABLE QUESTIONS

4.1 Responses to Hypotheses

Study 1: Thermal Hyperpnea and Temperature-Dependent Regional Differences in Cerebrovascular Responses in Humans

H1: The ICVC in the MCA will be maintained during poikilocapnic and eucapnic hyperthermia.

A1: The ICVC in the MCA was maintained during eucapnic hyperthermia, but not in poikilocapnic hyperthermia.

H2: During hyperthermia ICVC in the BA and PCA will not change or will increase.

A2: During hyperthermia ICVC in the BA and PCA did not change.

Study 2: Effects of Poikilocapnic and Eucapnic Voluntary Hyperventilation on Cerebrovascular Responses in Normothermic Humans

H1: During normothermia CBV and ICVC in the MCA, PCA, and BA will decrease during voluntary hyperventilation and hypocapnia.

A1: During normothermia CBV and ICVC in the MCA, PCA, and BA decreased during voluntary hyperventilation and hypocapnia.

H2: During normothermia, while controlling $P_{ET}CO_2$ at a eucapnic partial pressure and maintaining voluntary hyperventilation, CBV and ICVC in the MCA, PCA, and BA will return to normal resting values.

A2: During normothermia, while controlling $P_{ET}CO_2$ at a eucapnic partial pressure and maintaining voluntary hyperventilation, CBV and ICVC in the MCA, PCA, and BA returned to normal resting values.

4.2 Responses to Testable Questions

Study 1: Thermal Hyperpnea and Temperature-Dependent Regional Differences in Cerebrovascular Responses in Humans

Q1: Does passive poikilocapnic hyperthermia result in maintenance of MCA cerebral conductance? Is this MCA ICVC restored to resting values during eucapnic hyperthermia?

A1: Passive poikilocapnic hyperthermia results in a decrease of cerebral conductance, while ICVC in the MCA is restored in eucapnic hyperthermia.

Q2: Does passive poikilocapnic and eucapnic hyperthermia result in changes in PCA and BA ICVC that are parallel to changes in the MCA ICVC?

A2: Passive poikilocapnic and eucapnic hyperthermia does not result in changes in PCA and BA ICVC that are parallel to changes in MCA ICVC.

Study 2: Effects of Poikilocapnic and Eucapnic Voluntary Hyperventilation on Cerebrovascular Responses in Normothermic Humans

Q1: Does normothermic voluntary hyperventilation decrease CBV and ICVC in the MCA, PCA, and BA?

A1: Normothermic voluntary hyperventilation decreased CBV and ICVC in the MCA, PCA, and BA.

Q2: Does normothermic voluntary hyperventilation with eucapnic $P_{ET}CO_2$ result in a full restoration of CBV and ICVC in the MCA, PCA, and BA to normothermic resting values?

A2: Normothermic voluntary hyperventilation with eucapnic $P_{ET}CO_2$ restored CBV and ICVC in the MCA, PCA, and BA to normothermic resting values.

CHAPTER FIVE: OVERALL REFERENCE LIST

Ainslie PN, and Duffin J. Integration of Cerebrovascular CO_2 Reactivity and Chemoreflex Control of Breathing: Mechanisms of Regulation, Measurement, and Interpretation. *Am J Physiol Regul Integr Comp Physiol* 296: 1473-1495, 2009.

Asmussen E, and Nielsen M. Ventilatory Response to CO_2 During Work at Normal and at Low Oxygen Tensions. *Acta Physiol Scand* 39: 27-35, 1957.

Barker SJ, Hyatt J, Clarke C, and Tremper KK. Hyperventilation Reduces Transcutaneous Oxygen Tension and Skin Blood Flow. *Anesthesiology* 75: 619-624, 1991.

Bellapart J, and Fraser JF. Transcranial Doppler Assessment of Cerebral Autoregulation. *Ultrasound Med Biol* 35: 883-893, 2009.

Berne RM. The Cardiovascular System. In: *Principles of Physiology*, edited by Berne RM, Levy MN, Stanton BA, and Koeppen BM. St. Louis, MO: Mosby Inc., 1990, p. 454.

Bjurstedt H, Hesser CM, Liljestrand G, and Matell G. Effects of Posture on Alveolar-Arterial CO_2 and O_2 Differences and on Alveolar Dead Space in Man. *Acta Physiol Scand* 54: 65-82, 1962.

Blaber A, and Hughson R. Cardiorespiratory Interactions During Fixed-Pace Resistive Breathing. *J Appl Physiol* 80: 1618-1626, 1996

Bligh J, and Johnson KG. Glossary of Terms for Thermal Physiology. *J Appl Physiol* 35: 941-961, 1973.

Boden AG, Harris MC, and Parkes MJ. The Preoptic Area in the Hypothalamus Is the Source of the Additional Respiratory Drive at Raised Body Temperature in Anaesthetised Rats. *Exp Physiol* 85: 527-537, 2000.

Boden AG, Harris MC, and Parkes MJ. A Respiratory Drive in Addition to the Increase in CO_2 Production at Raised Body Temperature in Rats. *Exp Physiol* 85: 309-319, 2000.

Boggs D, and Tenney S. Scaling Respiratory Pattern and Respiratory Drive. *Respir Physiol* 58: 245-251, 1984.

Boggs DF. Comparative Control of Respiration. In: *Treatise on Pulmonary Toxicology: Comparative Biology of the Normal Lung*, edited by Parent RA. Boca Raton, FL: CRC Press, Inc., 1992, p. 309-349.

Brian JE. Carbon Dioxide and the Cerebral Circulation. *Anesthesiology* 88: 1365-1386, 1998.

Brian JE, Jr., Faraci FM, and Heistad DD. Recent Insights into the Regulation of Cerebral Circulation. *Clin Exp Pharmacol Physiol* 23: 449-457, 1996.

Brothers RM, Wingo JE, Hubing KA, and Crandall CG. The Effects of Reduced End-Tidal Carbon Dioxide Tension on Cerebral Blood Flow During Heat Stress. *J Physiol (Lond)* 587: 3921-3927, 2009.

Brown E. Physiological Effects of Hyperventilation. *Physiol Rev* 33: 445-471, 1953.

Brusilow SW, and Gordes EH. Ammonia Secretion in Sweat. *Am J Physiol* 214: 513-517, 1968.

Cabanac M. Selective Brain Cooling in Humans: "Fancy" or Fact? *FASEB J* 7: 1143-1147, 1993.

Cabanac M, and Brinnel H. Blood Flow in the Emissary Veins of the Human Head During Hyperthermia. *Eur J Appl Physiol* 54: 172-176, 1985.

Cabanac M, and Caputa M. Natural Selective Cooling of the Human Brain: Evidence of Its Occurrence and Magnitude. *J Physiol* 286: 255-264, 1979.

Cabanac M, and Massonnet B. Thermoregulatory Responses as a Function of Core Temperature in Humans. *J Physiol (Lond)* 265: 587-596, 1977.

Cabanac M, and White M. Heat Loss from the Upper Airways and Selective Brain Cooling in Humans. *Ann N Y Acad Sci* 813: 613-616, 1997.

Cabanac M, and White MD. Core Temperature Thresholds for Hyperpnea During Passive Hyperthermia in Humans. *Eur J Appl Physiol Occup Physiol* 71: 71-76, 1995.

Caputa M. Selective Brain Cooling: A Multiple Regulatory Mechanism. *J Therm Biol* 29: 691-702, 2004.

Caputa M, Perrin G, and Cabanac M. [Reversal of Human Ophthalmic Vein Blood Flow : Selective Cooling of the Brain]. *C R Acad Sci Hebd Seances Acad Sci D* 287: 1011-1014, 1978.

Carey BJ, Eames PJ, Panerai RB, and Potter JF. Carbon Dioxide, Critical Closing Pressure and Cerebral Haemodynamics Prior to Vasovagal Syncope in Humans. *Clin Sci* 101: 351-358, 2001.

Chambers WW, Seigel MS, Liu JC, and Liu CN. Thermoregulatory Responses of Decerebrate and Spinal Cats. *Exp Neurol* 42: 282-299, 1974.

Charkoudian N. Skin Blood Flow in Adult Human Thermoregulation: How It Works, When It Does Not, and Why. In: *Mayo Clinic* 2003, p. 603-612.

Clyde BL, Resnick DK, Yonas H, Smith HA, and Kaufmann AM. The Relationship of Blood Velocity as Measured by Transcranial Doppler Ultrasonography to Cerebral Blood Flow as Determined by Stable Xenon Computed Tomographic Studies after Aneurysmal Subarachnoid Hemorrhage. *Neurosurgery* 38: 896-896, 1996.

Crandall CG, Cui J, and Wilson TE. Effects of Heat Stress on Baroreflex Function in Humans. *Acta Physiol Scand* 177: 321-328, 2003.

Cremer OL, and Kalkman CJ. Cerebral Pathophysiology and Clinical Neurology of Hyperthermia in Humans. *Prog Brain Res* 162: 153-169, 2007.

Cunningham D, Howson M, Metias E, and Petersen E. Patterns of Breathing in Response to Alternating Patterns of Alveolar Carbon Dioxide Pressures in Man. *J Physiol (Lond)* 376: 31-45, 1986.

Curtis AN, Walsh ML, and White MD. Influence of Passive Hyperthermia on Human Ventilation During Rest and Isocapnic Hypoxia. *Appl Physiol Nutr Me* 32: 721-732, 2007.

Czosnyka M, and Pickard J. Monitoring and Interpretation of Intracranial Pressure. *J Neurol Neurosur Ps* 75: 813-821, 2004.

Dawson SL, Blake MJ, Panerai RB, and Potter JF. Dynamic but Not Static Cerebral Autoregulation Is Impaired in Acute Ischaemic Stroke. *Cerebrovasc Dis* 10: 126-132, 2000.

Dempsey JA. Crossing the Apnoeic Threshold: Causes and Consequences. *Exp Physiol* 90: 13-24, 2005.

Edvinsonn L KD. *Cerebral Blood Flow and Metabolism*. Philadelphia: Lippincott, Williams & Wilkins, 2002, p. 510.

Fan JL, Cotter JD, Lucas RA, Thomas K, Wilson L, and Ainslie PN. Human Cardiorespiratory and Cerebrovascular Function During Severe Passive Hyperthermia: Effects of Mild Hypohydration. *J Appl Physiol* 105: 433-445, 2008.

Fujii N, Honda Y, Hayashi K, Kondo N, Koga S, and Nishiyasu T. Effects of Chemoreflexes on Hyperthermic Hyperventilation and Cerebral Blood Velocity in Resting Heated Humans. *Exp Physiol* 93: 994-1001, 2008.

Fujii N, Honda Y, Hayashi K, Kondo N, and Nishiyasu T. Effect of Hypohydration on Hyperthermic Hyperpnea and Cutaneous Vasodilation During Exercise in Men. *J Appl Physiol* 105: 1509-1518, 2008.

Fujii N, Honda Y, Hayashi K, Soya H, Kondo N, and Nishiyasu T. Comparison of Hyperthermic Hyperpnea Elicited During Rest and Submaximal, Moderate-Intensity Exercise. *J Appl Physiol* 104: 998-1005, 2008.

Gaudio R, Jr., and Abramson N. Heat-Induced Hyperventilation. *J Appl Physiol* 25: 742-746, 1968.

Gitlitz PH, Sunderman Jr FW, and Hohnadel DC. Ion-Exchange Chromatography of Amino Acids in Sweat Collected from Healthy Subjects During Sauna Bathing. *Clin Chem* 20: 1305-1312, 1974.

Grubb RL, Jr., Raichle ME, Eichling JO, and Ter-Pogossian MM. The Effects of Changes in P_aCO_2 on Cerebral Blood Volume, Blood Flow, and Vascular Mean Transit Time. *Stroke* 5: 630-639, 1974.

Haines DE. *Neuroanatomy: An Atlas of Structures, Sections, and Systems*. Philadelphia, PA: Lippincott Williams & Wilkins, 2000, p. 256.

Haldane JS. The Influence of High Air Temperatures: No. 1. *J Hyg (Lond)* 5: 494-513, 1905.

Haldane JS, and Priestley JG. The Regulation of the Lung-Ventilation. *J Physiol (Lond)* 32: 225-266, 1905.

Harrison MR, Clifton GD, Penneil AT, and DeMaria AN. Effect of Heart Rate on Left Ventricular Diastolic Transmitral Flow Velocity Patterns Assessed by Doppler Echocardiography in Normal Subjects. *Am J Card* 67: 622-627, 1991.

Havenith G, Luttikholt VGM, and Vrijkotte TGM. The Relative Influence of Body Characteristics on Humid Heat Stress Response. *Eur J Appl Physiol* 70: 270-279, 1995.

Hayashi K, Honda Y, Miyakawa N, Fujii N, Ichinose M, Koga S, Kondo N, and Nishiyasu T. Effect of CO_2 on the Ventilatory Sensitivity to Rising Body Temperature During Exercise. *J Appl Physiol* 110: 1334-1341, 2011.

Huschak G, Hoell T, Wiegel M, Hohaus C, Stuttmann R, Meisel HJ, and Mast H. Does Brain Temperature Correlate with Intracranial Pressure? *Journal of Neurosurgical Anesthesiology* 20: 105-109, 2008.

Ito T, Moore JI, and Koss MC. Topical Application of CO_2 Increases Skin Blood Flow. *J Invest Dermatol* 93: 259-262, 1989.

Johnson JM, Brengelmann GL, Hales JR, Vanhoutte PM, and Wenger CB. Regulation of the Cutaneous Circulation. *Fed Proc* 45: 2841-2850, 1986.

Johnson JM, and Proppe DW. Cardiovascular Adjustments to Heat Stress. In: *Handbook of Physiology*, edited by Fregly MJ, and Blatteis CM. New York, NY: Oxford University Press, 1996, p. 215-243.

Jones R, and Berne R. Local Regulation of Blood Flow in Skeletal Muscle. *Circ Res* 15: 126-138, 1964.

Kamijo YI, Lee K, and Mack GW. Active Cutaneous Vasodilation in Resting Humans During Mild Heat Stress. *J Appl Physiol* 98: 829-837, 2005.

Kellogg D. In Vivo Mechanisms of Cutaneous Vasodilation and Vasoconstriction in Humans During Thermoregulatory Challenges. *J Appl Physiol* 100: 1709-1718, 2006.

Kellogg Jr DL, Pergola PE, Piest KL, Kosiba WA, Crandall CG, Grossmann M, and Johnson JM. Cutaneous Active Vasodilation in Humans Is Mediated by Cholinergic Nerve Cotransmission. *Circ Res* 77: 1222-1228, 1995.

Kety SS, and Schmidt CF. The Effects of Active and Passive Hyperventilation on Cerebral Blood Flow, Cerebral Oxygen Consumption, Cardiac Output, and Blood Pressure of Normal Young Men. *J Clin Invest* 25: 107-119, 1946.

Kety SS, and Schmidt CF. The Effects of Altered Arterial Tensions of Carbon Dioxide and Oxygen on Cerebral Blood Flow and Cerebral Oxygen Consumption of Normal Young Men. *J Clin Invest* 27: 484-492, 1948.

Koehle MS, Giles LV, Curtis AN, Walsh ML, and White MD. Performance of a Compact End-Tidal Forcing System. *Respir Physiol Neurobiol* 167: 155-161, 2009.

Koroxenidis GT, Shepherd JT, and Marshall RJ. Cardiovascular Response to Acute Heat Stress. *J Appl Physiol* 16: 869-872, 1961.

Landis E, Long W, Dunn J, Jackson C, and Meyer U. Studies on the Effects of Baths on Man: III. Effects of Hot Baths on Respiration, Blood and Urine. *American Journal of Physiology--Legacy Content* 76: 35-48, 1926.

Lassen NA. Cerebral Blood Flow and Oxygen Consumption in Man. *Physiol Rev* 39: 183-238, 1959.

Lim PK, and Grodins FS. Control of Thermal Panting. *Am J Physiol* 180: 445-449, 1955.

Marieb EN, and Hoehn K. *Human Anatomy & Physiology*. San Fransisco, CA: Pearson Education, 2010, p. 1156.

Martini FH. Blood Vessels and Circulation. In: *Fundamentals of Anatomy and Physiology*. San Fransisco, CA: Benjamin Cummings, 2006, p. 708-757.

Martini FH. The Brain and Cranial Nerves. In: *Fundamentals of Anatomy and Physiology*. San Fransisco, CA: Benjamin Cummings, 2006, p. 452-478.

Martini FH. The Respiratory System. In: *Fundamentals of Anatomy and Physiology*. San Fransisco, CA: Benjamin Cummings, 2006, p. 813-856.

McDonald PLL. *Effects of Hyperthermia on Human Middle Cerebral, Posterior Cerebral, and Basilar Artery Blood Velocities During Eucapnia*. Undergraduate Thesis. In: Biomedical Physiology and Kinesiology. Burnaby, BC.: Simon Fraser University, 2011, p. 80.

Mekjavic IB, and Rempel ME. Determination of Esophageal Probe Insertion Length Based on Standing and Sitting Height. *J Appl Physiol* 69: 376-379, 1990.

Mercer J, and Werner J. Glossary of Terms for Thermal Physiology. *Jpn J Physiol* 51: 245-280, 2001.

Milic-Emili J, Whitelaw W, and Grassino A. Measurement and Testing of Respiratory Drive. In: *Lung Biology in Health and Disease Regulation of Breathing*, edited by Hozbein T. NY, New York: Marcel Dekker, 1981, p. 675-743.

Miller JD, Pegelow DF, Jacques AJ, and Dempsey JA. Skeletal Muscle Pump Versus Respiratory Muscle Pump: Modulation of Venous Return from the Locomotor Limb in Humans. *J Physiol (Lond)* 563: 925-943, 2005.

Mitchell D, Wyndham C, Atkins A, Vermeulen A, Hofmeyr H, Strydom N, and Hodgson T. Direct Measurement of the Thermal Responses of Nude Resting Men in Dry Environments. *Pflugers Archiv: Eur J Physiol* 303: 324-343, 1968.

Moran DS, Shitzer A, and Pandolf KB. A Physiological Strain Index to Evaluate Heat Stress. *Am J Physiol-Reg I* 275: 129-134, 1998.

Nadel ER, Bullard RW, and Stolwijk JA. Importance of Skin Temperature in the Regulation of Sweating. *J Appl Physiol* 31: 80-87, 1971.

Nattie E. Julius H. Comroe, Jr., Distinguished Lecture: Central Chemoreception: Then ... And Now. *J Appl Physiol* 110: 1-8, 2011.

Nelson MD, Haykowsky MJ, Stickland MK, Altamirano-Diaz LA, Willie CK, Smith KJ, Petersen SR, and Ainslie PN. Reductions in Cerebral Blood Flow During Passive Heat Stress in Humans: Partitioning the Mechanisms. *J Physiol* 589: 4053-4064, 2011.

Nichols WW, and O'Rourke MF. Ultrasonic Blood Flow and Velocitometry. In: *Mcdonald's Blood Flow in Arteries*. London: Hodder Arnold, 2005, p. 151-163.

Nielsen M, and Smith H. Studies on the Regulation of Respiration in Acute Hypoxia; with a Appendix on Respiratory Control During Prolonged Hypoxia. *Acta Physiol Scand* 24: 293-313, 1952.

Novak V, Spies JM, Novak P, McPhee BR, Rummans TA, and Low PA. Hypocapnia and Cerebral Hypoperfusion in Orthostatic Intolerance. *Stroke* 29: 1876-1881, 1998.

Nybo L, and Nielsen B. Middle Cerebral Artery Blood Velocity Is Reduced with Hyperthermia During Prolonged Exercise in Humans. *J Physiol (Lond)* 534: 279-286, 2001.

Ogawa S, Handa N, Matsumoto M, Etani H, Yoneda S, Kimura K, and Kamada T. Carbondioxide Reactivity of the Blood Flow in Human Basilar Artery Estimated by the Transcranial Doppler Method in Normal Men: A Comparison with That of the Middle Cerebral Artery. *Ultrasound Med Biol* 14: 479-483, 1988.

Ogoh S, Nakahara H, Ainslie PN, and Miyamoto T. The Effect of Oxygen on Dynamic Cerebral Autoregulation: Critical Role of Hypocapnia. *J Appl Physiol* 108: 538-543, 2010.

Pallavicini JC, Gabriel O, Sant'Agnese PA, and Buskirk ER. Isolation and Characterization of Carbohydrate Protein Complexes from Human Sweat. *Ann N Y Acad Sci* 106: 330-338, 1963.

Park CW, Sturzenegger M, Douville CM, Aaslid R, and Newell DW. Autoregulatory Response and CO_2 Reactivity of the Basilar Artery. *Stroke* 34: 34-39, 2003.

Paulson OB, Strandgaard S, and Edvinsson L. Cerebral Autoregulation. *Cerebrovasc Brain Metab Rev* 2: 161-192, 1990.

Peebles K, Celi L, McGrattan K, Murrell C, Thomas K, and Ainslie PN. Human Cerebrovascular and Ventilatory CO_2 Reactivity to End-Tidal, Arterial and Internal Jugular Vein PCO_2. *J Physiol (Lond)* 584: 347-357, 2007.

Pergola PE, Kellogg DL, Jr., Johnson JM, and Kosiba WA. Reflex Control of Active Cutaneous Vasodilation by Skin Temperature in Humans. *Am J Physiol* 266: H1979-1984, 1994.

Potts JT, Shi XR, and Raven PB. Carotid Baroreflex Responsiveness During Dynamic Exercise in Humans. *Am J Physiol-Heart C* 265: 1928-1938, 1993.

Poulin MJ, Liang PJ, and Robbins PA. Fast and Slow Components of Cerebral Blood Flow Response to Step Decreases in End-Tidal in Humans. *J Appl Physiol* 85: 388-397, 1998.

Randall WC, and Kimura KK. The Pharmacology of Sweating. *Pharmacol Rev* 7: 365-397, 1955.

Rasch W, Samson P, Cote J, and Cabanac M. Heat Loss from the Human Head During Exercise. *J Appl Physiol* 71: 590-595, 1991.

Raven PB, Fadel PJ, and Ogoh S. Arterial Baroreflex Resetting During Exercise: A Current Perspective. *Exp Physiol* 91: 37-49, 2006.

Richards SA. The Biology and Comparative Physiology of Thermal Panting. *Biol Rev Camb Philos Soc* 45: 223-264, 1970.

Robertshaw D. Mechanisms for the Control of Respiratory Evaporative Heat Loss in Panting Animals. *J Appl Physiol* 101: 664-668, 2006.

Roddie IC, Shepherd JT, and Whelan RF. The Contribution of Constrictor and Dilator Nerves to the Skin Vasodilatation During Body Heating. *J Physiol* 136: 489-497, 1957.

Rossi S, Zanier ER, Mauri I, Columbo A, and Stocchetti N. Brain Temperature, Body Core Temperature, and Intracranial Pressure in Acute Cerebral Damage. *J Neurol Neurosurg Psychiatry* 71: 448-454, 2001.

Salamon G, and Huang YP. *Radiologic Anatomy of the Brain*. New York: Springer-Verlag, 1976, p. 404.

Sato K. The Physiology, Pharmacology, and Biochemistry of the Eccrine Sweat Gland. *Rev Physiol Biochem Pharmacol* 79: 51-131, 1977.

Saxton C. Effects of Severe Heat Stress on Respiration and Metabolic Rate in Resting Man. *Aviat Space Envir Md* 52: 281-286, 1981.

Sechzer P, Egbert L, Linde H, Cooper D, Dripps R, and Price H. Effect of Co2 Inhalation on Arterial Pressure, ECG and Plasma Catecholamines and 17-Oh Corticosteroids in Normal Man. *J Appl Physiol* 15: 454-458, 1960.

Serrador JM, Picot PA, Rutt BK, Shoemaker JK, and Bondar RL. Mri Measures of Middle Cerebral Artery Diameter in Conscious Humans During Simulated Orthostasis. *Stroke* 31: 1672-1678, 2000.

Snellen J, Mitchell D, and Wyndham C. Heat of Evaporation of Sweat. *J Appl Physiol* 29: 40-44, 1970.

Somers VK, Mark AL, and Abboud FM. Sympathetic Activation by Hypoxia and Hypercapnia-Implications for Sleep Apnea. *Clin Exp Hypertens* 10: 413-422, 1988.

Strandgaard S, and Paulson OB. Cerebral Autoregulation. *Stroke* 15: 413-416, 1984.

Szabo G. The Number of Eccrine Sweat Glands in Human Skin. *Adv Biol Skin* 3: 1-5, 1962.

Taylor WF, Johnson JM, O'Leary D, and Park MK. Effect of High Local Temperature on Reflex Cutaneous Vasodilation. *J Appl Physiol* 57: 191-196, 1984.

Toda N, and Okamura T. Cerebral Vasodilators. *Jpn J Pharmacol* 76: 349-367, 1998.

Van Lieshout JJ, and Secher NH. Point: Counterpoint: Sympathetic Activity Does/Does Not Influence Cerebral Blood Flow. *J Appl Physiol* 105: 1364-1366, 2008.

Wasserman AJ, and Patterson JL, Jr. The Cerebral Vascular Response to Reduction in Arterial Carbon Dioxide Tension. *J Clin Invest* 40: 1297-1303, 1961.

Weiner J. The Regional Distribution of Sweating. *J Physiol (Lond)* 104: 32-40, 1945.

West JB. Control of Ventilation - How Gas Exchange Is Regulated. In: *Respiratory Physiology: The Essentials*. Philadelphia, PA.: Lippincott Williams & Wilkins, 2008, p. 123-138.

Whipp BJ, and Pardy RL. Breathing During Exercise. In: *Comprehensive Physiology*, edited by Terjung R. San Fransisco, CA: John Wiley & Sons, Inc., 2008, p. 605-629.

White MD. Components and Mechanisms of Thermal Hyperpnea. *J Appl Physiol* 101: 655-663, 2006.

White MD, and Cabanac M. Exercise Hyperpnea and Hyperthermia in Humans. *J Appl Physiol* 81: 1249-1254, 1996.

White MD, and Cabanac M. Nasal Mucosal Vasodilatation in Response to Passive Hyperthermia in Humans. *Eur J Appl Physiol Occup Physiol* 70: 207-212, 1995.

White MD, Greiner JG, and McDonald PLL. Point: Counterpoint "Humans Do/Do Not Demonstrate Selective Brain Cooling During Hyperthermia.". *J Appl Physiol* 110: 569-574, 2011.

Willie CK, Macleod DB, Shaw AD, Smith KJ, Tzeng YC, Eves ND, Ikeda K, Graham J, Lewis NC, and Day TA. Regional Brain Blood Flow in Man During Acute Changes in Arterial Blood Gases. *J Physiol (Lond)* 2012.

Willis I, Harris DR, and Moretz W. Normal and Abnormal Variations in Eccrine Sweat Gland Distribution. *J Invest Dermatol* 60: 98-103, 1973.

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.

Zhang R, Zuckerman JH, Iwasaki K, Wilson TE, Crandall CG, and Levine BD. Autonomic Neural Control of Dynamic Cerebral Autoregulation in Humans. *Circulation* 106: 1814-1820, 2002.

CHAPTER SIX: APPENDICES

Effects of Time on Cerebrovascular Responses in Repeated Poikilocapnic Conditions in Hyperthermia and Normothermic Volitional Hyperventilation

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Running Head: Effects of Time

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6.1 Effect of Time on Cerebrovascular Responses During Thermal Hyperpnea in Hyperthermic Humans

Introduction

There was a concern that there was an effect of time on cerebrovascular responses in hyperthermia, and that ordering of the $P_{ET}CO_2$ conditions might confound the results of the hyperthermia study contained in this thesis. It was for this reason that a pilot study was performed to ascertain whether or not there was any preliminary evidence of an effect of condition timing on the cerebrovascular responses to hyperthermia. It was hypothesized that there would be no effect of time or ordering on cerebrovascular responses during hyperthermia.

Methods

Participants

This study was complete on three participants that participated in the previous study. For further information please refer to Chapter 2, Section 2.1.

Instrumentation

Please refer to Chapter 2, Section 2.2.

Protocol

Please refer to Chapter 2, Section 2.3. As well, an extra hyperthermic poikilocapnic period (HT-PC2) was added at the end of the study, after HT-EC.

Statistical Analysis

Please refer to Chapter 2, Section 2.4 for more information. Paired student's t-tests were performed between the data sets in the two poikilocapnic periods. The level of significance was set at an α of 0.05.

Results

There were no significant differences (P>0.05) between the first and second hyperthermic poikilocapnic conditions (HT-PC1 & HT-PC2) for each variable including: esophageal temperature (T_{ES}; Fig. 5.2.1A), mean skin temperature ($\bar{T}_{SK}$; Fig. 5.2.1B), expiratory ventilation ($\dot{V}_E$; Fig. 5.2.2A), end-tidal partial pressure of carbon dioxide (P_{ETCO2}; Fig. 5.2.2B), end-tidal partial pressure of oxygen ($P_{ET}O_2$; Fig. 5.2.2C), mean arterial pressure (MAP; Fig 5.2.3), middle cerebral artery mean blood velocity (MCA_V, Fig. 5.2.4A), posterior cerebral artery mean blood velocity (PCA_V, Fig. 5.2.4B), basilar artery mean blood velocity (BA_V, Fig. 5.2.4C), index of cerebrovascular conductance in the MCA ($ICVC_{MCA}$, Fig. 5.2.5A), index of cerebrovascular conductance in the PCA ($ICVC_{PCA}$, Fig. 5.2.5B), and index of cerebrovascular conductance in the BA ($ICVC_{BA}$, Fig. 5.2.5C).

Conclusions

There is no effect of ordering of $P_{ET}CO_2$ stages and time of hyperthermia on the cerebrovascular responses.

Figures

Figure 5.1.1: Mean values of esophageal temperature (T_{ES}, A) and mean skin temperature ($\bar{T}_{SK}$: B) for all participants (n=3) in normothermic rest (NT-REST), hyperthermic poikilocapnic 1 (HT-PC1), hyperthermic eucapnic (HT-EC), and hyperthermic poikilocapnia 2 (HT-PC2). NS = P > 0.05. For all figures, error bars indicate 1 SD.

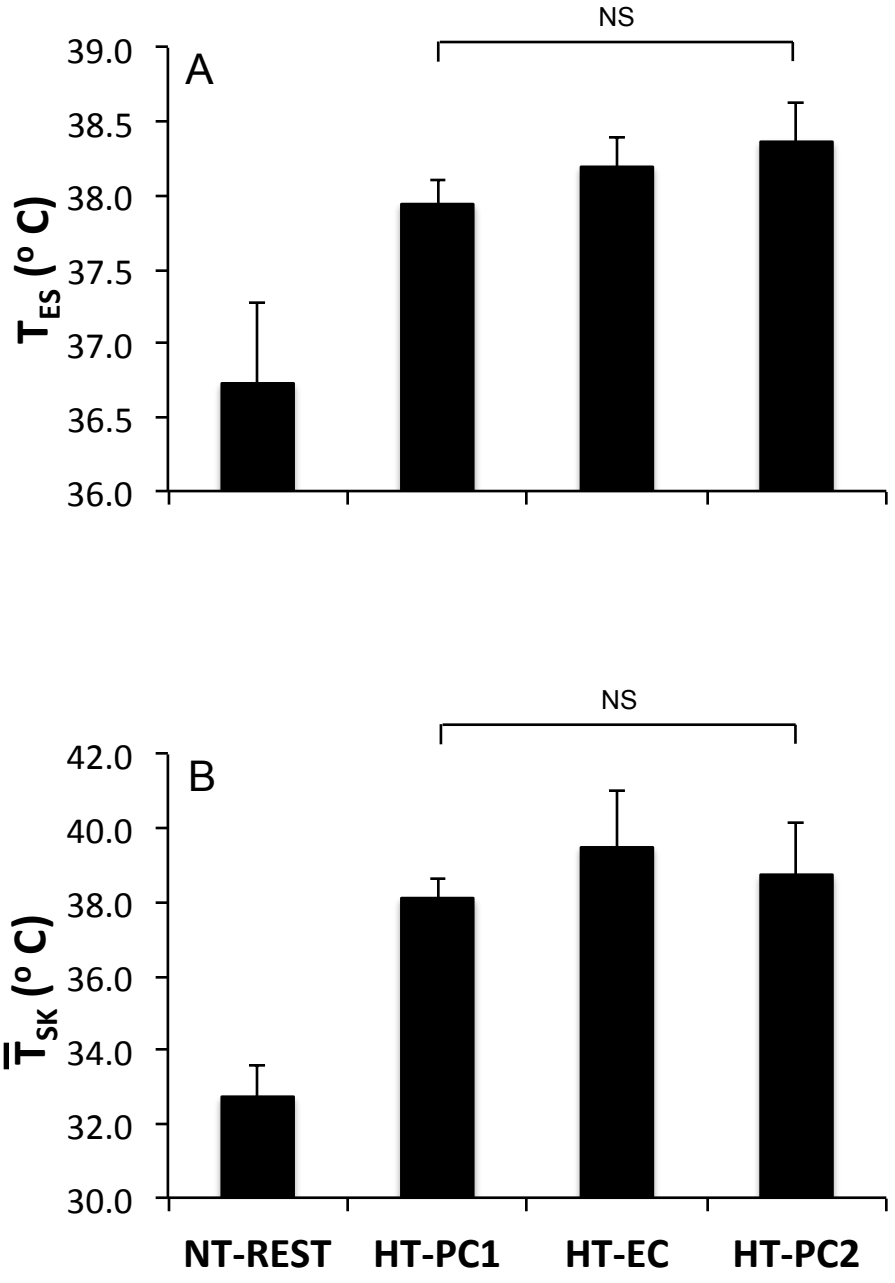


Figure 5.1.2: Mean values of pulmonary ventilation ($\dot{V}_E$, A) end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$; B), and end-tidal partial pressure of oxygen ($P_{ET}O_2$; C) for all participants (n=3) during normothermic rest (NT-REST), hyperthermic poikilocapnia 1 (HT-PC1), hyperthermic eucapnia (HT-EC), and hyperthermic poikilocapnia 2 (HT-PC2). NS = P > 0.05.

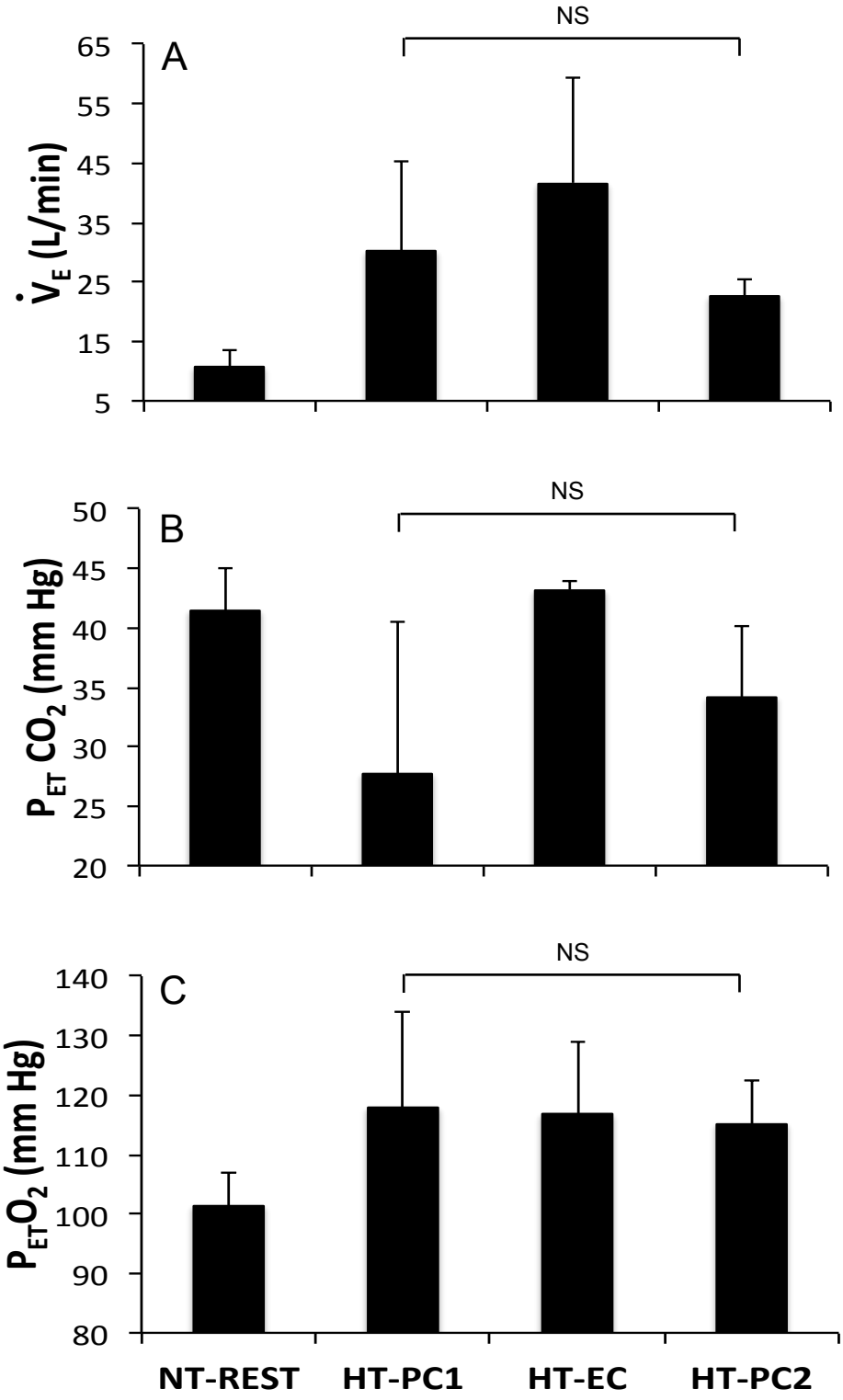


Figure 5.1.3: Mean values of mean arterial pressure (MAP) for all participants (n=3) during normothermic rest (NT-REST), hyperthermic poikilocapnia 1 (HT-PC1), hyperthermic eucapnia (HT-EC), and hyperthermic poikilocapnia 2 (HT-PC2). NS = P > 0.05.

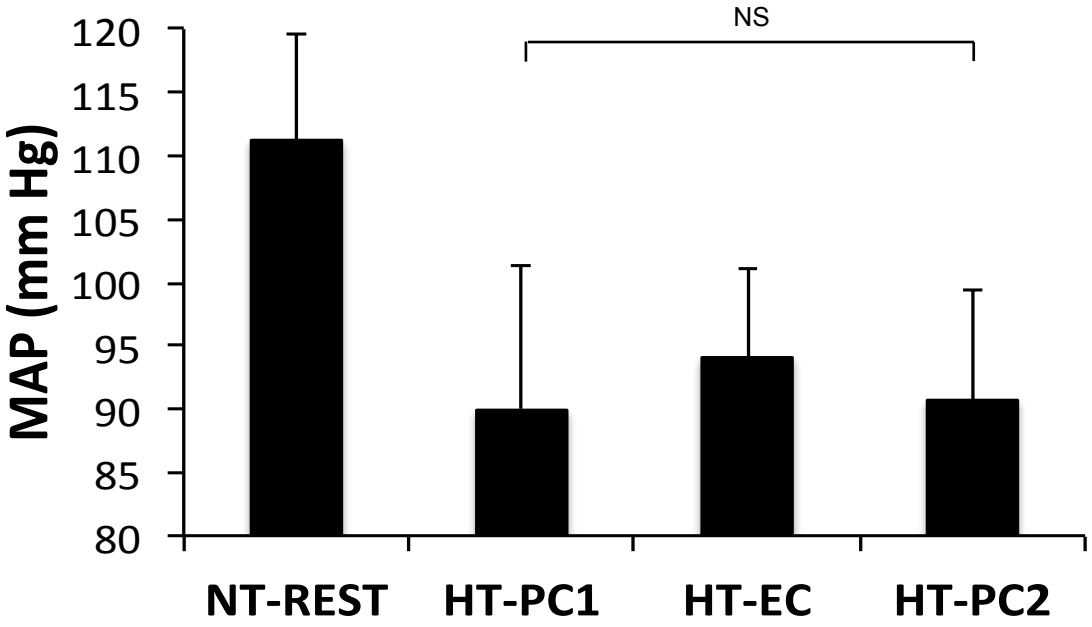


Figure 5.1.4: Mean percentage values of normothermic rest (NT-REST) cerebral blood velocities in the middle cerebral artery (MCAv; A), posterior cerebral artery (PCAv; B), and basilar artery (BAv; C) for all participants (n=3) during hyperthermic poikilocapnia 1 (HT-PC1), hyperthermic eucapnia (HT-EC), and hyperthermic poikilocapnia 2 (HT-PC2). NS = P > 0.05.

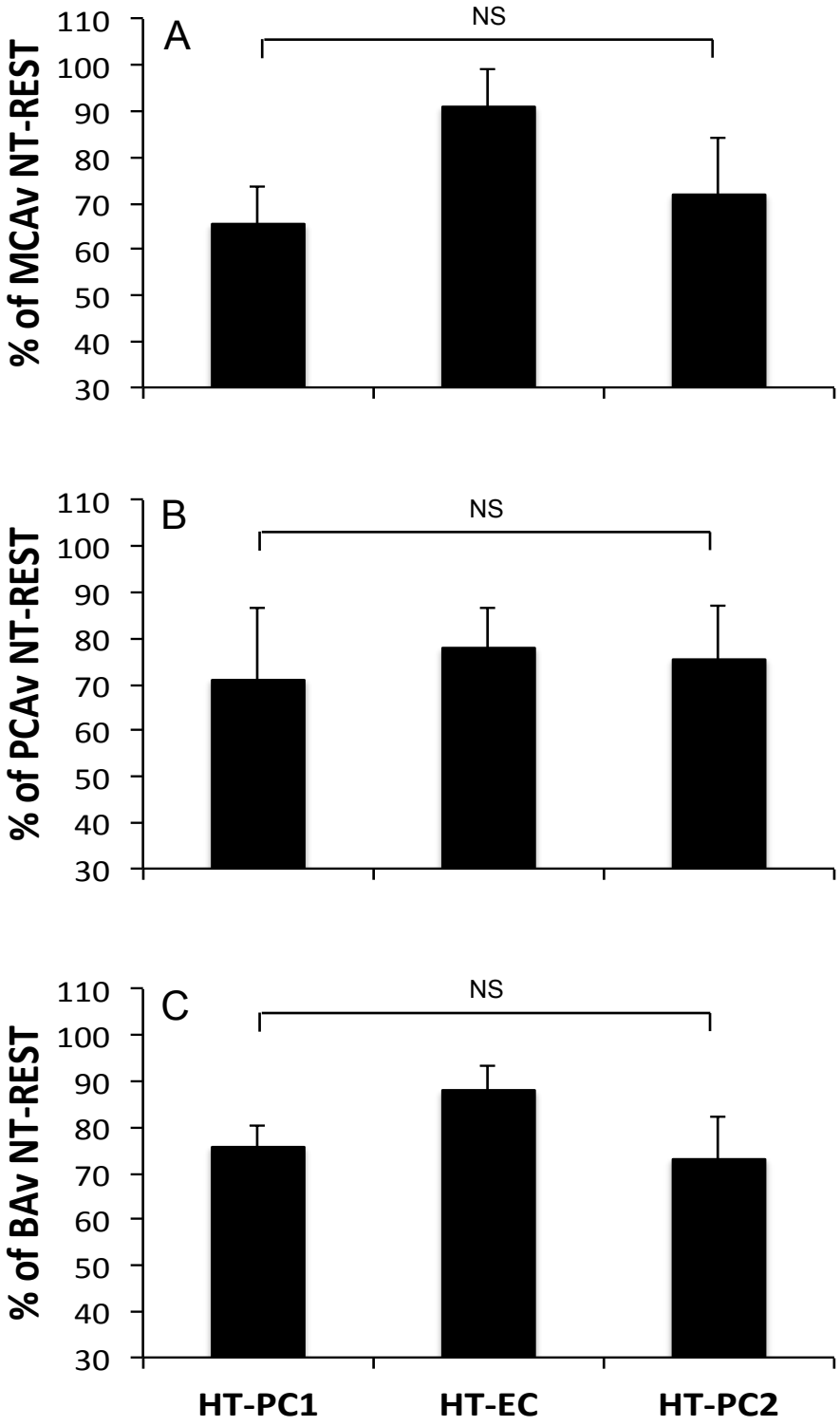
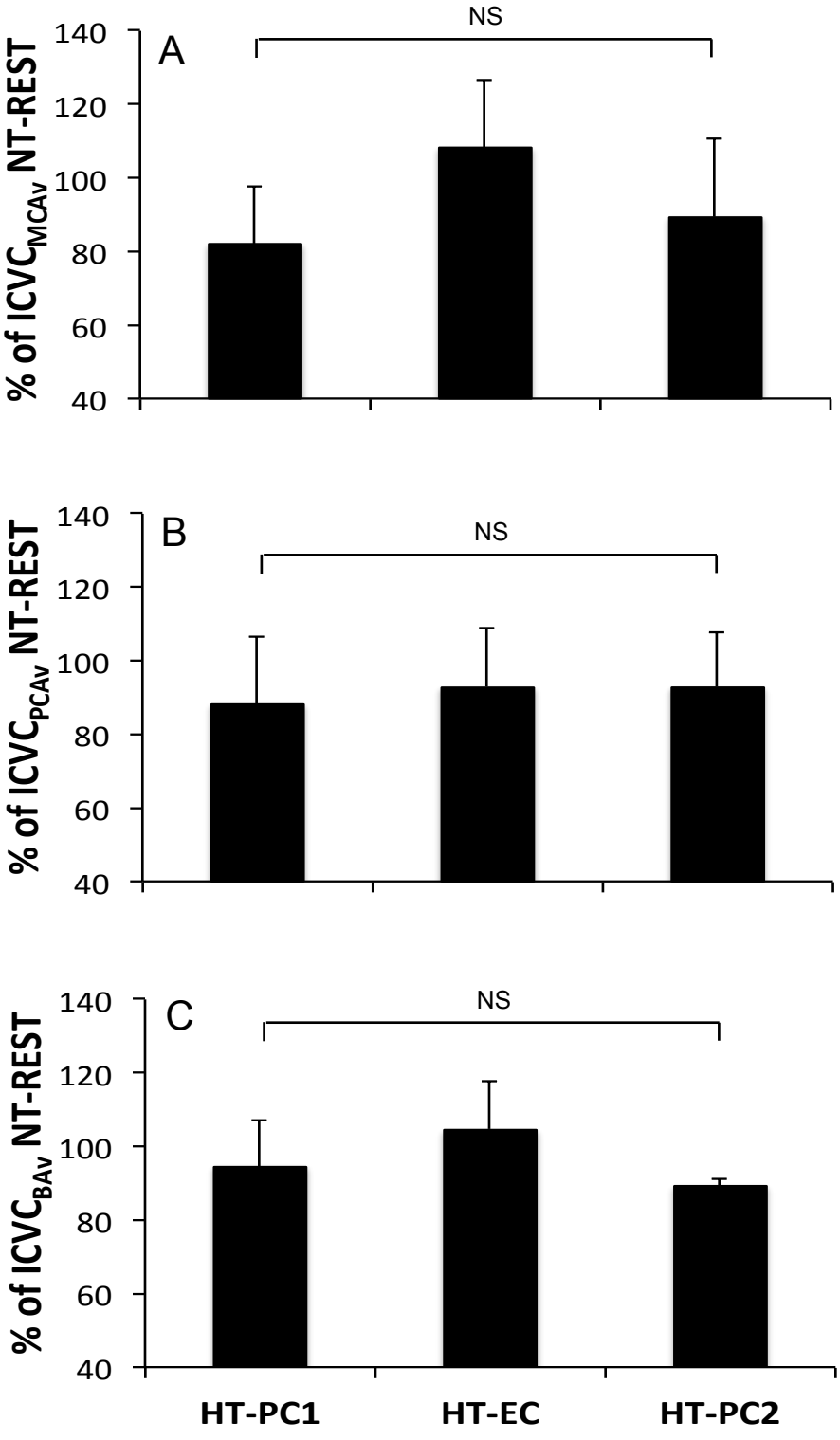


Figure 5.1.5: Indices of cerebrovascular conductance (ICVC, cm•s^{-1}•mm Hg^{-1}) expressed as a percentage of normothermic rest (NT-REST) in the middle cerebral artery (MCA; A), posterior cerebral artery (PCA; B), and basilar artery (BA; C) for all participants (n=3) during hyperthermic poikilocapnia 1 (HT-PC1), hyperthermic eucapnia (HT-EC), and hyperthermic poikilocapnia 2 (HT-PC2). NS = P > 0.05.



6.2 Effect of Time on Cerebrovascular Responses During Volitional Hyperventilation in Normothermic Humans

Introduction

There was a concern that there was an effect of time on cerebrovascular responses in normothermic volitional hyperventilation, and that ordering of $P_{ET}CO_2$ stages might confound the results of the hyperventilation study contained in this thesis. It was for this reason that a pilot study was performed to ascertain whether or not there was any preliminary evidence of an effect of condition timing or ordering on the cerebrovascular responses to hyperventilation. It was hypothesized that there would be no effect of time or ordering of $P_{ET}CO_2$ conditions on volitional hyperventilation in normothermic humans.

Methods

Participants

This study was complete on three participants that participated in the previous study. For further information please refer to Chapter 3, Section 3.1.

Instrumentation

Please refer to Chapter 3, Section 3.2.

Protocol

Please refer to Chapter 3, Section 3.3. As well, an extra hyperthermic poikilocapnic period (NT-PC2) was added at the end of the study, after NT-EC.

Statistical Analysis

Please refer to Chapter 3, Section 3.4 for more information. Paired student's t-tests were performed between the data sets in the two poikilocapnic periods. The level of significance was set at an α of 0.05.

Results

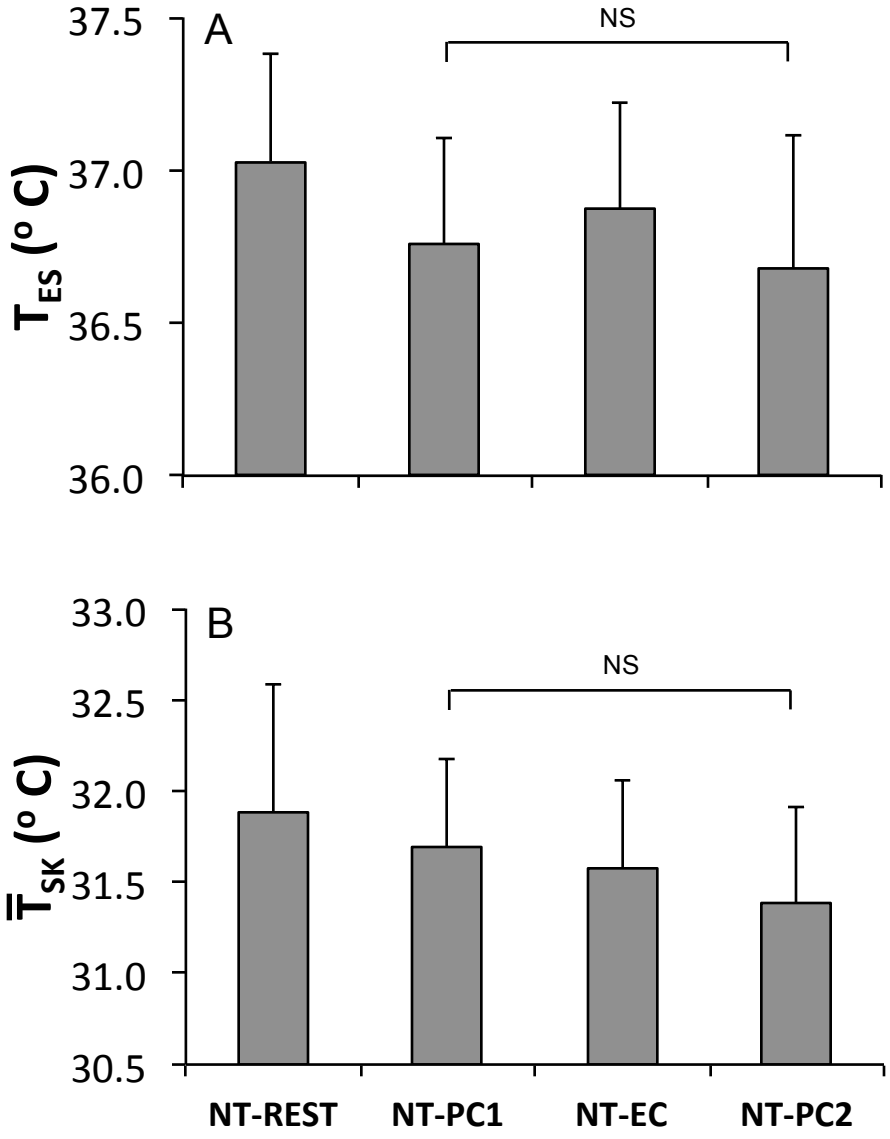
There were no significant differences (P>0.05) between the first and second normothermic poikilocapnic conditions (NT-PC1 & NT-PC2) for each variable including: esophageal temperature (T_{ES}; Fig. 5.2.1A), mean skin temperature ($\bar{T}_{SK}$; Fig. 5.2.1B), expiratory ventilation ($\dot{V}_E$; Fig. 5.2.2A), end-tidal partial pressure of carbon dioxide (P_{ETCO2}; Fig. 5.2.2B), end-tidal partial pressure of oxygen ($P_{ET}O_2$; Fig. 5.2.2C), mean arterial pressure (MAP; Fig 5.2.3), middle cerebral artery mean blood velocity (MCA_V, Fig. 5.2.4A), posterior cerebral artery mean blood velocity (PCA_V, Fig. 5.2.4B), basilar artery mean blood velocity (BA_V, Fig. 5.2.4C), index of cerebrovascular conductance in the MCA ($ICVC_{MCA}$, Fig. 5.2.5A), index of cerebrovascular conductance in the PCA ($ICVC_{PCA}$, Fig. 5.2.5B), and index of cerebrovascular conductance in the BA ($ICVC_{BA}$, Fig. 5.2.5C).

Conclusions

There is no effect of ordering of $P_{ET}CO_2$ stages and time of volitional hyperventilation on the cerebrovascular responses.

Figures

Figure 5.2.1: Mean values of esophageal temperature (T_{ES}, A) and mean skin temperature ($\bar{T}_{SK}$: B) for all participants (n=3) in normothermic rest (NT-REST), normothermic poikilocapnic 1 (NT-PC1), normothermic eucapnic (NT-EC), and normothermic poikilocapnia 2 (NT-PC2). NS = P > 0.05. For all figures, error bars indicate 1 SD.



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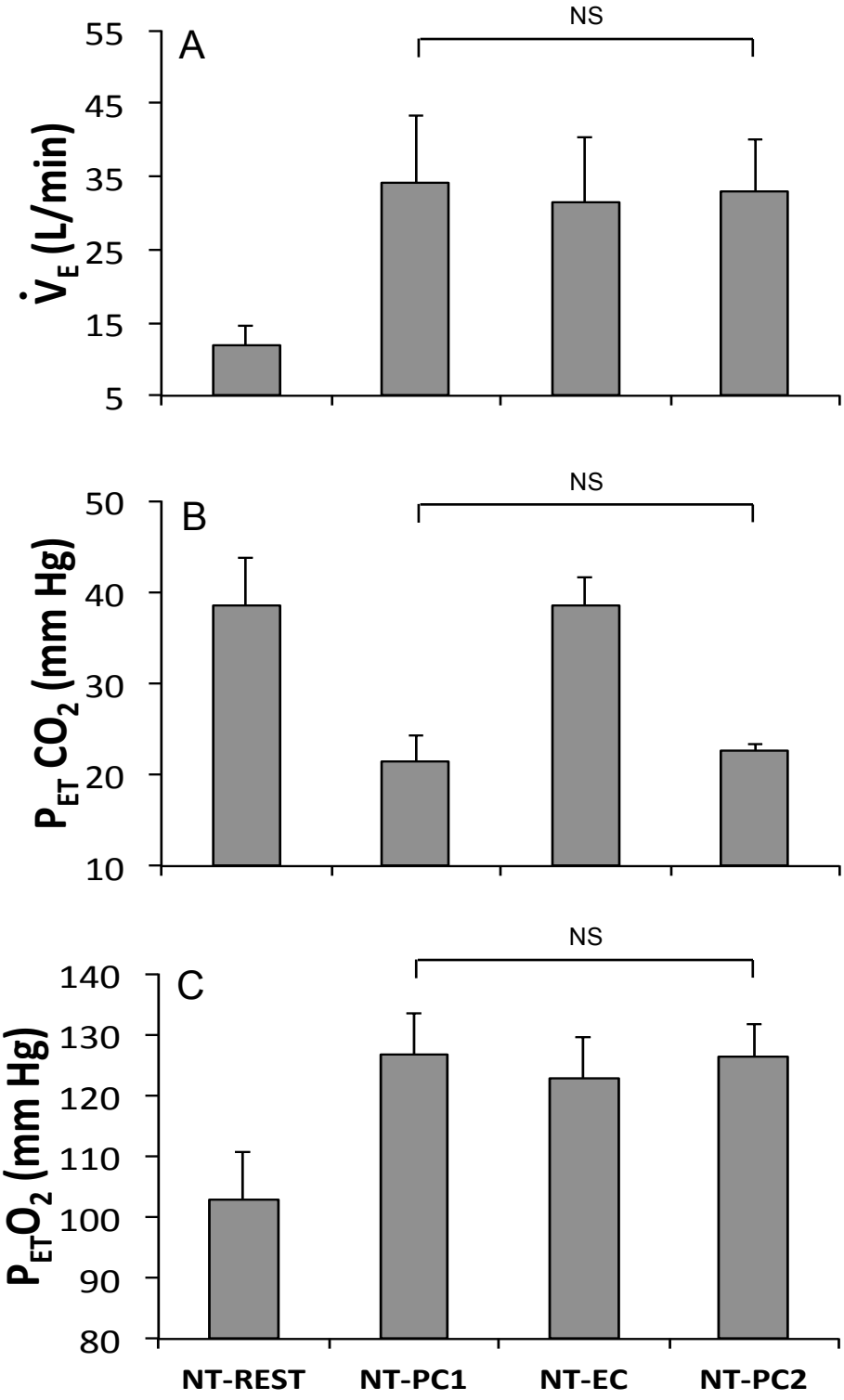
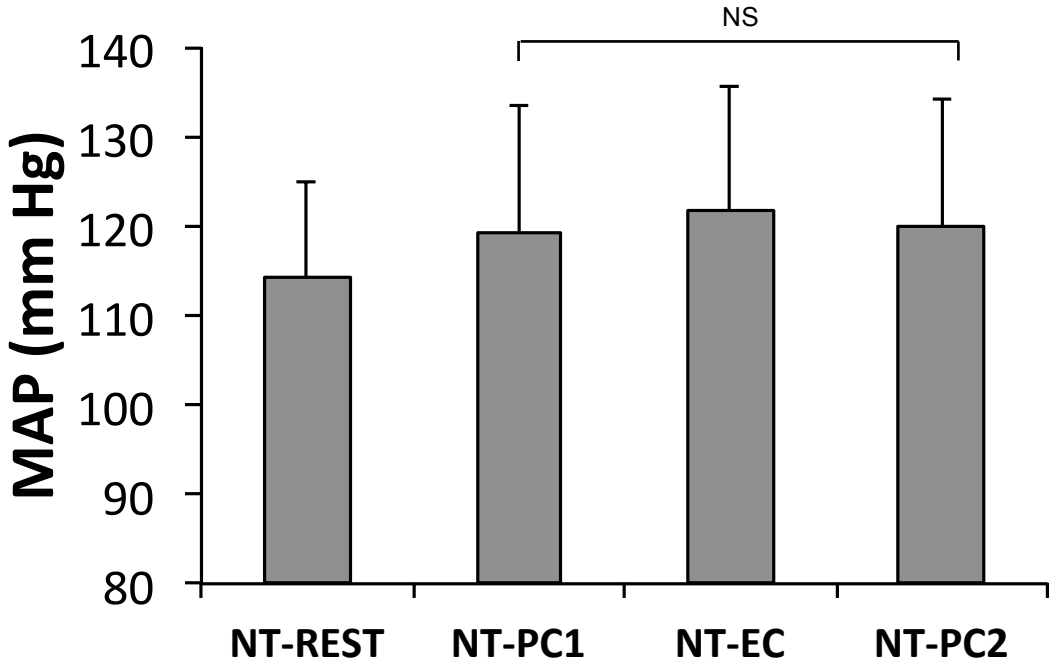


Figure 5.2.3: Mean values of mean arterial pressure (MAP) for all participants (n=3) during normothermic rest (NT-REST), normothermic poikilocapnia 1 (NT-PC1), normothermic eucapnia (NT-EC), and normothermic poikilocapnia 2 (NT-PC2). NS = P > 0.05.



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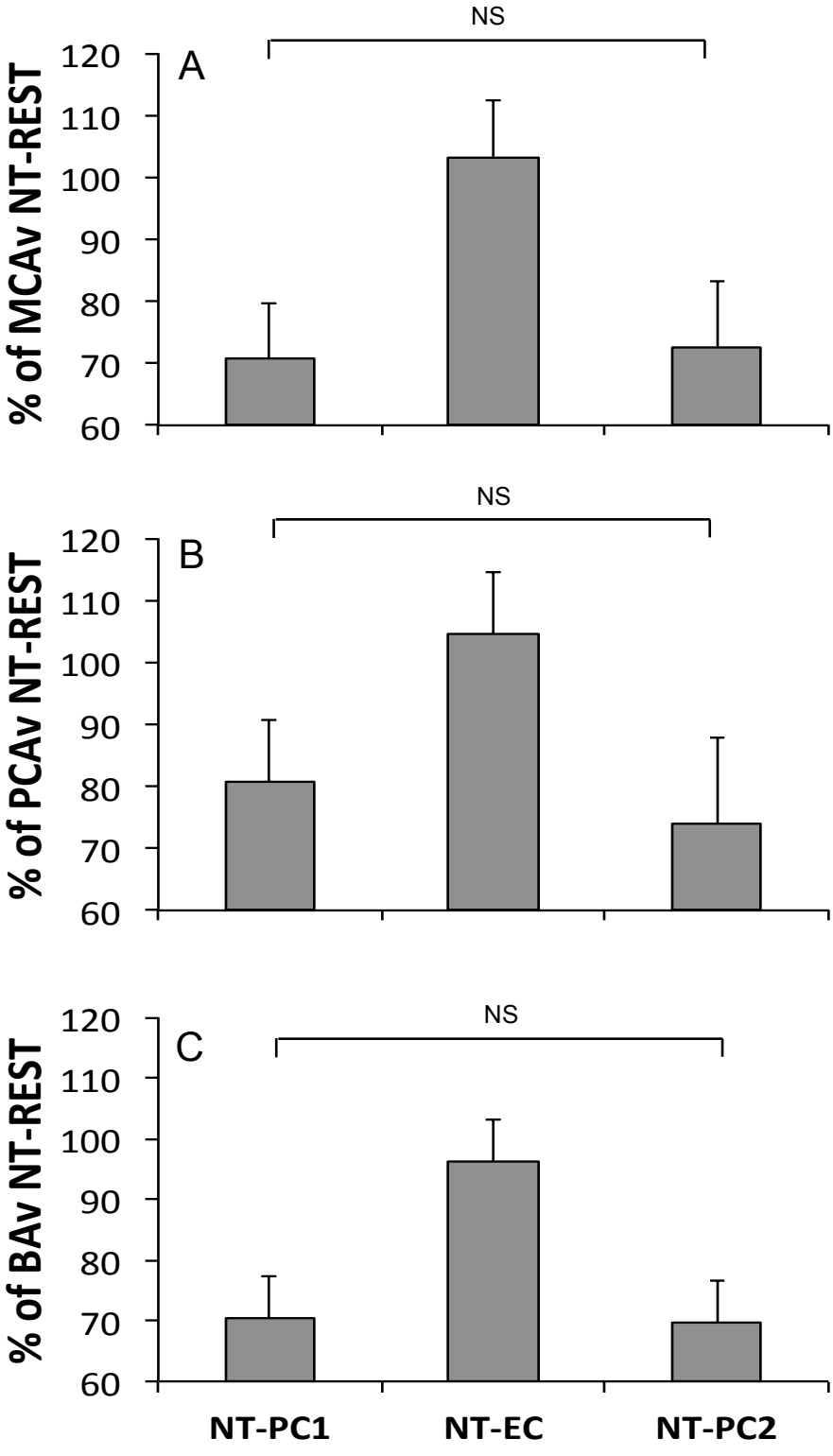

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