RELATIONSHIPS BETWEEN 30% NORMOXIC NITROUS OXIDE BREATHING, CORE TEMPERATURE AND EXERCISE VENTILATION

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by

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Overall Abstract

While working at depth air breathing commercial divers experience nitrogen narcosis and they can become hyperthermic with surface supply heating systems. It is unresolved to what extent narcosis and hyperthermia influence exercise or work ventilation. The 2 studies in this thesis examined the effects of nitrogen narcosis and hyperthermia on phase I and III of exercise ventilation. The first study examined the effect of 30% normoxic nitrous oxide (N_2O) induced narcosis on both phase III ventilation and on core temperature thresholds for ventilation in 6 male subjects performing an incremental exercise test to exhaustion. The second study examined independent effects of 30% normoxic N_2O induced narcosis and core temperature on phase I exercise ventilation for 6 male subjects exercising in 4 separate 30 s Wingate exercise tests. For 2 Wingate tests subjects remained normothermic for the exercise while for the 2 other Wingate tests prior to exercise they were rendered hyperthermic in a 40°C bath for the test. The first study showed relative to exercise with air breathing that N_2O breathing significantly suppressed exercise ventilation ($p < 0.05$) and the frequency of respiration ($p < 0.05$) while shifting esophageal temperature (T_{es}) thresholds for ventilation to significantly higher T_{es} levels ($p < 0.05$). The second study showed a significant ($p < 0.05$) decrease for total ventilation in N_2O normothermic relative to N_2O hyperthermic exercise and this decrease was due to significant decreases in tidal volume ($p<0.05$). In conclusion, the results support the hypothesis that the control of exercise ventilation includes a neural component as evidenced by nitrogen narcosis suppressing and hyperthermia elevating human ventilation during high intensity exercise.

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Table of Contents

List of Tables

List of Figures

List of Definitions

Carotid body resection: surgical removal of the carotid body (MedicineNet.com)

Frequency of respiration: the number of breaths per minute, at rest this value is approximately 12-15 breaths per minute.

Hyperpnea: breathing that is deeper and more rapid than at rest.

Isocapnic Buffering: the phase of exercise in which the lactate entering the blood stream is initially buffered leading to an increase in CO_2 without a decrease in blood pH.

Minute ventilation: a common measurement of pulmonary ventilation, it is the amount of air inspired or expired each minute, calculated as a product of tidal volume (V_T) and frequency of respiration (F_R). At rest minute ventilation is approximately 6.5 l per minute.

Nitrous oxide: a colorless, odorless gas used as an anesthetic and analgesic.

Tidal volume: the amount of air that is inspired or expired in a normal breath, it can reach 50% of an individual's vital capacity, at rest this value is ~ 0.5 l.

Ventilation: the exchange of oxygen and carbon dioxide through the common medium of the inert gas, nitrogen.

List of Abbreviations

ATA: Atmospheric Pressure Absolute

CO_2: Carbon Dioxide gas (mm Hg)

F_R: Respiratory Frequency (breaths/min)

H^+: Hydrogen ion

MVV: Maximum Voluntary Ventilation

N_2O: nitrous oxide gas

O_2: Oxygen gas

P_ACO_2: partial pressure of carbon dioxide in the alveoli

P_aCO_2: Partial Pressure of Carbon Dioxide in the arterial blood

P_AO_2: partial pressure of oxygen in the alveoli

P_aO_2: Partial Pressure of Oxygen in the arterial blood

R: Respiratory Quotient

T_{co}: Core Temperature (°C)

T_{es}: Esophageal Temperature (°C)

T_{sk}: Skin Temperature (°C)

T_V: Tidal Volume (l)

$\dot{V}_E$: Minute Ventilation ($l \cdot min^{-1}$)

$\dot{V}CO_2$: Volume of Carbon Dioxide ($l \cdot min^{-1}$)

$\dot{V}O_2$: Volume of Oxygen consumed ($l \cdot min^{-1}$)

$\dot{V}O_{2max}$: Maximum Volume of Oxygen Consumed ($l \cdot min^{-1}$)

$\dot{V}T_1$: Ventilatory Threshold 1 ($l \cdot min^{-1}$

$\dot{V}T_2$: Ventilatory Threshold 2 ($l \cdot min^{-1}$)

$\dot{V}_E/\dot{V}O_2$: Ventilatory Equivalent for Oxygen (unitless)

$\dot{V}_E/\dot{V}CO_2$: Ventilatory Equivalent for Carbon Dioxide (unitless)

Chapter 1 Thesis Overview

1.1 Introduction and Overview

Control of ventilation during exercise is a subject of great interest and controversy (7). At rest there is a consistent view of how humans control their breathing (9). However, during exercise conditions, the precise factors involved in ventilatory control have not been clearly identified (5, 8, 10). Several hypotheses on the control of ventilation observed during exercise have been developed. Still another area of interest is ventilation during exercise in extreme environments such as the hyperbaric conditions in the undersea. Unlike exercise at sea level pressures, in which cardiovascular parameters limit maximal aerobic performance, it is apparent that the increased gas density and the work of breathing are the limiting factors to exertion at depth (1). Also the narcotic effect of air under pressure are thought to influence ventilation of divers (1). The mechanism(s) by which this exertion is limited in hyperbaric environments has/have not been completely resolved.

At normal barometric pressure, it has been suggested that ventilation could be a thermoregulatory response and this supports temperature is a stimulus for ventilation (2). A body of literature is evident which supports passive and active body warming influence ventilation once core temperature thresholds for ventilation are reached (2, 11-13). However, the effect of temperature on the control of ventilation in hyperbaric or simulated hyperbaric conditions has received little attention in the literature (3, 6). This conclusion was reached at the end of the literature review in Chapter 2, where two

hypotheses and five testable questions were stated. Subsequently hypotheses and testable questions were addressed in the two studies of the thesis as described below.

The two studies conducted for this thesis focused on two forms of exercise. First, incremental exercise to maximal levels was conducted in which the body's core temperature is naturally raised (Chapter 3). Second, a 30s duration, high intensity Wingate exercise test was employed which involved a short burst of maximal effort and a large increase in ventilation that was not accompanied by a rise of core temperature (Chapter 4). For the incremental exercise protocol in Chapter 3 this allowed an examination of the effect 30% normoxic nitrous oxide relative to air breathing on Phase III of exercise ventilation and its components (4, 10). In the second study the short duration of exercise allowed a normothermic exercise without increasing core temperature. As such, a passively induced hyperthermia superimposed prior to the short duration exercise allowed the effects of core temperature to be assessed on phase I or the initial abrupt increase in ventilation at the start of exercise (4, 10). Similar to study 1 in Chapter 3, breathing either 30% normoxic nitrous oxide or air in study 2 or Chapter 4 allowed a separate effect of this simulated narcosis on ventilation to be assessed in during the Wingate exercise test.

Chapter 5 of this thesis gives the conclusions to the two research hypotheses and testable questions stated at the end of Chapter 2. Chapter 5 also concludes on how these

experiments contribute to the existing knowledge, on the effects of both nitrogen narcosis and hyperthermia on human exercise ventilation.

1.2 Co-Authorship Statement

i) Design and identification of the research proposal

I, the thesis author, was initially interested in occupational hazards with regards to maximal exercise in various working environments. Dr. Matthew White brought to my attention a topic area of commercial diving and maximal exertion in hyperthermic humans for my thesis. After an extensive review of the literature Dr. White and I decided to use 30% nitrous oxide to simulate the nitrogen narcosis conditions experienced at ~6 ATA without the effect of increased ambient pressure. We used an incremental and a short duration, high intensity exercise protocols for assessment of a diver's ventilation when exposed to a condition of hyperthermia combined with nitrogen narcosis. Together Dr White and I designed a thesis research proposal based on my review of literature that was presented to the School of Human Kinetics and Recreation.

ii) Practical aspects of the research

As the thesis author, I was present at all experimental sessions in Dr. White's laboratory. I was responsible for the set-up and preparation of the equipment for each test and for instrumentation of each subject. I helped prepare the data acquisition and metabolic cart to allow measurement of the subject's ventilation, thermoregulatory and

cardiorespiratory responses and performance. After each test I remained with the subject for at least 20 min to answer any questions or concerns they might have. I was also responsible for the clean-up, shut down and proper disposal (if required) of all equipment used. Dr. White was also present at large majority of the experimental sessions.

iii) Data analysis

I was responsible for the time sequencing of all raw data collected and combining it into a single file, which was then statistically analyzed by Dr. White and I. Dr White and I gave a combined effort to decide which statistical tests were the most powerful and appropriate for the data analyses. These were used in answer our testable questions as given in the literature review (Chapter 2). All stats were reviewed and the results agreed upon by both Dr. White and I.

iv) Manuscript preparation

For each study and the thesis I wrote initial versions of the abstract, introduction, methodology, results, discussion and conclusions. These versions were reviewed and edited by Dr. White and myself during several exchanges of each section or chapter of the thesis.

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Chapter 2: Review of Literature

A commercial deep-sea diver is met with considerable physiological challenges in his or her hyperbaric working environment. Divers are continually exposed to elevated ambient pressure and this has detrimental effects on the function of their cardio-respiratory system. The increased gas density and/or nitrogen narcosis of a hyperbaric environment are known to impair ventilation (1, 4, 80) and work performance (22). Typically coupled with the increased physiological demands on the cardio-respiratory system in the cold undersea work environment are deep body cooling and hypothermia. More recently, however, surface supply of hot water was shown to cause these divers to become hyperthermic (50). Little research has addressed this latter condition of a hyperthermic, high-pressure work environment for commercial deep-sea divers (9). It is the combination of hyperthermia and nitrogen narcosis, and how they may affect human ventilation during work or exercise in a hyperbaric environment that is the focus of this thesis.

The literature review for this thesis begins with a brief discussion of the control of resting ventilation followed by a description of the mechanisms thought to take part in regulation of ventilation during low, moderate and high intensity exercise. There are several mediators thought to influence ventilation during high intensity exercise. These include core temperature that is thought to positively influence high intensity exercise ventilation. A second part of this literature review is given on the effect of a hyperbaric environment on human ventilation. The literature review indicates that the influence of narcosis on relationships between body temperature and ventilation during exercise has

not been examined clearly in the literature. A Research Hypothesis and Testable questions that were addressed in the two studies in this thesis are given following the literature review.

2.1 Control of Resting Human Ventilation

The main signals in resting human ventilation arise from central tissues and peripheral receptors that respond directly or indirectly to increases in carbon dioxide production ($\dot{V}CO_2$). The peripheral chemoreceptors are found in both the carotid and aortic bodies, although the carotid bodies make the larger contribution to peripheral chemoreception (10, 29). Together peripheral chemoreceptors respond to lowering of arterial oxygen partial pressure (P_aO2) and to elevations in P_aCO_2. In addition, for the peripheral chemoreceptors only carotid chemoreceptors respond to a decreased plasma pH (54). As evidenced by a single breath hypoxic test, it is implied from resting responses by carotid body resection patients that the carotid bodies account for about 90% of the ventilation response that is attributed to hypoxia (29). In these same patients 70% of the hypercapnic response remains and this response is thought to arise from the central chemosensitive areas in the medulla oblongata. From this it is implied 30% of the CO_2 response of ventilation arises from the peripheral chemoreceptors (29).

The central chemosensitive centers are found in the medulla oblongata near the inputs from the glossopharyngeal nerve (9^{th} cranial nerve) that innervates the carotid body chemoreceptors, and from the vagus nerve (10^{th} cranial nerve) that innervates aortic

body chemoreceptors. These chemosensitive centers respond to increases or decreases of the pH of the cerebral spinal fluid (CSF), however, the blood brain barrier is impermeable to all known mediators of ventilation other than CO_2. The Henderson Hasselbalch relationship (Equation 1) describes how changes in CO_2 levels lead to centrally mediated changes in ventilation.

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+ \quad \text{(Henderson-Hasselbach equation)}.....(1)$$

By equation 1 an increase in CO_2 above normal will raise the concentration of H^+ ions through the production of carbonic acid (H_2CO_3) and its further dissociation into hydrogen ion (H^+) and bicarbonate (HCO_3^-). This decrease in pH stimulates the central chemosensitive areas and ventilation is increased. Likewise a raised pH by equation 1 will lead to a decrease resting ventilation.

2.2 Control of Human Ventilation During Exercise

The metabolic mediators and/or neural inputs involved in the control of exercise ventilation have not been clearly identified (16, 68). As such this area of research has generated great interest and controversy (15, 59). The main problem is illustrated by an approximately 15 fold increase in human ventilation during high intensity exercise (68) despite that the normal mediators of resting ventilation (54) remaining unchanged or are even lowered (68). The potential mechanisms thought to influence exercise ventilation are generally grouped as either as metabolic/humoral or as neural (46). Prior to

reviewing these potential mechanisms that may underlie the control of ventilation during exercise in these two groups, a section is given to describe how ventilation increases at different exercise intensities and durations.

2.2.1 Low to Moderate Intensity Exercise

During low to moderate exercise the metabolic demand increases mainly from the increased energy demand from contracting skeletal muscle. The body's response is to increase ventilation so that it quickly matches this increased metabolic demand. Between the onset of exercise until approximately two minutes into low to moderate intensity exercise, ventilation has a triphasic response when expressed as a function of exercise intensity or oxygen consumption (14). The first phase (phase I) is characterized by an abrupt increase in ventilation that is maintained for approximately 10 to 20 s (14, 70). The second phase (phase II) shows a slower exponential rise in ventilation from the initial increase to a steady state that is typically completed within two to three minutes of exercise. Phase III is the new steady state achieved and maintained for the duration of moderate steady-state exercise (75).

2.2.2 Moderate to High Intensity Exercise

Moderate to high exercise is of sub-maximal intensity at 60 to 75% of maximal work capacity or maximal oxygen consumption ($\dot{V}O_{2\,MAX}$). Under these exercise conditions phase II is longer in duration and after approximately 30 min of intense exercise,

ventilation undergoes a gradual rise compared to the pattern seen during lower intensity exercise (45). This effect has been coined the ventilatory drift, and the precise mechanisms causing this drift is unclear, although a rising body temperature may be implicated (45).

The linear relationship between ventilation and oxygen consumption maintained throughout Phase III is only observed for steady state exercise. If exercise is incrementally increased to a maximal level, additional changes in the pattern of ventilation are evident. As the exercise load is incremented progressively, ventilation begins to increase more quickly than oxygen consumption at higher intensities of exercise. The first break in the linear relationship between ventilation ($\dot{V}_E$) and oxygen consumption occurs at approximately 40 to 70% of a person's maximum workload. This breakpoint was described (47) as the first ventilatory threshold (VT_1). To define VT_1 during exercise hyperpnea McLellan (47) employed the ventilatory equivalents for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) and for oxygen ($\dot{V}_E/\dot{V}O_2$) each plotted as a function of oxygen consumption. The criteria to judge VT_1 from these relationships are a continued decrease in $\dot{V}_E/\dot{V}O_2$, with an increase in $\dot{V}_E/\dot{V}CO_2$ (47). VT_1 has also been referred to as the 'anaerobic threshold' or the 'lactate threshold' since it may coincide with rises in plasma lactate during exercise. Subsequent to VT_1 during incremental exercise is a second disproportionate increase in ventilation relative to $\dot{V}O_2$. This second ventilation threshold (VT_2) is thought to be of neurogenic origin and is identified by a steeper rise in

both ventilatory equivalents $\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_E/\dot{V}O_2$ when expressed as a function of $\dot{V}O_2$ (46, 48, 63). The following sections will describe the potential metabolic and/or neural changes that are thought to underlie these thresholds for ventilation and the pattern of ventilation during moderate to high intensity exercise.

2.2.2.1 Hypotheses of Mechanism(s) Underlying VT_1 and Low to Moderate Intensity Exercise Ventilation

At low to moderate intensity exercise a metabolic or humoral mechanism(s) is/are thought to initiate changes in ventilation. There are several hypotheses on how different metabolites might influence VT_1 and the pattern of ventilation during low to moderate intensity exercise. These are now presented with the evidence supporting or refuting each hypothesis.

Lactate Accumulation Hypothesis

Lactate and hydrogen ion are products of the dissociation of lactic acid in a fluid at a physiological pH (33). An accumulation of lactate and a lowered plasma pH occur when the balance between the rate of lactate production by working muscle and the rate of lactate removal from the bloodstream are not equal (59). Wasserman et al. (69) stated that the abrupt increase observed in minute ventilation during incremental exercise to maximum is secondary to two changes related to lactate production. These changes are the added amount of non-metabolic CO_2 produced from buffering of hydrogen ion by

bicarbonate and by the raised hydrogen-ion concentration caused by the reduced bicarbonate concentration (70). This concept is based on the chain of events that occur in response to a raised hydrogen ion concentration after lactic acid dissociation, as described above by the Henderson-Hasselbalch equation 1. Since lactic acid readily dissociates into lactate and H^+ ions, the elevated H^+ concentration result in a left shift of the equilibrium and increased non-metabolic CO_2 production. The elevated CO_2 production is sensed by central and peripheral chemoreceptors and this increases ventilation.

During progressive, incremental exercise the results from Glass et al. (24) do not favor the lactate accumulation hypothesis or the association between the onset of blood lactate accumulation (OBLA) and VT_1. Their study showed with a normal level of skeletal muscle glycogen, that lactate and ventilatory thresholds occurred at a similar level of exercise intensity or $\dot{V}O_2$. Under glycogen depletion conditions they reported the lactate threshold had shifted to a higher $\dot{V}O_2$ in relation to VT_1. This work and other studies (28, 32) suggest a similar view that VT_1 and OBLA can be separated after glycogen depletion. This suggests lactate accumulation is an unlikely stimulus or cause for VT_1 (24).

Evidence against the lactate hypothesis can be found from patients with McArdle's Syndrome (25, 27). McArdle's Syndrome patients are deficient in muscle phosphorylase. After each glucose unit is cleaved from glycogen, this enzyme is needed to allow

phosphorylation of each glucose molecule to glucose-1-phosphate. Glucose-1-phospate enters the glycolytic pathway and subsequently lactic acid concentration rises as a product of anaerobic glycolysis. Since no glucose-1-phospate is produced in McArdle's syndrome patients, no matter how hard these patients exercise, their plasma lactic acid remain negligible (25). Nevertheless, the ventilation of these McArdle's syndrome patients (27) showed the same distinct thresholds as normal subjects not deficient in muscle phosphorylase. The authors suggested (25) something other than the accumulation of lactic acid could be operating to explain the ventilatory response to exercise.

Carbon Dioxide Flow Hypothesis

The amount of carbon dioxide flowing to, or across the lungs is suggested to be both the sole mediator of ventilation during exercise and to maintain the arterial isocapnia that can be evident during exercise (70). One basis for this relationship between CO_2 flow through the lungs and ventilation is evidenced by parallel changes in $\dot{V}_E$ and $\dot{V}CO_2$ during exercise at different intensities (17). This view is further strengthened with studies that demonstrated elevations or decreases in cardiac output modified in CO_2 flow across the lungs and subsequently proportional changes in ventilation (6, 72). Similarly an extracorporeal gas exchanger was used to raise venous carbon dioxide levels in dogs when cardiac output and P_aCO_2 were at resting values (71). This increased CO_2 flow rate to the lungs of these dogs gave proportional increases in ventilation, while presumably

the peripheral and the central chemoreceptors activities were at resting levels (71). These studies (17, 70) supported the hypothesis that CO_2 flow across the lungs controlled the ventilation response during exercise.

In contrast to the results supporting the CO_2 flow hypothesis, Heigenhauser et al. (28), showed that for a given work rate $\dot{V}_E$ was higher in subjects with reduced muscle glycogen than in their control subjects with normal muscle glycogen content. Heigenhauser et al. (28) reasoned that muscle glycogen depletion would increase the reliance on fatty acids as an energy substrate and this would give a relative decrease of CO_2 flow to the lungs in their glycogen depleted group. Although both the respiratory exchange ratio (R) and CO_2 flow across the lungs remained unchanged for these 2 groups, an increase in $\dot{V}_E$, as anticipated, still came about in the glycogen depletion group. This suggested other factors besides lung CO_2 flow are responsible for the exercise hyperpnea (28). Further to these results there is no evidence identifying the location and mechanism of these CO_2 "sensors" thought to exist in the pulmonary circulation that would signal changes in CO_2 flow across the lungs. Also Dempsey commented (16) both venous CO_2 loading protocols or increased CO_2 flow induced by increasing cardiac output give an elevation of P_aCO_2. Presumably the increases in ventilation observed in these protocols elevate the arterial CO_2/H^+ sensed at the peripheral chemoreceptors and/or central chemosensitive areas and this is translated into an elevated ventilation. Together the results illustrate the CO_2 flow hypothesis can't fully

account for the changes in ventilation during exercise.

Carotid Body Stimulation Hypothesis

In order to help maintain the acid-base balance of the blood the human peripheral chemoreceptor sites respond to lowered P_aO_2, pH (carotid only) and raised P_aCO_2 (73). During exercise an absence of the carotid bodies was found to have no effect on ventilation that remained at an intensity below the anaerobic threshold or VT_1 (29, 43, 71). However when exercising above the anaerobic threshold these carotid-body-resected subjects did not hyperventilate contrary to subjects with intact carotid bodies (71). These studies suggest that carotid body chemoreceptors are in part responsible for the exercise hyperpnea observed at exercise intensities above the OBLA or anaerobic threshold.

In contrast to the studies cited above (43, 71) that suggest that carotid body stimulation at exercise intensities above the OBLA contributes to increase in ventilation, Mitchell et al. (51) obtained evidence of to the contrary. These authors (51) studied 4 groups of mild to moderately exercising goats (Group 1: goats with intact carotid bodies and serotonin depletion, Group 2: goats with carotid body denervation, Group 3: goats with carotid body denervation and serotonin depletion, and Group 4: intact goats). Tryptophan hydroxylase inhibition by *p*-chlorophenylalanine was employed to deplete serotonin and induce a hyperventilation with or without the carotid bodies (52). Overall

the results suggested that exercise hyperpnea may be evident without influence from the peripheral chemoreceptors including those in the carotid bodies (51). As such carotid body stimulation is not essential for exercise hyperpnea contrary to the studies cited above (29, 30, 43, 71).

Catecholamines and Ions Influencing Ventilation Hypotheses

Catecholamines and different ions have been suggested as a mediators involved in the control of ventilation by stimulating carotid body discharge during exercise. Two of the most predominantly studied mediators are the catecholamines norepinephrine and the cation potassium.

Norepinephrine Hypothesis

Continuous intravenous infusion of norardrenaline causes a transient stimulation of ventilation (74) either with a fall in P_ACO_2 (74) or without a fall in P_ACO_2 (2). Cunningham et al. (11) attempted to establish the effect of noradrenaline infusion on the relationship between pulmonary ventilation, P_AO_2 and P_ACO_2 by controlling the level of P_ACO_2. It was shown that the only consistent effect of noradrenaline was to increase hypoxic sensitivity and they (11) suggested that in the absence of hypoxia the effect of noradrenaline would disappear. Their results support that although noradrenaline may influence ventilation, as its levels increases during exercise, it is only during hypoxia. Thus, noradrenaline can not fully account for exercise hyperpnea in normoxic exercising

subjects.

Potassium (K^+) *Hypothesis*

Medbo and colleagues (49) suggested that doubling of the potassium concentration of arterial plasma in humans during muscular exercise may stimulate ventilation. These results (49) are in agreement with Patterson et al. (58) who showed that K^+ concentration in the arterial plasma of humans is highly correlated with ventilation throughout exercise (58). Potassium moves from the working muscles to the blood at all intensities of exercise and the resulting hyperkalemia may directly stimulate the carotid bodies. Burger et al. (7) studied the effects of potassium on the discharge of carotid bodies in cats. An intravenous infusion of 0.05 mmol • kg^{-1} • min^{-1} KCL repeatedly raised arterial K^+. This was accompanied by an increase in chemoreceptor discharge beginning in the first minute of infusion. The results showed that K^+ effects were enhanced by hypoxia and were either reduced by hyperoxia or didn't change with hypercapnia (7). Therefore, it seems possible that potassium during exercise may contribute to the increased slope of the relation between ventilation and metabolic rate, a change that is usually attributed to the lowered arterial pH (69). However, considering the contradictory effects in the presence of hypercapnia and hyperoxia, the exact contribution of potassium to the control of ventilation during exercise remains to be established.

Metabaroreflex or Muscle Chemoreflex Hypothesis

During exercise it has been suggested that the decreasing intracellular fluid (ICF) or extracellular fluid (ECF) pH of skeletal muscle is involved in the control of ventilation via the metabaroreflex or muscle chemoreflex. A lower tissue pH is thought to stimulate the group IV afferents that send a signal to the areas of the medulla that elevate ventilation (21). Evans (21) hypothesized in order for H^+ to be implicated in the regulation of ventilation that H^+ must "change concentration rapidly in the ECF, in a direction known to activate the ventilatory metabaroreflex, and must do so when arterial pH is thought to play little or no role in augmenting ventilation." Evans (21) used rats to test this hypothesis by stimulating the sciatic nerve to produce a "mixed lactic acidosis and respiratory alkalosis with no net change in arterial pH". They found (21) that the pH of the ECF dropped enough to initiate a ventilatory metabaroreflex and this result was suggested to support the metabaroreflex hypothesis. Likewise, Oelberg and colleagues (56) found ventilation and the pH of intracellular fluid were positively related (56) when the perfusion to the limbs was occluded to raise muscle acidity without a change in arterialized blood pH.

In contrast to studies cited above (21), Wasserman suggested (70) from his study with Brown and colleagues (6) that ventilation responded in a manner inconsistent with the metabaroreflex or muscle chemoreflex hypothesis. Injection of the beta adrenergic blocker propranolol decreased cardiac output and lowered tissue pH and PO_2 while tissue PCO_2 rose. These changes of tissue metabolites by the metabaroreflex or muscle

chemoreflex hypothesis should have increased ventilation, however the decreased cardiac output after injection of propranolol decreased ventilation (6). This discrepancy in the findings points to something other than a lowered ICF or ECF acidity as a mediator of ventilation during exercise.

2.2.3 High Intensity Exercise

Following the VT_1 threshold ventilation increases more quickly than $\dot{V}O_2$ after passing the second ventilatory threshold or VT_2 at approximately 70 to 90% of maximal attainable workrates during incremental exercise (47). The mechanisms underlying this second observed exercise hyperpnea are unclear, however, it is generally believed that it is of a neurogenic origin (47). The main theories on possible mechanisms responsible for the VT_2 and potential mediators of ventilation during high intensity exercise are discussed below.

2.2.3.1 Hypotheses on Mechanisms Underlying VT_2 and High Exercise Intensity Ventilation

Neurogenic Hypotheses

The neurogenic hypotheses relating to the control of ventilation suggests mechanisms involving either or the central nervous system (CNS) or the peripheral nervous system (PNS). Krough et al. (41) suggested the CNS controls ventilation with irradiation from the brain to the respiratory centers (41). The authors used a Bergonie

apparatus to apply a gradual current to the subjects' limbs so as to initiate limb movement. They found ventilation increased upon this externally induced limb movement (40) and the results support that CNS sensors detect this movement that is relayed to respiratory control centers that increase ventilation. Their study, however, does not support that movement of the limbs alone could be responsible for the increases in ventilation. Kao (36) electrically stimulated skeletal muscle without limb movement and this increased ventilation. They concluded that the exercise hyperpnea was stimulated by "ergoreceptors" located in the muscles themselves and that a neural pathway stimulated the respiratory centers to increase ventilation during exercise (36).

Raised Core Temperature Hypothesis

Another neurogenic hypothesis implicates core temperature as another centrally mediated stimulus influencing ventilation during exercise (77). This follows from studies of passive human body warming in a hot tub, when ventilation was observed to increase disproportionately relative to metabolic needs (8, 12, 26, 62). Core temperature has been associated to the regulation of ventilation at elevated core temperatures at rest (8) or during high intensity exercise (77). With (77) or without (8) exercise these ventilation thresholds were evident after body warming and at higher core temperatures than these thresholds ventilation and core temperature increased in direct proportion (8, 77). This suggested an important role of core temperature in the control of human exercise ventilation since its relationship to ventilation was evident by passive or active means of body warming.

The increased ventilation as a function of core temperature during exercise was shown by Sancheti and White (61) to result from an initial increase in tidal volume. This was followed by a plateau at maximal tidal volume values and subsequently the frequency of respiration and ventilation both increased proportionately to esophageal temperatures (61). These results suggested that hyperthermia induces a vestigial panting response (55, 77). Other support for this temperature hypothesis came from reproducible relationships between core temperature and each of tidal volume (61), frequency of respiration (61) and ventilation (76). In addition Mariak (44) showed that intra-cranial temperatures decreased up to $0.1°C \cdot min^{-1}$ as a result of subjects breathing intensively for three minutes. The air inhaled through the nasal cavity and upper airways is suggested to cool the temperature of the upper airways by counter-current heat exchange and this may help cool the brain during hyperthermia. Overall the results support that ventilation may act as a thermoregulatory effector response at elevated core temperatures.

A possible role for core temperature in the control of ventilation during exercise is by temperature influencing the sensitivity of central chemosensitive areas and/or peripheral chemoreceptors to carbon dioxide (12, 62). Saxton (62) and others (12) showed passive heating of core temperature increased ventilation and data from their experiments suggest there is an increased sensitivity of ventilation to CO_2 with rising body temperature (12, 62). Sancheti and White (61) strengthened this view when they showed CO_2 sensitivity increased following exercise during post-exercise hyperthermia.

In humans, maximal levels of ventilation during exercise can occur prior to any rise in core temperature. An example is the rapid increase in ventilation, prior to core temperature rise (67), during short duration, high intensity exercise (e.g.30 sec Wingate test). This might suggest that the effects of core temperature on the control of ventilation is limited to an exercise –induced hyperthermia. There is little evidence on how temperature influences ventilation during a short duration, high intensity exercise (67). A single study demonstrated during a short duration, high intensity exercise test that hyperthermia elevated the respiratory rate (f) during first 2 breaths after the onset of exercise and during the first two breaths after the cessation of exercise (67). This suggested that hyperthermia at the onset and cessation of exercise may interact with the central respiratory control centers (67). It is not clear if and how a passively induced hyperthermia, prior to an exercise induced increase core temperature, would influence ventilation during these intense exercise protocols.

In contrast to the evidence presented above, that supports that hyperthermia elevates human ventilation, in the hyperbaric conditions of the undersea work environment there is a suppression of ventilation. This effect is discussed in the next section.

2.3 Exercise in a Hyperbaric Environment

2.3.1 Ventilation as a Limiting Factor of Maximal Exertion at Depth

Several studies on exertion in hyperbaric conditions involves submaximal exercise tests (22, 42, 53, 64, 65). This is since it has been shown that maximal exertion is severely limited in the hyperbaric environment, when compared to surface pressure or 1 ATA (5). Unlike exercise at sea level pressures, where cardiovascular parameters limit maximal aerobic performance, it is apparent that ventilation is the limiting factor to exertion at depth (5). This change appears to arise in part due to the increased gas density and the associated increase in the work of breathing in this environment (22, 79). This is especially evident at extreme depths (64). Divers working at depths of 49.5 ATA have reported inability to sustain moderate levels of exertion due to feelings of dyspnea (64). During compressed air dives the effect of elevated nitrogen that is loaded on to human tissues also has a narcotic affect and is also implicated in the changes in ventilation (3, 13, 23, 65). This is since inert gas narcosis is thought to influence ventilation either stimulating it (23) or suppressing it (1, 3, 65).

2.3.2 The Effect of Increased Pressure on Cardio-respiratory Function

In a study by Fagraeus, Hesser and Linnarsson (22), the effects of increased O_2 and N_2 pressures on cardiorespiratory responses to graded exercise were studied in three separate conditions: (i) air at 1.0 ATA, (ii) 100% O_2 at 1.0 ATA, and (iii) air at 4.5 ATA. Comparison of cardiorespiratory responses in air at 1.0 ATA or at 4.5 ATA showed that

elevated N_2 and O_2 pressures were associated with increased oxygen consumption, end-tidal CO_2 (as indicative of carbon dioxide retention) and reduced heart rate. The elevated O_2 and N_2 pressures and/or the added work of breathing were though to suppress ventilation as indicated by lower $\dot{V}_I/\dot{V}CO2$ and $\dot{V}_I/\dot{V}CO_2$ during exercise. These results further suggest that the rise in $\dot{V}O_2$ and $\dot{V}CO_2$ were in part from elevated O_2 pressure and improved oxygen delivery to the tissues. Also the elevated tissue N_2 pressure and the increased gas density that increased the work of breathing were implicated in the elevated $\dot{V}O_2$ at 4.5 ATA. The reduced heart rate they reported was thought to arise from the elevated O_2 pressure (22). They suggested (22) that elevated N_2 pressure does not give an additive decrease in ventilation over and above the increased work of breathing. Despite this latter conclusion their study did not allow them to separate the influences on ventilation from the increased work of breathing and the effect of elevated N_2 pressure. Elevated N_2 pressures are well known to have a narcotic effect on the central nervous system (3) and it remains to be shown whether this depressant effect extends to exercise ventilation at elevated pressures.

Oxygen consumption and oxygen tissue delivery at depth were shown to increase by Fagraeus, Hesser and Linnarsson (22). This result suggests that exercise would at depth have a smaller anaerobic component. Neubauer et al. (53) assessed the blood lactate changes during graded exercise at both normal (1 ATA) and hyperbaric (3 ATA) conditions. They found a significantly lower mean blood lactate concentration in hyperbaria than for the same moderate and heavy workloads performed at sea level.

They (53) postulated that the lower blood lactate may indicate that either the oxygen demand during exercise at hyperbaria was being met faster during hyperoxia or an overall improvement in lactate metabolism took place at elevated pressure. This suggests the lower ventilation at depth is in part attributed to by the enhanced oxygen delivery to the tissues.

Tetzlaff et al. (65) looked specifically at the ventilation responses to exercise for subjects at ambient pressures of 0.1 Mpa or 0.4 Mpa (3 ATA). These authors (65) reported that it has already been shown that hyperoxia itself causes a decrease in exercise ventilation at moderate workloads. At maximal workloads, however, they pointed out the decrease in exercise ventilation during hyperoxia is negligible (Pirnay, 1973, as cited by (65)). In Tetzlaff et al.'s study a 19% decrease in ventilation at maximal workloads was found at 3 ATA while the inspired PO_2 was kept equal to that at sea level. Therefore, these authors contributed the decrease in $\dot{V}_E$ more to hyperbaria than to hyperoxia (65). In other studies (1, 34, 79) similar decreases in ventilation were reported for subjects exercising in air under elevated pressure. From these (1, 34, 65, 79) and similar studies (22) it was not possible to separate the influences of increased gas density from the possible influence of elevated tissue N_2 pressures.

In summary, the literature on exercise or work performance in hyperbaric conditions supports that ventilation is limited in part by mechanical factors (64). As well the literature recognizes that the elevated partial pressure of inert gas (e.g. nitrogen) at depth may pose additional limitations on cardio-respiratory function. The centers

responsible for the control of ventilation in the medulla oblongata may have a depressed response as a function of elevated inert gas partial pressures. In a hyperbaric environment, however, it is not possible to assess this contribution of inert gas on ventilation independently from the effects of increased density of gas on ventilation. Another approach is to employ subanesthetic levels of nitrous oxide that gives similar narcotic effects and that can be breathed at 1 ATA with normal gas density (9). The following section reviews nitrous oxide and its influences on cardiorespiratory function in humans.

2.3.3 Nitrous Oxide

Nitrous oxide is a colorless, odorless gas used as an anesthetic and analgesic. Nitrous oxide's narcotic effects become evident for humans when it makes up only a low percentage of an inhalate. These effects include an insensibility or stupor such as that associated with any anesthetic drug, natural or synthetic, that has morphine like actions (35). As mentioned above, the second potential limitation to ventilation at depth is hypothesized to be due to inert gas narcosis associated with breathing compressed air. In order to study diving ventilation independent of changes in gas density, studies have used breathing mixtures including sub-anesthetic levels of nitrous oxide (9, 13, 20, 66, 80). The sub-anesthetic gas mixture of 30% nitrous oxide (N_2O), 21% oxygen and 49% nitrogen simulates the breathing of compressed air at 7-10 ATA. Thus nitrous oxide has been used to mimic inert gas narcosis experienced by divers and to study the cardiovascular and respiratory systems changes during this inert gas narcosis (9).

2.3.4 Cardiovascular Effects of Nitrous Oxide

There is some controversy on the cardiovascular response to breathing sub-anesthetic concentrations of nitrous oxide. During resting conditions, Kawamura (37), showed no significant change in cardiovascular effects over a two-hour period with subjects breathing gas mixtures including 20% or 40% normoxic N_20 (37). In the same study subjects breathing gas mixtures with 60% normoxic N_20 had transient increases in cardiac output as well as decreases in systemic vascular resistance that returned to control levels after 1hr of continuous N_20 breathing. The results were attributed to the elevated P_aCO_2 and its effect as a peripheral vasodilator during 60% normoxic N_20 inhalation (37). Other work also showed no influence with 50% normoxic N_20 on heart rate or blood pressure (38, 66). Another body of evidence reviewed by Jastek and Donaldson (35) supports the contrary, that nitrous oxide does indeed possess significant cardiac depressant effects (35). Eisele employed 40% normoxic nitrous oxide and found small but significant decreases in heart rate and cardiac output but this did not influence blood pressure (20). Despite these significant depressions in cardiovascular variables, with inhalation of normoxic N_20 at concentrations of 40% or greater, Jastek and Donaldson (35) state (p. 145) that the depressant effects of nitrous oxide are 'clinically unimportant'.

Nitrous oxide has also been studied for its influence on cardiovascular function during exercise. Ostlund et al. (57) compared supine and upright dynamic leg exercise on an ergometer mounted on a tilt board. They (57) observed no effect of breathing air or 30% normoxic N_20 on steady state heart rate or mean arterial pressure for supine or

upright subjects. However, following either an up-tilt or a down-tilt, there was a significant 16% decrease in baroreflex sensitivity as reflected by the measurements obtained from dividing the maximum change in heart rate by the maximum change in carotid distending pressure (57). The postulated mechanism for this change was due to N_20 suppressing vagal and not sympathetic induced modulations of heart rate. This is since vagally induced responses are faster and follow short lasting baroreflex stimuli such as a body tilt. In contrast, sympathetically induced autonomic autoflow to the heart is slower and is responsible for adjustments to steady state levels of heart rate. It was concluded from this paper that 30% nitrous oxide attenuates baroreflex sensitivity via a vagally induced response (57). This is in contrast to the original thinking that nitrous oxide has inherent sympatho-stimulation (18). Ostlund et al. (57) also suggested that since no alteration in mean heart rate and mean arterial pressure were observed, inert gas narcosis alone cannot account for the relative bradycardia in subjects breathing dense and narcotic gases in hyperbaric conditions (57).

Under resting or submaximal exercise conditions nitrous oxide does not appear to have an effect on oxygen utilization (9). However, during maximal exercise for the same subjects a significant seven percent increase was reported for maximal $\dot{V}O_2$ (9). The authors (9) suggested that a possible mechanism for the increased maximal $\dot{V}O_2$ reported was a decreased affinity of haemoglobin for O_2 as a consequence of N_2O interfering with the O_2-Fe bond in haemoglobin. This would limit oxygen exchange in the lungs but would enhance O_2 release to the tissues. Therefore, the observed narcosis-induced

increase in maximal $\dot{V}O_2$ may be due to a progressive increase in sensitivity of haemoglobin to pH drop that arises from lactate accumulation at higher exercise intensities; that is, lowered pH caused hemoglobin to release more oxygen to the tissues (Bohr effect) (9).

2.3.5 Ventilatory Response to Nitrous Oxide Inhalation

In subanesthetic doses nitrous oxide is not thought to depress respiration but the gas can affect ventilation at rest and during exercise. Breathing nitrous oxide at rest at 1.55 ATA of pressure, amongst other symptoms, increased f although this response was subsequently absent when pressure was reduced to 1.1 ATA (31). The increased f is coupled with a decreased V_T proportional to the inspired concentration of N_2O (19). This decreased V_T is compensated by a corresponding increased f and the net result is a modest increase in resting ventilation (19, 35). Fothergill et al. (23) showed for resting subjects breathing normoxic 23% N_2O that tidal volume increased which gave an increase of ventilation (23). Another finding related to exercising ventilation with 23% N_2O (23) was a slightly larger respiratory effort as indicated by a larger mouth occlusion pressure ($P_{0.1}$) with no change in expiratory reserve volume. However, this stimulatory effect was not strong enough to overcome an added inspiratory load that was imposed on their subjects (23). Fothergill et al. (23) also found at high workloads during exercise that the N_2O narcosis raised f significantly but did not change V_T (23). At rest or during exercise some reports indicate a small increase in ventilation when breathing nitrous

oxide (19, 23, 35). In contrast to the results of Fothergill (23), Ciammaichella (9) found no changes in ventilation between subjects at 1 ATA breathing 30% normoxic N_20 oxide or air during incremental exercise to maximal attainable workrates.

Concentrations of 40% normoxic nitrous oxide but not 20% normoxic nitrous oxide were also shown to effect steady state ventilation during unloaded breathing at rest (60). Royston and colleagues showed that the inspiratory time and $P_{ET}CO_2$ decreased while the frequency of ventilation increased for their exercising subjects (60). They (60) also showed a decrease in ventilation on first breath with 40% normoxic N_2O upon increasing the inspiratory load. They suggested this decrease was due to a reduced ability to sense the load during mild narcosis and concluded that 40% normoxic nitrous oxide was a mild stimulant for ventilation in resting humans.

The chemoreflex loop for ventilation has also been studied during nitrous oxide induced narcosis (13, 39, 78, 80). Dahan et al. (13) found no effect of subanaesthetic concentrations of 20% normoxic N_2O on the chemoreflex loop (13). In contrast, Yacoub et al. (80) found large decreases in the hypoxic ventilation response with breathing of 30 to 50 % normoxic N_2O and others found the ventilation response hypercapnia was also suppressed by N_2O inhalation (39, 78).

In conclusion to the section on nitrous oxide, there does not appear to be a consistent view in the literature on the effects of nitrous oxide on ventilation at rest or

during exercise. Breathing nitrous oxide at concentrations over 20% does provide a means of assessing the affects of the narcosis on human ventilation independently from the affects of elevated gas density that are evident in hyperbaric conditions.

2.4 Summary of Literature Reviewed

The Research Hypotheses and Testable Questions of this thesis follow the four summary points, as given below.

1. Many hypotheses exist on the regulation of ventilation during exercise from low to high intensities. No single hypothesis has received unified support and is able to account for all aspects of the control of exercise ventilation. Core temperature is one hypothesized mediator of human ventilation during moderate to high intensity exercise (8, 77). Inconsistent with this hypothesis of core temperature as sole influence on ventilation is that during short duration, high intensity exercise ventilation can increase to maximum prior to any rise in body temperature. This is a topic that remains to be investigated.

2. Ventilation is a limiting factor for maximal physical exertion of divers at high ambient pressure (5). The increased work of breathing due to an increased gas density at depth plays a significant role in the limits placed on ventilation while at depth (64). Nitrogen narcosis is also thought to influence the respiratory control centers in the medulla for individuals working in hyperbaric conditions.

3. The use of sub-anesthetic levels nitrous oxide in normoxic mixtures provides a means to separate the influences of gas density and the narcotic effects of inert gases under pressure on ventilation. Evidence in the literature (35) suggests that nitrous oxide influences the central respiratory control center for ventilation by changing the sensitivity of central chemosenstive areas and/or peripheral chemoreceptors to mediators of ventilation (13, 39, 78, 80).

4. For commercial divers working in hyperbaric conditions, with elevated or hyperthermic body temperatures (50), it is unclear how the separate effects of hyperthermia and nitrogen narcosis influence exercise ventilation. Core temperature is shown to be positively associated to ventilation (8, 77) and nitrogen narcosis is known to impair ventilation.

2.4.1 Research Hypotheses

Research Hypothesis #1: If ventilation is neurally mediated at high exercise intensities (46, 48, 63) it is hypothesized that the relationship between ventilation and core temperature (8, 77) will be influenced by inhalation of normoxic nitrous oxide.

Research Hypothesis #2: If ventilation is neurally mediated at high exercise intensities (46, 48, 63), it is hypothesized that ventilation during short duration, high intensity exercise will be influenced by both normoxic nitrous oxide and passively

induced hyperthermia (8, 77).

2.4.2 Testable Questions

1. How do the core temperature thresholds for ventilatory equivalents of carbon dioxide and oxygen consumption (8, 77) compare during the same incremental exercise sessions from rest to maximal attainable workrates with subjects breathing either air or normoxic nitrous oxide?

2. How do tidal volume and frequency of respiration compare during identical incremental exercise sessions from rest to maximal attainable workrates with subjects breathing either air or normoxic nitrous oxide?

3. Does ventilation during short duration, high intensity exercise change for a hyperthermic relative to a normothermic core temperature?

4. Does ventilation during short duration, high intensity exercise change for 30% normoxic nitrous oxide versus air breathing?

5. Are the effects of hyperthermic core temperatures and normoxic nitrous oxide on ventilation short duration, high intensity additive or do they interact?

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Chapter 3: Influence of Normoxic 30% Nitrous Oxide on Ventilation and Core Temperature Thresholds for Ventilation during Exercise

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Keywords: diving, exercise, inert gas narcosis, temperature regulation, ventilation

3.1 Abstract:

In this study we hypothesized if human ventilation during high intensity exercise has a neurally mediated component, that exercise ventilation would be affected by a sub-anesthetic level of a narcotic breathing gas. To test this hypothesis 6 untrained college-aged (23.6 ± 0.3 y) males of normal height (1.80 ± 0.01 m), weight (77.2 ± 4.1 kg) and physique (Body Mass Index = 24.8 ± 1.1 kg • m^{-2}) performed a progressive incremental exercise test on a seated cycle ergometer to voluntary fatigue in 2 sessions on 2 days. Subjects breathed room air was in one session (AIR) and 30% nitrous oxide (N_2O), 21% oxygen (O_2) and 49% nitrogen (N_2) gases in the other session (N_2O). During exercise, oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and ventilation ($\dot{V}_E$) were measured on a breath-by-breath basis with a metabolic cart while esophageal temperature (T_{es}) was recorded by a temperature data logger. From each session ventilatory equivalents for oxygen consumption ($\dot{V}_E/\dot{V}_{O2}$) and carbon dioxide production ($\dot{V}_E/\dot{V}_{CO2}$) were expressed as a function of T_{es}. The results showed mean T_{es} thresholds of for $\dot{V}_E/\dot{V}_{CO2}$ ($p=0.0002$) and $\dot{V}_E/\dot{V}_{O2}$ ($p = 0.0001$) in the AIR trial were significantly lower than in the N_2O trial. Also, ventilation in the N_2O session was significantly lower than in the AIR session at 75% ($p=0.03$) and 100% ($p=0.0001$) of the mean maximal workrate. In conclusion, the results support that normoxic N_20 inhibited $\dot{V}_E$, and this influenced the relationship of $\dot{V}_E$ and T_{es}. The results support the hypothesis that the control of ventilation during intense exercise includes a neurally mediated component.

3.2 Introduction

Across numerous studies (9) of the control of human ventilation ($\dot{V}_E$) during incremental exercise from rest until the point of exhaustion, a consistent observation is that there are two inflection points or thresholds in the relationship between ventilation and oxygen consumption ($\dot{V}O_2$). There is not a single hypothesis to explain the pattern of ventilation during exercise and the mediators that may account for these changes in ventilation at, or about the exercise intensity at these thresholds (9). The first ventilatory threshold (VT_1) occurs at 40 to 70% of the maximal attainable work rates and is thought to be of metabolic origin (17, 21). Subsequently, a second $\dot{V}_E$ threshold (VT_2) occurs at approximately 70 to 95% of maximum attainable work rates and it is thought to be neurally mediated (17, 21). One hypothesis on the origin VT_2 and the subsequent hyperpnea of intense exercise is the response is thermolytic and that it contributes to cranial heat loss in hyperthermia (7, 16, 24). This follows from studies that indicated VT_2 coincides with thresholds for core temperature (T_{es}) for $\dot{V}_E$ during exercise (25, 26), T_{es} thresholds for $\dot{V}_E$ were also evident for passively induced hyperthermia (7) and that even small increases in ventilation were shown to decrease direct measures of human intracranial temperatures (16).

The potential mechanisms underlying VT_2 and the hyperpnea of intense exercise

were the focus of this study. Specifically, we investigated whether a simulated nitrogen narcosis, that was induced with a normoxic sub-anesthetic level of nitrous oxide, influenced ventilation and its relationship to T_{co} (25, 26) during incremental exercise from rest to maximal attainable work rates. We hypothesized that breathing a narcotic gas N_2O would suppress ventilation and influence its relationship with T_{co} (7, 24-26) if the control of ventilation during intense exercise has a neural component.

3.3 Methods

3.3.1 Subjects

The subjects' physical characteristics appear in Table 3-1. All participants were made aware of any risks associated with the protocol used in this experiment. After reading a detailed outline of the study all participants signed informed consent. The sample size was determined using a power calculation. The difference worth detecting was set at 10%, with an alpha level of 0.05, a beta value of 0.8 and a standard deviation of 7% of the estimated mean scores. The proposed research was approved by two ethical review boards for human experimentation at Memorial University and at Dalhousie University.

3.3.2 Instrumentation

A Vmax229 series metabolic cart (Sensormedics, CA, USA) was employed to measured the expired gases. Breath-by-breath samples were collected from a sample line fitted close to the subject's mouthpiece. Gases were analyzed for O_2 with a paramagnetic gas analyzer and for CO_2 content with an infrared gas analyzer. A mass flow sensor was employed to measure expired gas flow. Prior to all trials the analyzers were calibrated against gases of known concentration. The pneumotach was calibrated before each experiment using a syringe of known volume. The influence of 30% nitrous oxide on infrared carbon dioxide sensing (13) were accounted for in these calibrations.

Esophageal temperature (T_{es}) was measured as an indice of core temperature. A T_{es} probe (size 9Fr, Mallinkroft Medical Inc., St Louis, MO, USA) was inserted via the nostril into the esophagus to the level of the left ventricle (19). Mean unweighted skin temperatures were estimated from sites at the chest and forehead with surface copper constantan thermocouples. All thermocouples were connected to a 32-channel data acquisition converter (National Instruments, SCXI – 1000, USA) and controlled by a National Instruments software package (Labview version 5-1) and values were continually displayed on a computer screen.

The gas inhalate included either nitrous oxide (30% N_2O, 21% O_2, balance N_2, Air Liquide Canada, INC.) or air that were stored in a Tissot spirometer (Model 1464, Boston, Massachusetts, USA) and supplied to the subject in an open circuit via corrugated Collins respiratory fiber tubing.

3.3.3 Protocol

Each subject performed two incremental exercise tests from rest until exhaustion while breathing either air or normoxic nitrous oxide. Trials were performed 1 week apart and all participants were asked to refrain from ingesting nicotine or coffee for a 12 hr period prior to testing. In the control session subjects inspired room air and in the test session normoxic nitrous oxide. Each trail included an incremental exercise test to maximal exertion using a seated, electrically braked, cycle ergometer (LODE, Excalibur, The Netherlands). The test protocol used was an adapted form of the Thoden protocol

(23). Each subject had a 5 min warm-up period consisting of a 2 min familiarization while pedaling at 40 revolutions per minute (rpm) with a load of 20 Watts (W) followed by a 3 min warm up at a cadence of 70 rpm and a workload of 40 W. The intensity was then increased by 40 Watts every two min thereafter until the subject met any one of the following 3 conditions: could no longer maintain the 70 rpm pedaling speed, reached their $\dot{V}O_{2max}$ or their reached age predicted maximal heart rate. Room temperature was ~24 ± 1.0°C during the trials.

3.3.4 Statistical Analyses

An ANOVA model was employed with repeated factors of Gas Type (Levels: AIR, N_2O) & Threshold Type (Levels: $\dot{V}_E/\dot{V}CO_2$, $\dot{V}_E/\dot{V}O_2$) for comparison of esophageal core temperature thresholds for ventilatory equivalents for $\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_E/\dot{V}O_2$ between conditions. A second ANOVA model was employed with repeated factors of Gas Type (Levels: AIR, N_2O) & Exercise Intensity (Levels: 0, 25, 50, 75 and 100% of $\dot{V}O_{2MAX}$) to compare ventilation, tidal volume and frequency of respiration between exercise conditions. *A priori* orthogonal contrasts were employed for means comparisons and the level of significance was 0.05.

3.4 Results

Ventilation (Fig. 3-1a), tidal volume (Fig. 3-1b) and frequency of respiration (Fig. 3-1c) are each plotted as a function of percentage of maximal exercise intensity in Figure 3-1. Values for ventilation increased in an approximately linear manner until 50% of the maximal workload. Subsequently their slope of ventilation versus workload increased more steeply until 75% of the maximal workload and then again more steeply from 75% to 100% of the maximal workload. Between AIR and N_20 trials ventilation was significantly greater at 75% ($p=0.03$) and 100% ($p=0.0001$) of the maximal workload.

Between AIR and N_2O trials there were no significant differences for tidal volume (V_T). The mean tidal volume values tended to increase in a similar manner from a resting level of 1.0 L • $breath^{-1}$ to a maximal level of 2.5 L • $breath^{-1}$ at 100% of $\dot{V}O_{2MAX}$ (Fig. 3-1b).

Frequency of respiration (F_R) increased in both conditions in approximately linear manner until 50% of the maximal workload (Fig 3-1c). Subsequently, similarly for $\dot{V}_E$ in Fig 3-1a, the slope of F_R versus workload increased more steeply until 75% of the maximal workload and then again more steeply from 75% to 100% of the maximal workload. Between AIR and N_2O trials, there was no significant differences of F_R at 0, 25 and 75% of the maximal workload (Fig 3-1c). However, at during 100% of the

workload attained, F_R in the AIR trial of 51.1 ± 3 breaths • min^{-1} was significantly greater ($p=0.02$) than the corresponding maximal F_R of 45.3 ± 2.6 breaths • min^{-1} in the N_20 trial.

Esophageal temperature thresholds for $\dot{V}_E/\dot{V}CO_2$ ($p=0.0002$) and for $\dot{V}_E/\dot{V}O_2$ ($p=0.0001$) were found to occur at significantly higher T_{es} during the N_2O trail than during the AIR trial (Fig 3-2). In addition, within a given trial for AIR or N_2O, T_{es} thresholds for $\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_E/\dot{V}O_2$ were not significantly different (Fig 3-2). It follows that the pooled mean thresholds for $\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_E/\dot{V}O_2$ for AIR versus N_20 trials were also significantly different ($p=0.0001$). A sample subject's T_{es} thresholds for ventilatory equivalent for oxygen in these exercise conditions (Fig. 3-3).

The T_{es} and T_{sk} in AIR and N_2O trials are given in Figure 3-4 as a function of the percentage of the maximal work load achieved. The mean T_{es} of 37.25 ± 0.07°C in the N_20 trial was significantly greater than the T_{es} of 37.10 ± 09°C in the AIR trial (Figure 3-4). There were no significant differences in T_{sk} between conditions.

3.5 Discussion

The main findings in this study were that for the exercise with N_2O relative to the control exercise with AIR, phase III ventilation was reduced for subjects exercising at levels of exertion greater than 75% of their maximal workload (Fig. 3-1a). In addition, the T_{es} thresholds for ventilation were delayed to higher T_{es} in the N_20 condition (Fig. 3-2). The source of the decrease in ventilation appears to have arisen from the lower frequency of ventilation in the N_20 relative to the AIR exercise (Fig. 3-1c) since tidal volume was similar between conditions (Fig. 3b). The results support that, at exercise intensities greater than approximately 75% of the maximal workload, the increases in ventilation are neurally mediated since breathing of the narcotic gas N_20 reduced ventilation. Reports in the literature support that compressed nitrogen gas has a narcotic effect on ventilation of divers (2, 4).

White and Cabanac (7, 24) demonstrated T_{co} thresholds for ventilation with both passively (7) and actively (24) induced hyperthermia. Following these T_{co} thresholds, ventilation and T_{co} increased in direct proportion and the results supported an association between elevated T_{co} and increased ventilation during exercise. These T_{co} thresholds for ventilation were shown to be at an intensity of exertion that was significantly greater than VT_1 (26), that has been suggested to be of metabolic origin (17, 21). In addition it was reported (17, 21) these T_{co} thresholds were not significantly different than VT_2. The second ventilatory threshold at VT_2 is suggested to be neurally mediated (17) and together with the present results this supports the view that the hyperpnea of intense

exercise is a vestigial panting in humans (24). Evidence supportin this view was given by Nybo and Nielsen (20) who showed hyperthermia superimposed on a submaximal exercise session at ~57% of $\dot{V}O_{2MAX}$ gave a hyperventilation relative to exercise without the superimposed hyperthermia. Overall it appears that ventilation is a neurally mediated response that acts to help heat loss from the upper airways as evidenced by its direct influence on human cranial temperatures at higher levels of exertion (16).

The literature is not consistent on effects of N_2O on ventilation during exercise. Ciammaichella and Mekjavic (8) in a similar exercise protocol to that employed presently, saw no influence of 30% normoxic N_2O on ventilation at all levels of exertion from rest until maximal work rates. In contrast Fothergill et al. (11) focused on the response of minute ventilation rate with inhalation of 23% N_2O during both submaximal and maximal exercise and reported a 2% increase in V_E during maximal exercise. The current study supports the view that N_2O impairs exercise ventilation (14, 28).

At sea level the limitation to muscular work is attributed from the inability of the circulatory system to supply oxygen (O_2) to the tissues quickly enough at high exercise intensities. However, for work or exercise in hyperbaric conditions, the limiting factors for maximal exertion are from gas density, which increases the work of breathing (3), and from the narcotic effects of nitrogen gas in central nervous system tissues, which impedes action potentials and synaptic transmission. This mechanism is hypothesized to lead to decreased ventilation (2, 3). Several studies have illustrated a decrease in exercise

ventilation in hyperbaric conditions (1, 12, 22, 27), however, these studies have not separated the limitations placed on ventilation by either an increased gas density or the narcotic effects of nitrogen gas. Linnarson and colleagues. (15) studied the ventilation responses to exercise at successive workloads of 50, 150 and 250 W at 5.5 Bar with a mixture of nitrogen and oxygen, that has effects similar to N_2O, and compared them with air at 1.0 Bar. They found a decreased heart rate (HR), maximal voluntary ventilation, but did not see an effect of hydrostatic pressure on ventilation in their study (15). The current study employing normoxic nitrous oxide supports ventilation at depth would in part be limited by narcosis, if the assumption that elevated N_2 and N_20 partial pressures have the same effects on ventilation (5, 6). Despite a higher T_{es} (Fig. 3-5) for the N_20 trial, a lower ventilation (Fig. 3-2) was evident supporting its central narcotic effects on ventilation.

Nitrous oxide is known to influence temperature regulation and was found to significantly enlarge the null zone for T_{co} (18). In this study by Mekjavic and Sundberg (18) subjects performed submaximal exercise while immersed in a 28°C water bath (18). While there was no difference in the T_{co} threshold for cessation of sweating in their study (18), the T_{co} threshold temperature for the onset of shivering was shifted significantly to lower T_{co}. The null zone measured by T_{es} was increased from ~0.6°C to ~0.9°C with the inhalation of 30% N_2O (18). Nitrous oxide was suggested to affect neural mechanisms (18) through modifications to synaptic transmission (Bennet, 1982, as cited by (18)) and the propagation of action potentials (Carpenter, 1954 as cited by (18)). Our results

suggest that T_{es} thresholds for ventilation were also influenced by N_2O through a similar mechanism as suggested by Mekjavic and colleagues (Figure 3-2).

Another possible mechanism that may have contributed to changes in ventilation was that N_2O acted at cortical level and subjects consciously breathed less. This may be complementary or in addition to a direct narcotic effect on the respiratory control center where the frequency and depth of ventilation are thought to originate. In the absence of exercise, Eisele (10) examined the cardiovascular responses to 40% N_2O and reported without providing any reported experimental data that "respiration appeared to be slower and deeper"(10). This observation was also reported during exercise by Mekjavic and Sundberg (18) in their study of human exercise immersed in 28°C water with inhalation of 30% N_2O. They found, although not statistically significant, that there was a tendency for ventilation to be lower during N_2O breathing (18).

3.6 Conclusions

For subjects exercising from rest until maximum levels of exertion, inhalation of normoxic 30% N_2O significantly decreased ventilation at higher exercise intensities. This type of exercise with nitrous oxide inhalation raised T_{es} thresholds for ventilation. Together the results support that at higher exercise intensities, a neural component is evident in regulation of human ventilation.

3.7 Acknowledgements

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Table 3.1. Subject ages and physical characteristics.

Subject	Age (yrs)	Height (m)	Weight (kg)	BMI ($kg \cdot m^2$)
1	25.0	1.76	68.6	22.9
2	23.0	1.76	65.9	21.3
3	24.0	1.81	86.4	26.5
4	24.0	1.74	77.3	25.5
5	22.0	1.78	88.0	27.8
6	24.0	1.73	70.9	23.7
Mean	23.6	1.77	77.2	24.8
SE	0.5	0.01	4.1	1.1

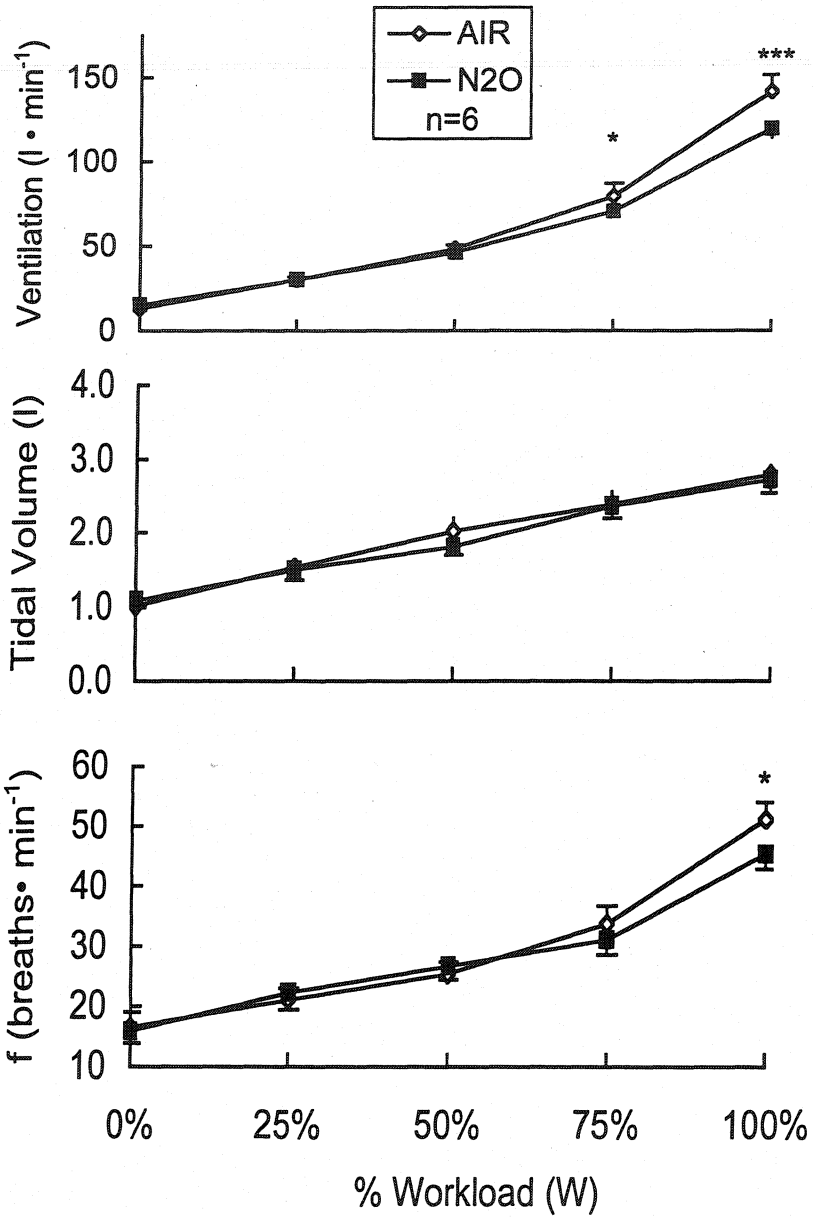

Figure 3-1 (a) Mean ventilation ($\dot{V}_E$), (b) Tidal Volume (V_T), and (c) Frequency of Respiration (f) expressed as function of percent of maximal workload for subjects exercising from rest until maximal attainable level of exertion The values were calculated over the duration each workload of 0, 25, 40, 75 or 100%. Subjects breathed either AIR or normoxic 30% N_20 during the two trials (*$p<0.05$, ***($p<0.0001$).

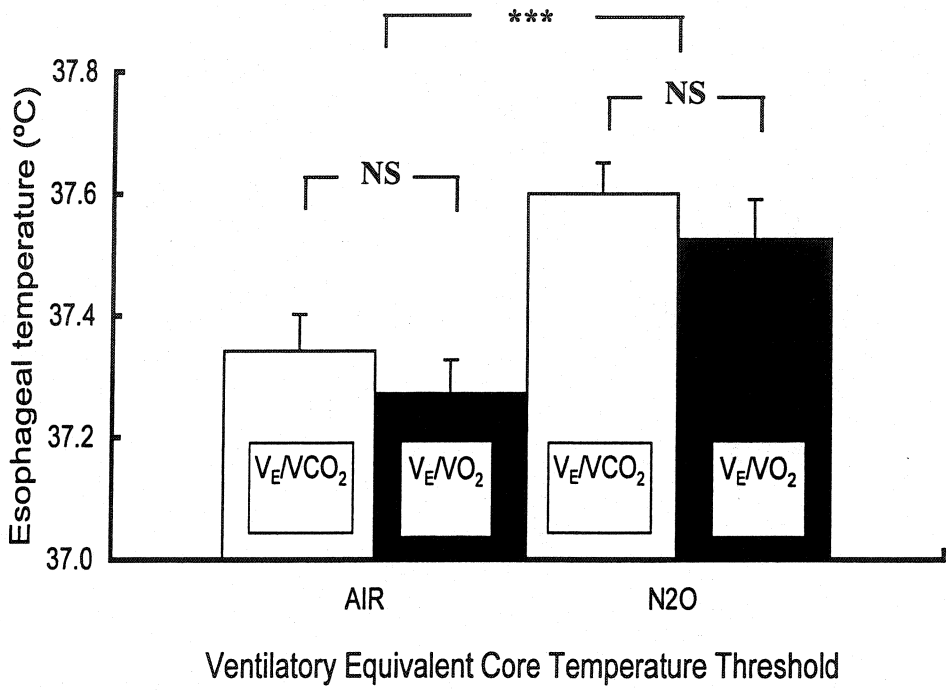

Figure 3-2. Esophageal temperature thresholds (mean ± SE) for ventilatory equivalents for carbon dioxide production ($\dot{V}_E/\dot{V}CO_2$) and oxygen consumption ($\dot{V}_E/\dot{V}O_2$) for subjects exercising from rest until exhaustion on a seated cycle ergometer. Subjects breathed either AIR or 30% normoxic nitrous oxide (N_2O) in separate trials **($p<0.001$).

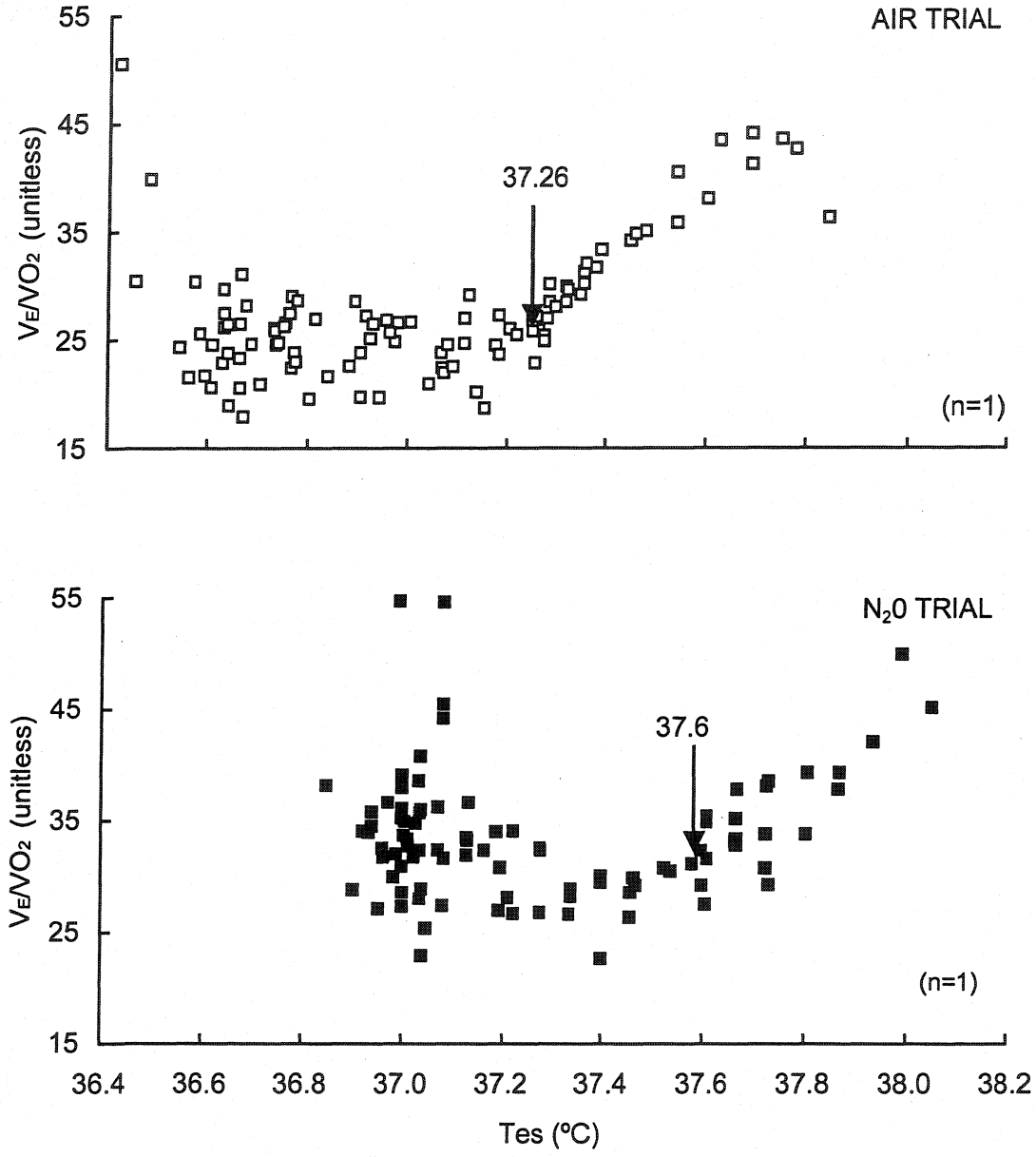

Figure 3-3. Sample subject's esophageal temperature (T_{es}) thresholds for ventilation during an incremental exercise from rest until exhaustion. The subject breathing AIR (top panel) or 30% normoxic nitrous oxide (bottom panel).

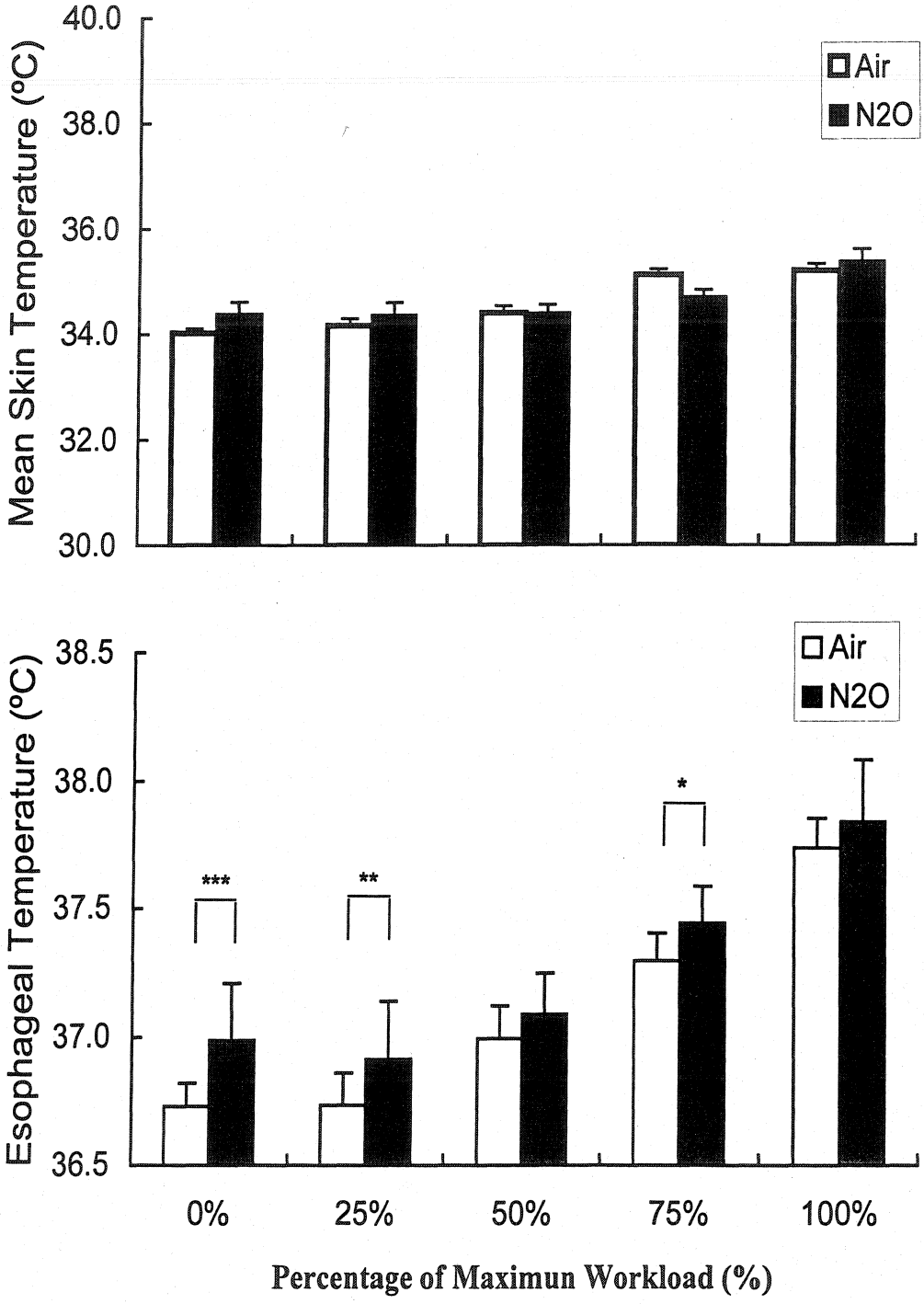

Figure 3-4 Mean skin temperatures (top) and mean esophageal temperature (bottom) each expressed as a function of percent of maximal workload for subjects exercising from rest until maximal attainable levels of exertion (*$p<0.05$, ** $p<0.01$, ***($p<0.0001$). .

Chapter 4: Effects of elevated core temperature and 30% normoxic nitrous oxide on human ventilation during short duration, high intensity exercise.

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4.1 Abstract

The influence of normoxic 30% nitrous oxide and passively induced hyperthermia on phase I exercise ventilation were examined during short duration, high intensity exercise. Six college age males (24.0 ± 0.8 y; mean ± SE), of normal physique (BMI, 23.8 ± 1.0 kg • m^{-2}), performed 4 separate 30-s Wingate tests on an electrically braked, seated, cycle ergometer. Subjects were monitored for total ventilation ($\dot{V}_E$) in 30 s, oxygen consumption and carbon dioxide production on a breath-by-breath basis as well as for esophageal temperature (T_{es}) and skin temperatures. Prior to 2 Wingate tests subjects T_{es} was elevated to ~38.5 ± 0.04°C in a 40°C bath. For the 2 other Wingate tests, subjects were not pre-warmed and exercise T_{es} remained at a normothermic level of ~36.8± 0.05°C. For hyperthermic or normothermic conditions, subjects had one Wingate test with room air inhalation (AIR) and in another Wingate test with 30% normoxic nitrous oxide (N_2O) inhalation. Results indicated the $\dot{V}_E$ of 43. 5 ± 5.1 l • 30 s^{-1} in the normothermic N_2O condition of was significantly lower ($p<0.05$) than the hyperthermic N_2O $\dot{V}_E$ of 61. 5 ± 8.7 • 30 s^{-1}. The normothermic N_2O tidal volume (V_T) of 1.71 ± 0.2 l was significantly lower ($p<0.05$) than both the normothermic AIR V_T of 1.99 ± 0.15 l and the hyperthermic N_2O V_T of 1.94 ± 0.20 l. In conclusion, the results support that the control of exercise ventilation in these conditions has a neural component since narcosis in normothermic exercise suppressed tidal volume and total ventilation while hyperthermia combined with normoxic N_2O increased both tidal volume and total ventilation.

4.2 Introduction

As ambient pressure increases in hyperbaric environments, the air is compressed and this has detrimental effects on a diver's performance. Divers breathing compressed air between 4 and 6 ATmospheres Absolute (ATA) of pressure experience nitrogen narcosis, the effects of which are similar to breathing 30% normoxic nitrous oxide (N_2O) under normobaric conditions (5). Thirty-percent-nitrous-oxide has been studied for its effects on psychomotor performance (6), cardiorespiratory function at rest (5, 11, 15, 23) and during exercise (9, 15, 22) and on human thermoregulation (8, 9, 18). The nature of human ventilation during intense exercise for divers under nitrogen narcosis has, however, received considerably less attention (9).

Divers conducting physical work at depth can be rendered hyperthermic with hot water from a surface supply warming system (19). This gives divers working with three potentially interacting influences on their ventilation. These are nitrogen gas under pressure (3), compressed air with a higher gas density (4), and elevated body temperatures (10, 29). At depth both the increased density and the narcotic effects of compressed air are thought to inhibit ventilation (4), although the relative contributions of these influences are difficult to assess. In contrast, an elevated core temperature (T_{co}) is known to stimulate human ventilation at rest (7, 16) or during exercise (10, 21, 29). In divers working in hyperbaric environments, each factor of elevated T_{co}, gas density, and effects of narcotic gases on peripheral chemoreceptors and/or central respiratory control

centers need to be considered to explain changes in their ventilation during exertion.

The present study was conducted to study the separate influences of hyperthermia and narcotic gases on human ventilation during intense exercise. To induce a large initial increase in ventilation without time for a change in T_{co}, a 30-s Wingate exercise test was employed in 4 exercise sessions. This is also described as phase I of exercise ventilation (12, 28). Narcosis was induced during the Wingate tests with inhalation of 30% normoxic nitrous oxide at 1 ATA. To allow a test of the separate effect of hyperthermia on ventilation, subjects were also immersed in a 40°C bath prior to two Wingate tests. As such, hyperthermic narcotic subjects', normothermic narcotic subjects', and hyperthermic air breathing subjects' responses were all compared to the control condition of normothermic subjects breathing air. It was hypothesized that N_2O would inhibit ventilation (4) and that increased T_{co} would enhance ventilation in these exercise conditions (10, 29).

4.3 Methodology

4.3.1 Subjects

The subjects' physical characteristics appear in Table 4-1. All participants were male, physically fit, non-smokers and made aware of any risks associated with the protocol used in this experiment. After reading a detailed outline of the study all participants signed informed consent. The sample size was determined using a power calculation. The difference worth detecting was set at 10%, with an alpha level of 0.05, a

beta value of 0.8 and a standard deviation of 7% of the estimated mean scores. The proposed research was approved by ethical review boards for human experimentation at Memorial University and at Dalhousie University.

4.3.2 Instrumentation

A Vmax229 series metabolic cart (Sensormedics, CA, USA) was employed to measured the expired gases. Breath-by-breath samples were collected from a sample line fitted close to the subject's mouthpiece. Gases were analyzed for O_2 with a paramagnetic gas analyzer and for CO_2 content with an infrared gas analyzer. A mass flow sensor was employed to measure expired gas flow. Prior to all trials the analyzers were calibrated against gases of known concentration. The pneumotach was calibrated before each experiment using a syringe of known volume. The influence of 30% nitrous oxide on infrared carbon dioxide sensing were accounted for in these calibrations.

Esophageal temperature (T_{es}) were estimated using an esophageal temperature probe (size 9Fr, Mallinkroft Medical Inc., St Louis, MO, USA) and the probe was inserted to the level of the left ventricle (20). Mean unweighted skin temperatures (T_{sk}) were estimated from sites at the chest, thigh and forehead with surface copper constantan thermocouples. All thermocouples were connected to a 32-channel data acquisition converter (National Instruments, SCXI – 1000, USA) and controlled by a National Instruments software package (Labview version 5-1) and values were continually displayed on a computer screen.

The gas inhalate included either normoxic nitrous oxide (30% N_2O, 21% O_2, balance N_2, Air Liquide Canada, INC.) or AIR that were stored in a Tissot spirometer (Model 1464, Boston, Massachusetts, USA) and supplied to the subject in corrugated Collins respiratory fiber tubing.

4.3.3 Protocol

Following instrumentation the subject exercised in one of four 30-s Wingate tests on an electrically braked, seated, cycle ergometer (2). Trials were performed 1 week apart and all participants were asked to refrain from ingesting nicotine or coffee for 12 hr prior to exercise tests. Subjects inhaled either room air or 30% normoxic N_2O in a given Wingate test. The subjects were normothermic (T_{es}~36.8°C) in two Wingate tests and hyperthermic in two other Wingate tests (T_{es}~38.5°C). Prior to the hyperthermic session subjects were warmed in a 40°C water bath and they started exercise within approximately 2 minutes after exciting the bath. This gave four conditions of exercise as shown in Table 4-2. The esophageal temperature (T_{es}) levels in the four conditions are given in Figure 4-1.

At the start of the test the subject was seated on the cycle ergometer and began breathing air or N_2O through the mouthpiece for 4.5 min baseline, followed by a 30 sec warm-up at 40 W to initiate a pedaling cadence between 80 to 90 rpm. The subject was given a 5 second countdown to the time of the end of warm-up and then proceeded to perform a 30 second Wingate test, with instructions to go and pedal as hard and as fast as

possible with a resistance of 0.09 kp (0.88 N)/kg and an approximate cadence of 80 to 90 rpm.

4.3.4 Statistical Analysis

The dependent variables of interest were the total ventilation, mean V_T, and mean F_R during the 30s Wingate tests. An ANOVA model (Table 4-2) was employed with repeated factors of Gas Type (AIR, N_2O) inhaled and Thermal State (Normothermic and Hyperthermic) of the subject. A priori orthogonal contrasts were employed to compare means and results were considered significant at 0.05.

4.4 Results

The T_{es} prior to and following each test Wingate test are given in Figure 4-1. The level of T_{es} in both normothermic trials were similar (e.g. ~36.8°C). This T_{es} level was significantly lower than the T_{es} of ~38.5°C in the two hyperthermic conditions. The means of T_{es} in the two hyperthermic trials were not significantly different.

Figure 4-2 gives the mean total ventilation over 30 s during the four Wingate exercise conditions. The total ventilation was lowest at 43.5 l ± 5.1 liters • 30 s^{-1} during the normothermic N_2O condition. Total $\dot{V}_E$ was at similar levels of 55.1 ± 4.5 liters• 30 s^{-1} in the normothermic AIR and of 54.6 ± 8.2 l • 30 s^{-1} in hyperthermic AIR. The highest total ventilation was of 61.5 l ± 8.7 l • 30 s^{-1} in the hyperthermic N_2O condition and this value was significantly greater ($p < 0.05$) than the level seen in the normothermic N_2O.

The lower total ventilation in normothermic N_2O condition was contributed to by a lower mean tidal volume in that exercise condition (Figure 4-3). There were significant decreases in the mean tidal volume to 1.7± 0.2 l in normothermic N_2O relative to the that of 2.0 ± 0.2 l ($p<0.05$) in the normothermic AIR condition and of 1.9 ± 0.2 l ($p<0.05$) in the hyperthermic N_2O condition.

The total number of breaths taken by each subject during the Wingate is given in

Figure 4-4. Across the four conditions there were no significant differences in total number of breaths.

The mean skin temperature (T_{sk}) responses are given in Figure 4-5 in each experimental condition. The level of T_{sk} was not significantly different between the start and the end of a given Wingate rest. There was no effect of gas type or thermal state on T_{sk} although there was a tendency for an interaction between gas type and thermal state ($F=4.7$, $p=0.08$) that was explained by a trend for a higher T_{sk} in the hyperthermic N_20 condition.

4.5 Discussion

By employing normoxic nitrous oxide inhalation during exercise our results separated the combined effects of narcosis and elevated ambient pressure that are thought to decrease exercise ventilation in hyperbaric conditions (14, 27). Also the pre-warming of subjects provided a means to assess the separate effect hyperthermia on initial exercise ventilation (12, 28). The results supported that N_2O inhalation significantly inhibited $\dot{V}_E$ under normothermic conditions as relative to hyperthermic conditions with N_2O (Fig. 4-2). This change in ventilation appears to have resulted due to a decrease in tidal volume in the normothermic N_2O condition (Fig. 4-3) since frequency of ventilation was not significantly different between conditions (Fig. 4-4).

Exercise ventilation during diving conditions appears to be inhibited by the combined effects of increased ambient pressure and nitrogen narcosis. Tetzlaff and colleagues found a significant decrease in $\dot{V}_E$ and V_T during exercise at 0.4 MPa (4 ATA) relative to exercise at 0.1 MPa (1 ATA) (27). The current finding that N_2O decreases total ventilation under intense exercise is in agreement with Tetzlaff and colleague's study (27) as well as results of Fagraeus and colleagues (14). Fagraeus and colleagues (14) also showed a decrease in $\dot{V}_E$ during heavy exercise (100 W, 150 W) at 4.5 ATA breathing compressed air as compared to 1.0 ATA breathing air. The current results support that the central narcotic effect of N_2O, or possibly nitrogen gas in the CNS for divers breathing air, should be considered in addition to the decrease in ventilation in that

is attributed to the increased density of air in hyperbaric conditions (25).

Hyperthermia has been linked to ventilation in incremental exercise (29), as well as in warm water immersion (7, 16). In both hyperthermic states ventilation increases out of proportion to oxygen consumption after T_{co} thresholds are reached during body warming (7, 29). In the present short duration, high intensity exercise, however, our data did not support an influence of increased T_{es} on ventilation unless it was combined with nitrous oxide inhalation (Fig. 4-2). This might suggest that the neurally mediated component, that is thought to account for the initial phase I increases in ventilation during exercise (12), is inhibited by narcosis and subsequently elevated by T_{es} back to levels seen in for exercise with air as the inhalate (Fig. 4-2).

When 30% normoxic N_2O was inhaled during submaximal exercise (18), the null zone of T_{co} was enlarged from ~0.6°C to ~0.9°C due to a suppression of the core temperature threshold for shivering with no change in the T_{co} threshold for cessation of sweating (18). Mekjavic and colleagues suggested that nitrous oxide affected neural mechanisms (18) through modifications to synaptic transmission and the propagation of action potentials (4). Our results suggest that ventilation was also influenced by inhalation of N_2O in terms of decreasing tidal volume during high intensity, short term exercise. The mechanism through which ventilation is reduced in exercise may be similar to what has been suggested by Mekjavic and colleagues (18), however, at the present time the neural pathways by which N_2O may influence tidal volume are

unknown. These authors (18) also observed a tendency for ventilation to be lower during N_2O breathing (18) although in a subsequent study with incremental exercise to maximum, ventilation was not reduced with 30% N_2O breathing (9). Another observation made by Eisele (13) is relevant to discussion on the potential mechanisms responsible for N_2O influencing ventilation. These authors (13) reported that inhalation of 40% N_2O under resting conditions induced slower and deeper ventilation in their subjects since they 'felt better', but they did not include any ventilation data in support of their observation. This suggested the effect of N_2O on the conscious control of breathing may be separate or in combination with N_2O's influence on the respiratory control center where efferent outputs changing frequency of respiration and tidal volume are believed to originate. In any case, our results clearly show that subjects took deeper breaths while breathing 30% N_2O. A future study is envisioned to quantify how the subjects "feel" during the exercise trials, so as to verify or refute Eisele's (13) observation that deeper breathing is a conscious experience for subjects breathing N_2O.

During exercise at higher intensities T_{co} may influence ventilation, although the mechanisms have not yet been clearly analyzed (17). This may result from a physical effect of temperature on peripheral chemoreceptors and/or central chemosensitive areas that may increase their responses to normal metabolic stimuli, such as seen for carbon dioxide with body warming (10, 24). Other possibilities include body warming that gives an increased central metabolic or a Q_{10} effect and associated increased in ventilation to meet metabolic demands. Also the activity of hydrogen ions is higher at elevated

temperatures (1) possibly providing greater central and/or peripheral stimulation of ventilation. Finally a decreased buffer capacity for CO_2 by body fluids takes place at higher temperatures (26) and this may lead to a lowered pH and compensatory hyperventilation.

4.6 Conclusion

In conclusion, the results support the hypothesis that N_2O inhibited ventilation. In these conditions core temperature did not affect ventilation unless combined with hyperthermia in this short duration, high intensity exercise. Overall this study supports that the effects of N_2O and T_{es} may have counteracting influences on exercise ventilation in these conditions.

4.7 Acknowledgements

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Table 4.1. Subject ages and physical characteristics.

Subject #	Age (yrs)	Height (m)	Weight (kg)	BMI* ($kg \cdot m^{-2}$)
1	25	1.76	71.8	23.2
2	23	1.78	65.9	20.8
3	26	1.86	87.7	25.4
4	22	1.73	66.8	22.3
5	22	1.78	86.8	27.4
6	26	1.73	70.5	23.5
Mean	**24.0**	**1.77**	**74.9**	**23.8**
SE (±)	**0.8**	**0.02**	**4.0**	**01.0**

*Body Mass Index (BMI)

Table 4.2. This table summarizes the four experimental conditions employed in this study. Each subject had four sessions of exercise for each of the experimental conditions as given in the table below.

		Gas Type	
		Air	**30% N_2O**
Thermal State	T_{es}~36.8°C	Normothermic Air	Normothermic N_2O
	T_{es}~38.5°C	Hyperthermic Air	Hyperthermic N_2O

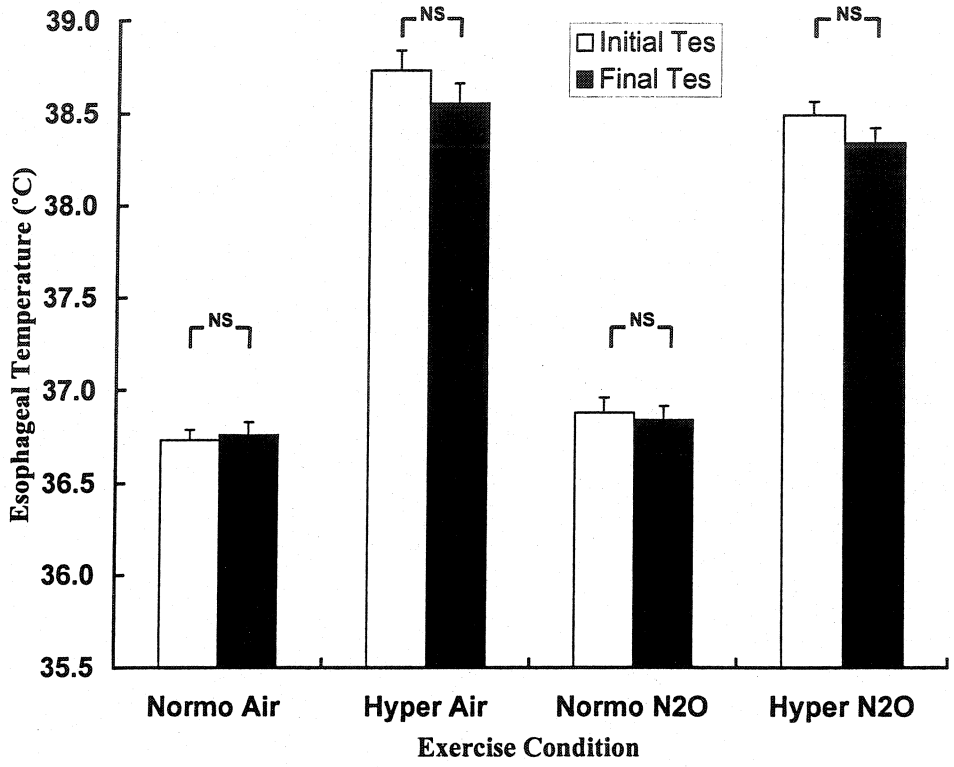

Figure 4-1. Initial esophageal temperature (T_{es}, open bar) prior to the Wingate exercise and the final esophageal temperature (T_{es}, black bar) at the completion of the Wingate exercise are shown in each of the four test conditions. Each vertical bar represents the mean response for 6 subjects and the error bars present the standard error of the mean (NS = Non- Significant).

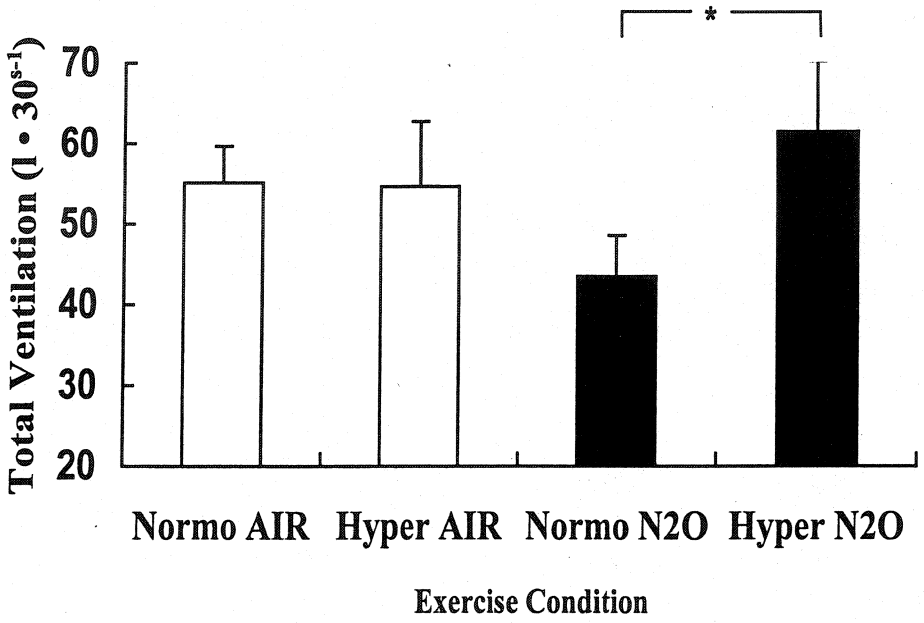

Figure 4-2. Mean total ventilation ($\dot{V}_E$) or the sum of all V_T during the Wingate exercise in each of the four conditions. AIR conditions are open bars and N_2O conditions are black bars. Each vertical bar represents the mean response for 6 subjects and the error bars present the standard error of the mean (*p <0.05).

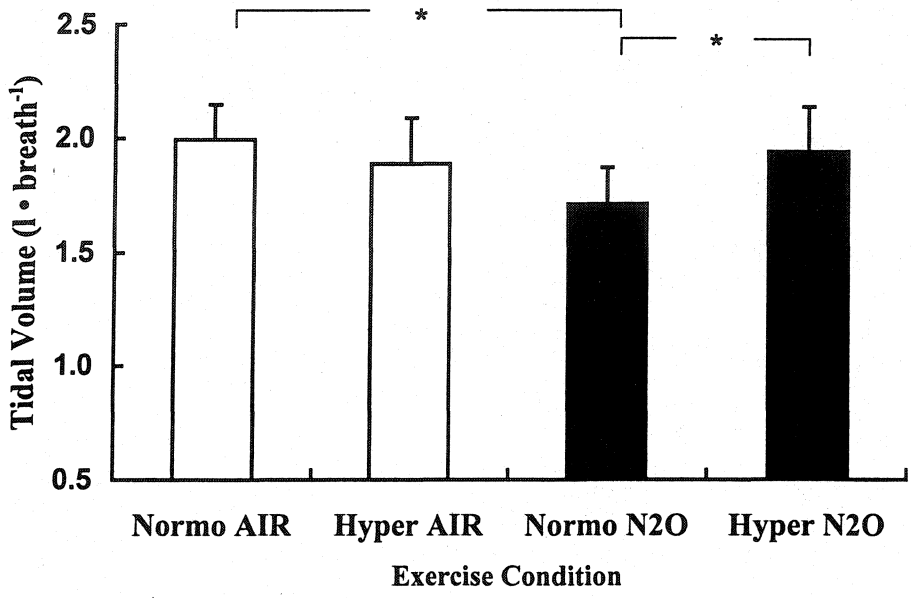

Figure 4-3. Mean tidal volume during the Wingate test in each of the four conditions. AIR conditions are open bars and N_2O conditions are black bars. Each vertical bar represents the mean response for 6 subjects and the error bars present the standard error of the mean.

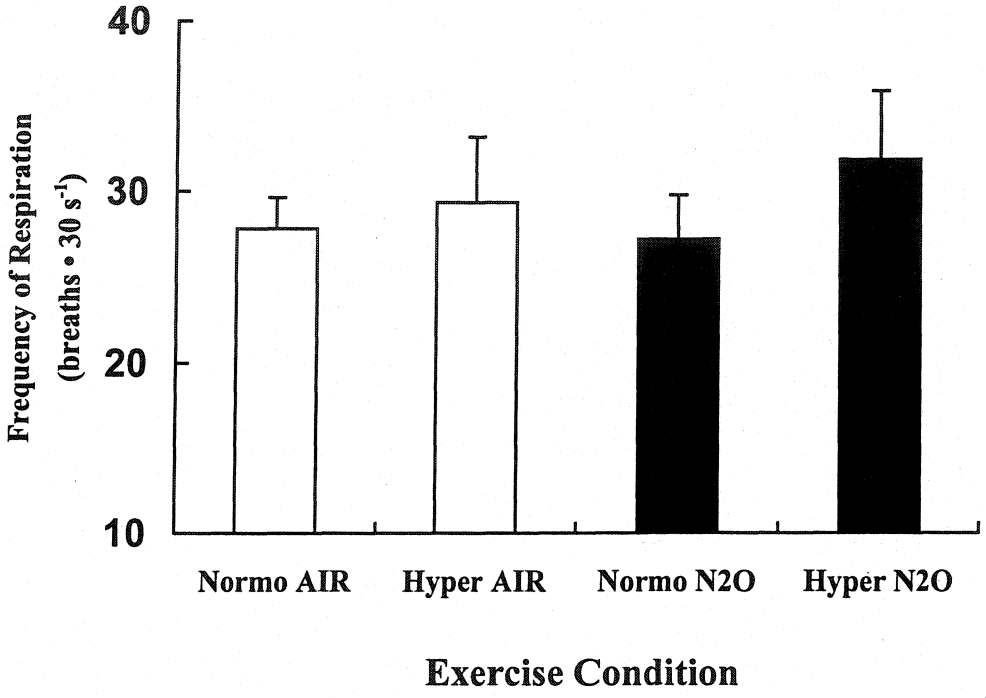

Figure 4-4. Mean total number of breaths taken during the Wingate exercise in each of the four test conditions. AIR conditions are open bars and N_2O conditions are black bars. Each vertical bar represents the mean response for 6 subjects and the error bars present the standard error of the mean.

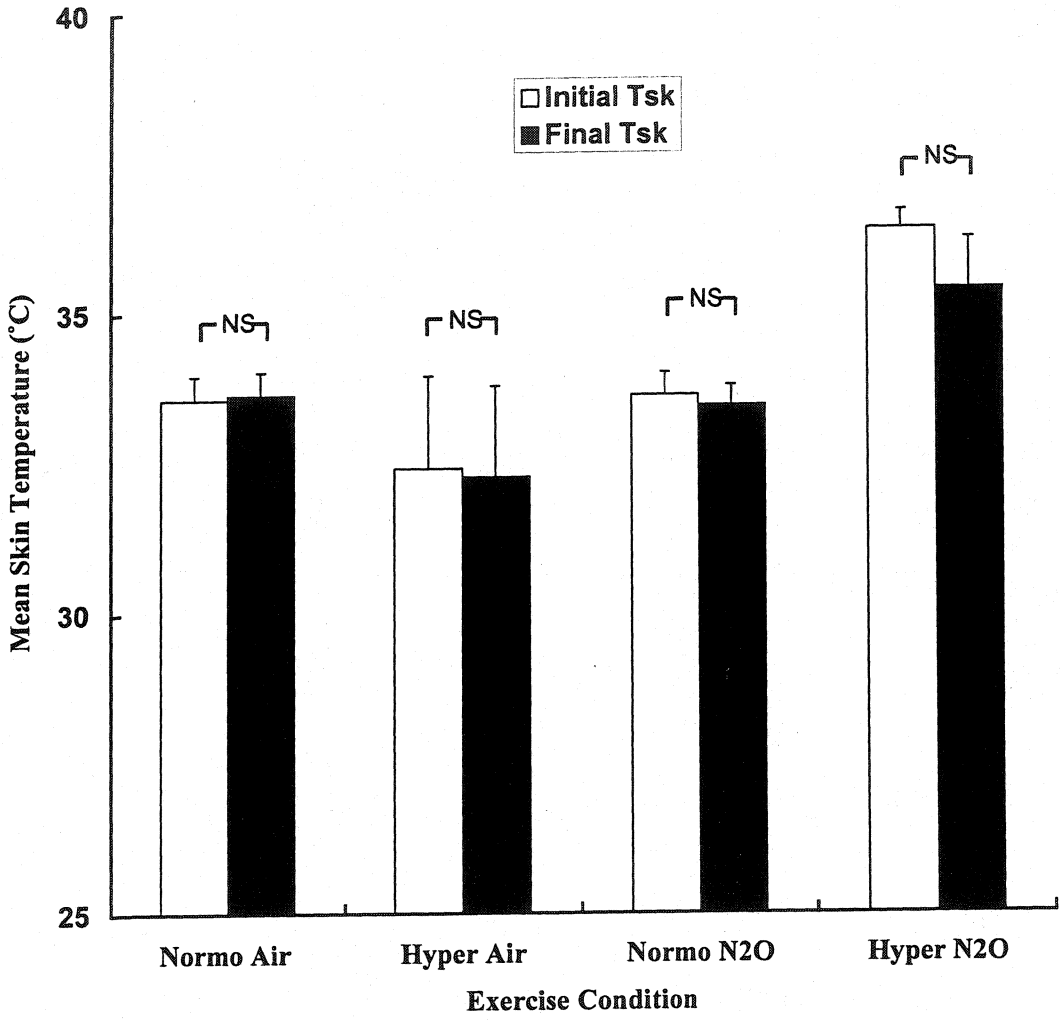

Figure 4-5. Initial (open bar) and the final (shaded bar) mean skin temperature (T_{sk}) prior to and following the Wingate exercise in each of the four test conditions. Each vertical bar represents the mean response for 6 subjects and the error bars present the standard error of the mean. (NS = not significantly different)

Chapter 5: Thesis Summary and Conclusions

5.1 Thesis Summary and Conclusions

It was hypothesized in this thesis that the relationship between ventilation and T_{co} (1, 8) would be influenced by N_2O if ventilation is neurally mediated at high exercise intensities (3-5). This hypothesis was addressed in the first study of this thesis in Chapter 3, where the effect of normoxic N_2O on ventilation was examined during phase III (2, 6) of the ventilatory response to exercise.

A second hypothesis in this thesis was that ventilation during short duration, high intensity exercise will be influenced by both normoxic N_2O and T_{co} (1, 8) if ventilation is neurally mediated at high exercise intensities (3-5). This hypothesis was addressed in the second study of this thesis in Chapter 4 where the effects of normoxic N_2O and T_{co} on ventilation were examined during phase I (2, 6) or during the initial increases in ventilation that are observed at the onset of exercise. This study was made possible with an innovative protocol that allowed a 'normothermic' exercise to be compared to a passively induced 'hyperthermic' exercise. Both these conditions were compared between air and 30% normoxic N_2O breathing conditions.

There were five testable questions stated at the end of the literature review in Chapter 2 of this thesis. Given below in this chapter are these five testable questions and their replies. The questions are separated into the two studies that were conducted in this thesis.

Study #1: Chapter 3: Influence of Normoxic 30% Nitrous Oxide on Ventilation and T_{co} Thresholds for Ventilation during Exercise

1. **How do the T_{es} thresholds for ventilatory equivalents of carbon dioxide and oxygen consumption (1, 8) compare during the same incremental exercise sessions from rest to maximal attainable work rates with subjects breathing either air or normoxic nitrous oxide?**

The results of this study indicated that, when subjects breathed a 30% normoxic nitrous oxide gas mixture, the core temperature thresholds (7-9) for ventilation were delayed to a significantly higher core temperature during incremental exercise. This was evidenced by a lower exercise ventilation in subjects breathing normoxic nitrous oxide than in those breathing air.

2. **How do tidal volume and frequency of respiration compare during identical incremental exercise sessions from rest to maximal attainable workrates with subjects breathing either air or normoxic nitrous oxide?**

The results indicated that, for exercising subjects who breathed a normoxic 30% nitrous oxide gas mixture, that the tidal volume was the same at all levels of exercise from rest until maximal attainable workrates as that in the same exercise in a control condition when air was breathed. In contrast, frequency of respiration was significantly lower at the highest exercise workload for the 30% normoxic nitrous oxide condition

relative to the air-breathing-condition. This decrease in the rate of breathing accounted for the lower observed ventilation at the maximal level of exercise for these subjects.

Conclusion to Chapter 3, Study #1

In conclusion, the results of study 1 indicated during (2, 6) that normoxic nitrous oxide inhibited phase III exercise ventilation and influenced the relationship between core temperature and ventilation during exercise. The results support that ventilation at high exercise intensities is neurally mediated as evidenced by this narcotic gas that inhibited ventilation.

Study #2: Chapter 4: Effects of hyperthermia and 30% normoxic nitrous oxide on human ventilation during short duration, high intensity exercise.

In this second set of experiments, independent of nitrogen narcosis, we determined whether a hyperthermic core affects ventilation during a 30-s, high intensity Wingate exercise test. Also, independent of raised core temperature, we determined whether nitrous oxide influenced ventilation in these exercise conditions. Finally, when a hyperthermic core temperature level was combined with 30% normoxic nitrous oxide breathing, we determined how ventilation responded relative to levels under control, air breathing conditions. Replies to the testable questions to address these potential effects of 30% normoxic nitrous oxide and core temperature on exercise ventilation are as

follows:

3. **Does ventilation during short duration, high intensity exercise change for a hyperthermic relative to a normothermic core temperature?**

Ventilation during short duration, high intensity Wingate exercise tests was the same during hyperthermia and normothermia in these exercise conditions.

4. **Does ventilation during short duration, high intensity exercise change for 30% normoxic nitrous oxide versus air breathing?**

Ventilation was lower during 30% normoxic nitrous oxide breathing than with air breathing for hyperthermic subjects during short duration high intensity exercise. The decrease in ventilation resulted from a significant decrease in tidal volume. The results support that nitrous oxide breathing inhibited ventilation through its narcotic effects on the central nervous system.

5. **Are the effects of hyperthermia and nitrous oxide on ventilation short duration, high intensity additive, or do they interact?**

When 30% normoxic nitrous oxide was combined with hyperthermia, ventilation was similar to that observed during air breathing (Figure 4-1). This suggested nitrogen

narcosis, induced by 30% normoxic nitrous oxide breathing, and core temperature have additive effects on ventilation. Stated otherwise, the ventilation that was lowered by 30% normoxic nitrous oxide breathing was returned to normal levels when hyperthermia was combined with this narcotic gas treatment.

Conclusion to Chapter 4, Study #2

In conclusion, the results of study 2 indicated that nitrous oxide suppressed ventilation by decreasing the tidal volume or depth of respiration during phase I exercise ventilation (2, 6). The results support that ventilation is neurally mediated since nitrous oxide and core temperature both influence ventilation during short duration, high intensity exercise.

Overall Thesis Conclusions

Phase I and III of exercise ventilation were examined in this thesis. During phase III (Study 1) and phase I (Study 2) of exercise ventilation, nitrous oxide decreased ventilation. This effect came about differently in each phase of exercise ventilation. In phase III, 30% normoxic nitrous oxide decreased the frequency of respiration and as a result the ventilation. In phase I exercise ventilation 30% normoxic nitrous oxide lowered ventilation by decreasing the depth of the tidal volume and did not influence the frequency of respiration. Although hyperthermia alone did not influence exercise

ventilation in Phase I, when hyperthermia was combined with nitrous oxide the effect appeared additive. This thesis supports the hypothesis that the control of exercise ventilation in Phase I and Phase III has a neural component.

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