

Sex Differences in the Physiological Response to the Modern Fire Environment

by

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A thesis

presented to the University of Waterloo

in fulfillment of the

thesis requirement for the degree of

Master of Science

in

Kinesiology

Waterloo, Ontario, Canada, 2024

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## **Author's Declaration**

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

## **Abstract**

Due to recent changes in building design and materials, modern structural fires tend towards a ‘ventilation-limited’ fire environment, resulting in globally low levels of oxygen (O<sub>2</sub>) and increased amounts of carbon monoxide (CO) and smoke. It is unknown how the dynamic hypoxic and hypercapnic environment as a result of the fire impacts an occupant’s physiological and cognitive ability to evacuate. Moreover, it is unknown if physiological sex differences in males and females may further impact egress abilities. This work explored the effects of this dynamic hypoxic and hypercapnic environment on the ability to egress by exposing males and females to sub-incapacitating levels of hypoxic and hypercapnic gases measured in large-scale ventilation-limited fires. Thirty participants (n=15 females) completed three testing days. Day 1 was a familiarization day, intended for participants to familiarize themselves with the experimental protocol of the egress scenario in ambient conditions. Day 2 consisted of five trials of the simulated evacuation scenario wherein real-time changes to O<sub>2</sub> and CO<sub>2</sub> were administered with CO saturations (%COHb) of 4% and 7%. Day 3 consisted of four trials of the simulated egress scenario wherein changes to O<sub>2</sub> and CO<sub>2</sub> were carried out in tandem and in isolation. The egress scenario consisted of the following 12.5 minute sequence: 1 min seated pre-test baseline, 5 mins seated, 3.5 mins walking, 4 mins walking carrying a 20lb weight and 2.5 mins seated post-test baseline. This scenario was intended to simulate a realistic evacuation of an occupant from a residential structure, however did not include the more dangerous fire elements (increased temperature, smoke and particulate matter). End-tidal gases, ventilation, heart rate and oxygen saturation were measured continuously. Response (decision, answer and reaction) time was assessed by participants answering a prompt every 15s throughout

each trial. The prompts consisted of a directional EXIT sign in which participants had to select the arrow corresponding to the direction of the EXIT sign, as well as a modified Stroop Colour Test. Results demonstrate that females elicited a greater percent change within a condition compared to males for heart rate ( $p=0.04$ ), tidal volume ( $p=0.03$ ) and fraction of hemoglobin bound to oxygen ( $p=0.02$ ). Physiological changes in responses for all participants were significantly greater during the hypercapnia egressing trials compared to hypoxia and control trials (Ventilation:  $72\pm 20$  L/min,  $34\pm 8.9$  L/min,  $33\pm 6.4$  L/min,  $p < 0.05$ ; tidal volume:  $2.3\pm 0.6$ L,  $1.5\pm 0.4$ ,  $1.4\pm 0.3$ ,  $p < 0.05$ ). Physiological responses during 4% COHb and 7% COHb trials did not differ other than the fraction of hemoglobin bound to oxygen during pre and post baselines ( $p < 0.05$ ). Overall, the presence of CO<sub>2</sub> resulted in the greatest physiological response and coincided with a decrement in ability to complete the egress protocol. Smaller females appeared to be more affected by fire conditions during egress than males. These results indicate that the modern ventilation-limited fire environment results in physiological responses that could negatively impact an occupant's ability to effectively evacuate.

## **Acknowledgments**

I would like to acknowledge all of the participants who volunteered their time and efforts to contribute to the research.

I would like to thank my supervisor Dr. Paolo Dominelli whose mentorship and guidance have been invaluable throughout my master's thesis.

I would like to thank my committee members, Dr. Beth Weckman and Dr. Michaela Devries-Aboud for their knowledge and support throughout my project.

To my lab mates: Bronwyn Forrest, Ben Thompson, Connor Doherty, Leah Mann, Sarah Angus, Paige Rynne, Victoria Chang, Aaron Thompson and Maddie Wright, thank you for supporting me and always be willing to offer a helping hand when needed. Thank you for supporting me throughout my time at the University of Waterloo

Finally, thank you to my family and friends for the constant encouragement, positivity and being present though out my entire academic career.

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## List of Abbreviations

Alveolar-arterial oxygen difference ( $A-aDO_2$ )  
Alveolar partial pressure of oxygen ( $PAO_2$ )  
Arterial partial pressure of carbon dioxide ( $PaCO_2$ )  
Arterial partial pressure of oxygen ( $PaO_2$ )  
Breathing frequency ( $F_b$ )  
Carbon dioxide ( $CO_2$ )  
Carbon monoxide (CO)  
Cardiac output (Q)  
Expiratory ventilation ( $V_E$ )  
Fraction of carbon monoxide bound to hemoglobin (FCOHb)  
Fraction of expired carbon dioxide ( $FeCO_2$ )  
Fraction of expired oxygen ( $FeO_2$ )  
Fraction of oxygen bound to hemoglobin ( $FO_2Hb$ )  
Hemoglobin (Hb)  
Hydrogen ion ( $H^+$ )  
Hydrogen cyanide (HCN)  
Inspiratory ventilation ( $V_I$ )  
Loaded exercise (LE)  
Maximal oxygen consumption ( $VO_2 \text{ max}$ )  
Nitric oxides ( $NO_x$ )  
Oxygen ( $O_2$ )  
Oxygen saturation ( $SaO_2$ )  
Oxygen saturation measured by a pulse oximeter ( $SpO_2$ )  
Partial pressure of carbon dioxide ( $PCO_2$ )  
Partial pressure of oxygen ( $PO_2$ )  
Percentage carboxyhemoglobin (% COHb)  
Post-baseline (PoB)  
Pre-baseline (PrB)  
Rate of perceived exertion (RPE)  
Tidal volume ( $V_T$ )  
Unloaded exercise (ULE)  
Ventilation-perfusion (V-Q) mismatching  
Volume of  $CO_2$  produced ( $VCO_2$ )  
Volume of oxygen consumption ( $VO_2$ )  
Worst-case loaded exercise (WCLE)

## List of Equations

**EQ 1.**  $\text{Fuel} + \text{O}_2 \rightarrow \text{CO} + \text{CO}_2 + \text{C} + \text{H}_2\text{O}$

**EQ 2.**  $n\text{Hb total} = \text{Hb mass in the body} / \text{Hb molar Mass}$

**EQ 3.**  $n\text{Hb tagged} = n\text{CO absorbed} / 4$

**EQ 4.**  $PV = nRT$  (equation 4)

**EQ 5.**  $\% \text{COHb} = (n\text{Hb tagged} / n\text{Hb total}) \times 100\%$

**EQ 6.**  $\text{Total \%COHb theoretical} = \text{baseline \%COHb} + \% \text{COHb}$

**EQ 7.**  $V_I = V_T \times F_b$

**EQ 8.**  $V_E = V_I / ((1 - (\text{FeO}_2/100)) - (\text{FeCO}_2/100)) / (1 - 20.93/100) - (0.03/100))$

**EQ 9.**  $\text{SpO}_2 = \text{FO}_2\text{Hb} + \text{FCOHb}$

# 1 Literature Review

Due to changes in building design and materials, modern house fires are evolving from well-ventilated to a ventilation-limited mode of burning. This is resulting in a fire environment that contains relatively lower levels of oxygen and increased smoke production, as well as higher levels of carbon monoxide (CO) and other incomplete combustion products. The individual effects of hypoxia, hypercapnia and carbon monoxide poisoning have all been well characterized in the literature but the effects of these gases in combination and in the face of acute exercise is poorly understood. As such, there is a dearth in knowledge of the physiological and cognitive deficits that might impact occupants' ability to evacuate from a modern fire environment. Previous exercise physiology research largely focused on young, healthy males; and with respect to toxic impacts of fires, the research that has largely informed egress (evacuation) design parameters used today mainly utilized animal studies to characterize incapacitation and lethal levels of exposure to fire gases. The need to understand impacts of modern fire exposures on humans paired with known physiological sex differences between males and females revealed from recent studies, which could suggest differences in abilities to egress in a fire scenario, form the basis for this research. We aim to characterize the physiological and cognitive response of individuals who are exposed to concentrations of fire gases measured during a large-scale ventilation-limited furniture fire in an upstairs bedroom in order to identify any differences in responses between sexes.

## 1.1 Characterizing the Modern Fire Environment

### 1.1.1 Modern Dwelling Fire Environment

With the drive to be more energy efficient, homes in recent decades are built to be well-sealed, which allows for minimal exchange between controlled indoor conditions and the ambient outdoor environment. Simultaneously, building and furnishing materials are being made with more synthetic materials (i.e. polyurethane foams) instead of natural ones (i.e. wool) as seen in the past (1–3). In addition to material differences, legacy homes, built in 1950s-1970s, tend to be smaller, single storey and were designed to be more compartmentalized (1).

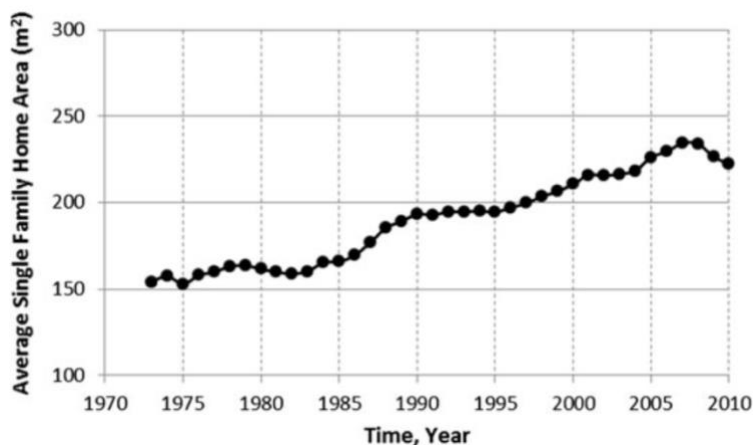


Figure 1: Average single family home size 1970 to 2010 in the United States (1).

Figure 1 illustrates the increase in area for single family homes in the last 40 years (1). In the 21<sup>st</sup> century, modern homes tend to be large, multiple-storey, with open floor plans becoming increasingly common (4). Homes that are open concept can pose a challenge in a fire scenario, as it can be difficult to contain fires to a single space by simply closing a door and isolating the fire to the room of origin, a viable tactic in compartmentalized legacy homes. Additionally, open floor plans of modern homes allow for continuous airflow throughout rooms on a given floor, which can promote mixing between the smoke layer and ambient air (1, 3, 5). This mixing tends

decrease the levels of ambient oxygen throughout adjacent rooms during a fire as the rooms fill with smoke. From 2010-2014, 62-66% of fires in Canada were residential fires (6). From 2011-2020, there were approximately 220 fire-related death per year, and 46% of these deaths took place in a detached, semi-detached or row house (7). The new materials and design of modern homes have led to implications for occupant safety as modern fires tend to develop much faster than previously seen in legacy homes (1). In addition, larger homes usually have more furniture, which in turn increases the available fuel supply to support a fast fire growth (3). The fuel supply provided by furniture within the home, specifically those made with synthetic materials, in conjunction with large, open and tightly sealed building envelopes can alter the fire environment to a ventilation- limited burning regime. The implications this acute exposure has on human health will be further detailed later on.

### *1.1.2 Materials and Fire Development*

Synthetic and composite materials (i.e. engineered timber products) are typically used to furnish homes instead of natural materials such as wool and timber (1–3). Due to the high levels of energy contained in the bonds of synthetic materials, high amounts of energy and heat are released when bonds are broken during the combustion process. This promotes rapid fire growth, which in turn increases the rate of oxygen consumption by the fire. This rapid depletion of available oxygen can lead towards ventilation-limited environments as oxygen is drawn first from areas close to the fire origin and can eventually lead to globally low oxygen levels throughout the home as the fire continues burning and pulls oxygen from the areas much further away to support combustion (8). To demonstrate the impact of materials on fire development, six experiments were set up using two different room sizes and fires were ignited via a candle placed

on top a sofa from the corresponding period: modern or legacy. Experiments were conducted in simulated living rooms to allow a comparison to be made between modern and legacy furnishings. Modern rooms utilized synthetic contents that were readily available at common retail outlets whereas legacy rooms utilized contents purchased at second hand outlets (1, 9). Despite minimal changes to burn room size, all experiments contained similar types and amounts of furniture and fuel loads. The results of these tests comparing the fire growth of modern and legacy materials revealed that synthetic materials result in very rapid fire growth (Figure 2) (9). Within 10 minutes, temperatures in modern fire environments fuelled by synthetic materials can reach upwards of 1000 °C, whereas slower burning natural material fires take over 25 minutes to reach these extreme temperatures (9).

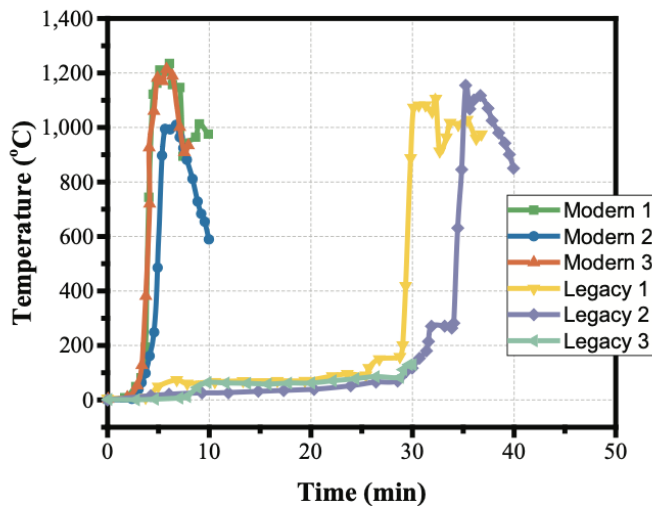
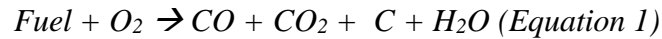


Figure 2: Temperature changes over time when comparing heat release in modern (polyurethane and polyester couches) and legacy furniture (wool and cotton couches) (1, 9).

In modern homes, ventilation is often considered to be the limiting factor preventing fire growth (10, 11). Once the balance of oxygen and fuel can no longer be sustained, namely when oxygen levels decrease below a threshold to support efficient combustion pathways, more products of incomplete combustion will be produced. The process of incomplete combustion

produces more dense and toxic smoke as relatively more particulate matter and harmful by-products are produced, including gases like carbon monoxide and hydrogen cyanide as well as irritants such as hydrogen chloride and nitrogen oxides (1). The basic equation for incomplete combustion of a hydrocarbon is shown by Equation 1 below:



Incomplete combustion produces higher concentrations of CO and other toxic gases while maintaining production of CO<sub>2</sub> and consumption of O<sub>2</sub> (12), as such the accumulation of asphyxiant gases can occur to a higher degree throughout the building structure. Additionally, the dense smoke as a result of this can result in a decrease in visibility and increased irritation to the eyes and airways (1, 13). In order to ignite and sustain burning, fires require a balance of heat, fuel and ventilation (oxygen), and these must be maintained to allow for the fire to grow and continue burning. Heat release rate (a measure of the rate that heat is generated by the fire) rise in temperature and gas concentrations of combustion products are all reliant on the amount of oxygen available to the fire (14). In modern airtight dwellings, a reduction of the available oxygen concentration over the course of the fire can become a limiting factor in sustained burning (12). Overall, fast-growing fires with synthetic materials as the fuel load in airtight (energy efficient) structures can progress to a ventilation-limited fire environment. These changes to our homes and furnishings can create a unique fire environment that has altered impacts to human survival. The following section will provide more details on the ventilation-limited fire environment as well as a brief introduction to common toxic gases found in fires.

## 1.2 Large-scale Ventilation-Limited Fires and Toxic Gases

The production of toxic gases in the modern fire environment appear to occur sooner and in higher concentrations than previously seen (5, 11). Natural materials produce toxic gases at a relatively slower rate compared to synthetic materials, in part due to a relatively slower fire growth and thus oxygen depletion, promoting more efficient combustion pathways for a longer period of time as the fire grows (15). Laboratory scale experiments have found the asphyxiant gases CO, CO<sub>2</sub> and hydrogen cyanide (HCN) and the irritant nitric oxides (NO<sub>x</sub>) to be the most deadly gases in fires and create a highly toxic environment (14, 16). As such, the toxicity of the fire and inhalation of asphyxiant gases is the most likely cause of most smoke inhalation fire deaths (14, 16–18). Effects from inhalation of these gases are usually minimal at low concentrations until a critical dose is reached, and following this critical dose, intoxication and loss of consciousness are likely to occur (18, 19).

The previous work done at a laboratory scale informs important gases to measure at large scale to quantify concentrations of these toxic gases that can be produced in a large-scale fire scenario. The gas concentrations presented in Figure 3 below are from a large-scale ventilation-limited fire, fuelled by a couch (commercially available in Canada), placed on the main floor of a two-storey structure sealed to the outside environment with no additional ventilation sources (20). Gas concentrations were collected by custom-made gas sensor boxes placed at various locations and levels throughout the second storey of the structure (indicated by GIS number in Figure 3). These gas sensor boxes were placed at different heights (0.3, 0.9 and 1.5m above floor level) and locations to collect concentrations of different gases, O<sub>2</sub>, CO, HCN and NO<sub>x</sub>, present in the environment (Figure 3). The similar concentrations of each gas over time at the varying heights indicates the prevalent mixing of gases that is seen in the upstairs fire environment. This

is seen in the fairly uniform decreases in oxygen (minimum between 12-16% O<sub>2</sub>) throughout all locations and heights on the upper floor. Similarly, carbon monoxide concentrations reach a uniform peak (approximately 2500ppm) at all heights and upstairs locations. At the top of the staircase (GIS 5), the measured combination of 12% O<sub>2</sub>, 2500ppm CO, 225ppm NO<sub>x</sub> and 125ppm HCN could pose significant danger to an individual attempting to egress the structure.

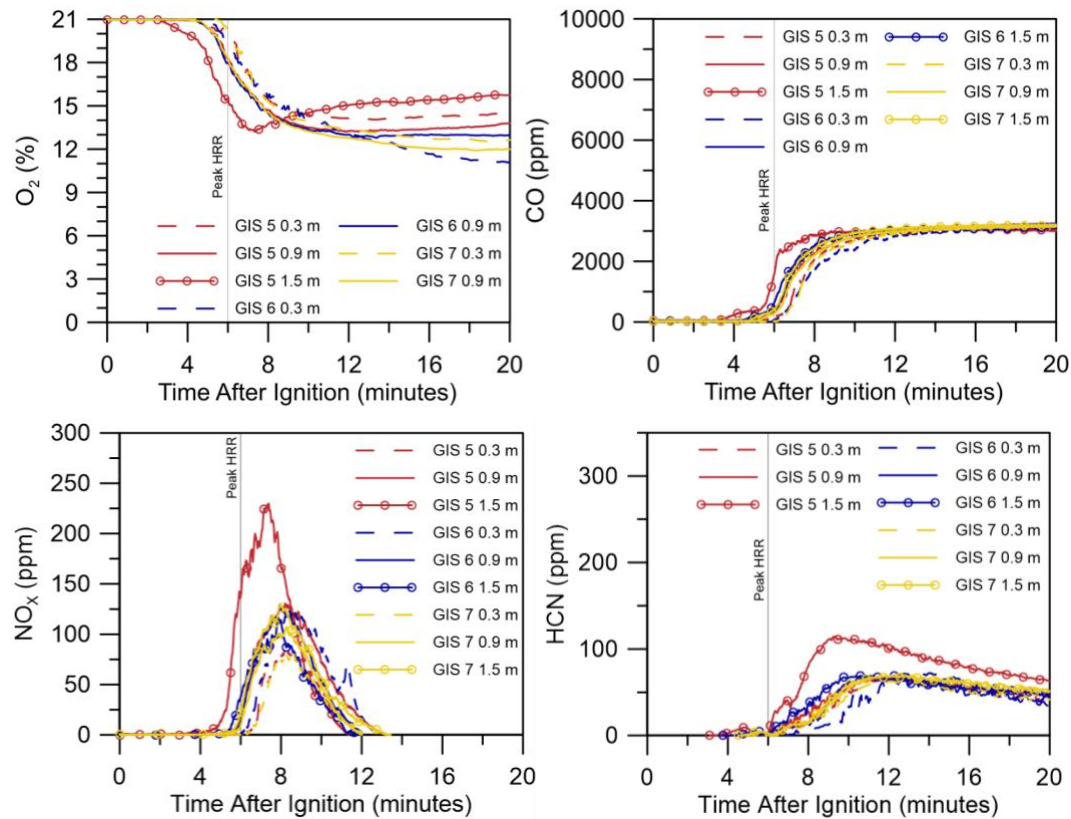


Figure 3: Gas concentration traces over time in the upstairs bedroom during a large-scale furniture fire. GIS 5 placed on the top of the stairs leading from downstairs, GIS 6 placed in the small upstairs bedroom and GIS 7 placed in the large upstairs bedroom. All measurements were taken at 3 heights, 0.3, 0.9 and 1.5 m above the floor. Concentration of oxygen (upper left), carbon monoxide (upper right), nitric oxides (lower left) and hydrogen cyanide (lower right) were collected throughout the duration of the fire (20). Reprinted from Fire Safety Journal, 141, Bronwyn Forrest, Alexander DiPaola, Vusal Ibrahimli, Ayaan Lakhani, Elizabeth Weckman, Towards characterizing full-scale furniture fires in a two-storey house: Gaseous species concentration during a ventilation-limited fire., Copyright (2023), with permission from Elsevier.

Unfortunately, fire statistics from 1955 to 2013 show an increase in the proportion of fire deaths (21, 22). Considering the gas concentration plots presented in Figure 3, this increased prevalence in fire deaths could be a result of the ventilation-limited fire environment, as the hypoxic (as a result of rapidly depleted oxygen, O<sub>2</sub>) and hypercapnic (due to the production of carbon dioxide, CO<sub>2</sub>, the primary product of combustion) conditions throughout the structure in conjunction with increased production of carbon monoxide (CO), dense smoke and other harmful by-products (HCN, NO) make the environment very untenable (21, 22). The physiological effects of inhaling increased amounts of CO<sub>2</sub> and CO, and decreased O<sub>2</sub> in isolation is further detailed below in sections 1.3, 1.4 and 1.5. Overall, the likely major contributors to a fire death are O<sub>2</sub> deficiency, toxicity of inhaled asphyxiant gases and heat. The physiological impact of these gases in tandem has not yet been explored but the individual effects of CO<sub>2</sub>, O<sub>2</sub> and CO will be discussed below.

### **1.3 Acute Effects of Hypoxia on Human Function**

During a dwelling fire, O<sub>2</sub> is decreased, while CO<sub>2</sub> and CO are increased. Global decreases in O<sub>2</sub> are uniquely prevalent in the modern ventilation-limited fire environments. In ambient air, O<sub>2</sub> is 20.93%, however during a fire it is possible that O<sub>2</sub> content can be significantly decreased to 16% or lower (20). When arterial partial pressure of oxygen (PaO<sub>2</sub>), is lowered, ventilation increases to increase O<sub>2</sub> levels in the body. However, increases in ventilation cannot always fully compensate for the decreased inspired oxygen pressures, at which time the individual becomes hypoxic. Hypoxia is a state of insufficient O<sub>2</sub> availability caused by exposure to a reduced inspired partial pressure of oxygen (PO<sub>2</sub>), and broadly can be viewed as insufficient amounts at the tissue level to maintain adequate homeostasis (23). Insufficient oxygen content can

incapacitate individuals by impairing cognitive, physiological and physical abilities (18). Effects of hypoxia are commonly seen when individuals ascend to altitudes greater than 1500m (24, 25), which is similar to the acute effects within a fire environment. However, the effects are dose-dependent to a given individual's PaO<sub>2</sub>. Resting normal PaO<sub>2</sub> is usually between 90-100mmHg, and mild to moderate effects of hypoxia are elicited when PaO<sub>2</sub> is between 45-70mmHg, with loss of consciousness likely occurring below 30mmHg (26). During hypoxia, PaO<sub>2</sub> and oxygen saturation (SaO<sub>2</sub>) are decreased. As seen in Figure 4, moving left along the slope of the oxygen dissociation curve, hemoglobin (the oxygen-carrying protein on our red blood cells) is less saturated, which decreases oxygen content in the blood (27). Hypoxic exposure can affect both mental and physiological function and declines are exacerbated during exercise compared to rest, as exercising muscles require further oxygenation (28). Decrements due to hypoxia on both cognition and physiological implications will be detailed in subsequent sections.

### *1.3.1 Impact of Hypoxia on Physiological Function*

Hemoglobin is the main protein that transports oxygen. Approximately 98% of total O<sub>2</sub> transported in the blood is bound to hemoglobin (Hb), while the remaining 2% is dissolved in the plasma (29). Through the process of diffusion in the alveoli, O<sub>2</sub> binds Hb in the red blood cells. Oxygen is then transported by the red blood cells and offloaded at the site of the tissue. There is a sigmoidal relationship between the partial pressure of O<sub>2</sub> and percentage of Hb saturated within the body. This relationship is illustrated in Figure 4, and is more commonly known as the oxygen dissociation curve (30). This sigmoidal oxyhemoglobin curve demonstrates that at high PO<sub>2</sub> (80-100mmHg), there is little change to oxygen saturation with alteration in PO<sub>2</sub>. When at rest, there is minimal oxygen demand, this is met by more than adequate oxygen supply and extraction of only what is needed. Moving left along the slope of the oxygen dissociation

curve, hemoglobin becomes less saturated, which decreases  $PO_2$  in the blood. If  $O_2$  delivery were to fall, or during exposure to hypoxia, extraction from the blood must increase to compensate and meet the increasing  $O_2$  demand of the tissue (30). However, there are limitations to the overcompensatory mechanism of extraction to meet demand in the tissues.

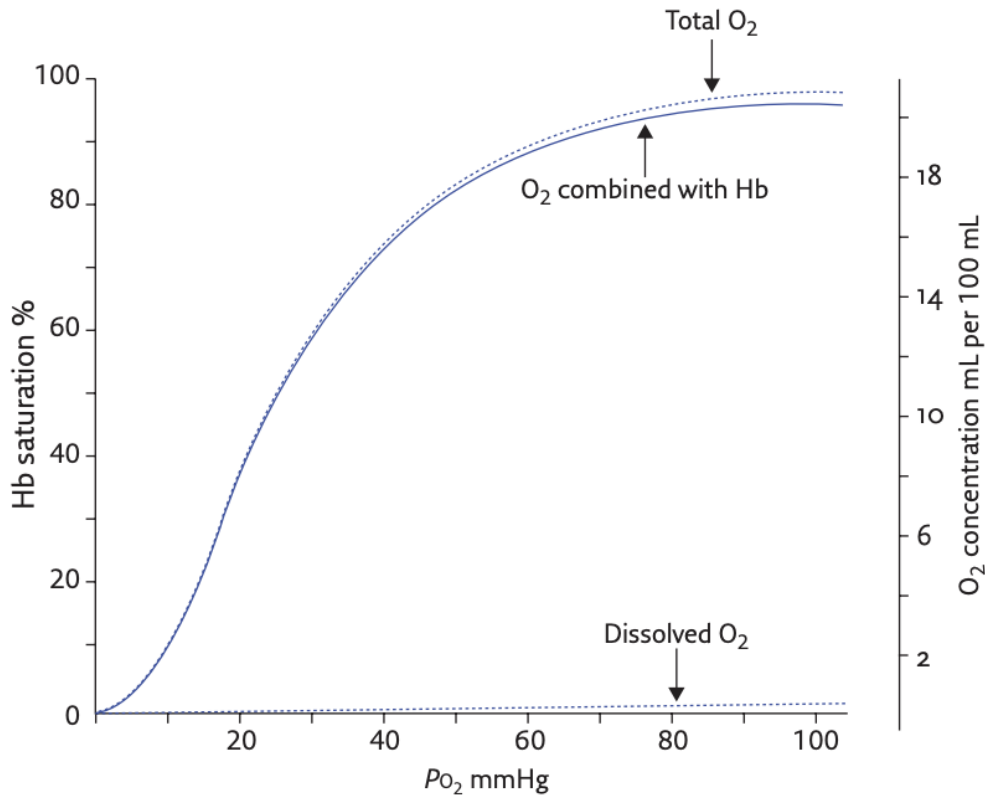


Figure 4: The oxygen and hemoglobin dissociation curve (27).

The alveolar-arterial oxygen difference ( $A-aDO_2$ ) gradient describes this relationship as it compares the partial pressure of oxygen in the alveoli to arterial oxygen partial pressure, essentially the overall efficiency of diffusion of oxygen into pulmonary capillary blood (31). During exercise to meet the  $O_2$  demand in the tissues, alveolar partial pressure of oxygen ( $PAO_2$ ) rises due to the relative hyperpnea, increase in depth and/or speed of breathing. This creates a higher  $PO_2$  in the alveoli compared to the arterial blood and thus the alveolar-arterial oxygen gradient widens. With exercise, ventilation and heart rate are increased in order to meet the  $O_2$

demands of the metabolically active tissues. However, the increased ventilation and heart rate can lead to ventilation-perfusion (V-Q) mismatching, meaning that as larger volumes of air are being inhaled at increasing frequencies and blood flow is accelerated (30), the available time for gas exchange is reduced. As a result, O<sub>2</sub> is not able to diffuse through the pulmonary capillary at a sufficient speed relative to the velocity of blood flow and there is a decrease in PO<sub>2</sub> in the body.

While exercising in hypoxic environments, the decrements to PO<sub>2</sub> are more severe leading to further widening of the A-aDO<sub>2</sub> gradient. During exposure to acute hypoxia, the slope of the oxygen dissociation curve is steeper as a lower PO<sub>2</sub> is present. The resulting physiological changes include increases in ventilation, work of breathing (the mechanical work necessary to maintain a breathing pattern), muscle fatigue, heart rate and cardiac output, along with decreases in PaO<sub>2</sub> and SaO<sub>2</sub> (32, 33). Following exposure to hypoxia, there is an initial increase in ventilation due to the stimulation of the peripheral chemoreceptors to increase the drive to breathe. The carotid and aortic bodies sense the drop in PaO<sub>2</sub> and stimulate ventilation and vasodilation to the muscle to increase O<sub>2</sub> content (34). The increase in the drive to breathe increases minute ventilation and the work of breathing. During sustained above suprathermal exercise, blood flow competition between respiratory and locomotor muscles transpires (32), as exercises persists, this can lead to greater diaphragmatic fatigue.

Between individuals, the ventilatory response will also differ as abilities to tolerate hypoxia ranges. At around 50-60 mmHg PO<sub>2</sub>, the hypoxic ventilatory response will be triggered, this increase the drive to breathe to varying degrees (30). Individuals who are more sensitive to hypoxia will experience less of a decline in SaO<sub>2</sub> and volume of oxygen consumption (VO<sub>2</sub>) and elicit a greater ventilatory response (30). As tissues require adequate oxygenation to function,

hypoxia limits this ability; every 1% decline in SaO<sub>2</sub> below 95%, there is a resulting 2% decline in VO<sub>2</sub> max (maximal oxygen consumption) (35). Ability to exercise is closely aligned with ability to maintain tissue oxygenation. Although the decrements to VO<sub>2</sub> max are modest; the resulting decline in performance especially when in combination with other asphyxiant gases can pose significant challenges to an evacuating, subsequently known as egressing, occupant.

### *1.3.2 Impact of Hypoxia on Cognition*

The human brain requires continuous supply of O<sub>2</sub> to function effectively and can be vulnerable to environments with low atmospheric O<sub>2</sub> availability. A study of exposure to hypoxia at rest and during moderate exercise found that hypoxia induces progressive brain desaturation, leading to cognitive impairments and delayed reaction times (28). Cognitive impairments include but are not limited to decrements in attention, learning and memory, processing speed and executive function (36). The severity of cognitive decrement is correlated with the degree and duration of hypoxia (28). As PaO<sub>2</sub> and SaO<sub>2</sub> progressively decrease with increasing severities of hypoxia, declines in cognitive function are exaggerated (37). Participants acutely given 12% inspired O<sub>2</sub>, experienced impairments in neural activity, motor executive and inhibitory processing and delayed higher cognitive processing (38). These declines in cognitive impairment are more significant during moderate exercise compared to rest (28, 29, 38).

Hypoxia can be insidious and impair one's ability to identify cognitive impairments within oneself (23). Individuals can experience pleasant sensations such as euphoria, decreased inhibitions and a strong sense of wellbeing; all which will diminish any sense of urgency. This may extend time spent in the fire environment, inhaling the toxic gases. Egressing individuals may be more likely to misidentify or fail to recognise if emergency procedures are required, such

as evacuating following the sounding of an alarm if hypoxic (23, 39). The inability to recognize the severity of the situation and need for action to evacuate or call for further professional assistance (i.e. emergency personnel) is diminished which can result in life threatening situations escalating.

#### **1.4 Acute Effects of Carbon Dioxide on Human Function**

In a fire, carbon dioxide generation is highest when there is sufficient ventilation and heat, promoting efficient combustion pathways for the production of a complete product. In most compartment fire scenarios, CO<sub>2</sub> is the most common combustion product, as similar amounts of CO<sub>2</sub> can be produced depending on the fire. While the concentrations of CO<sub>2</sub> produced are typically not sufficient enough to cause significant toxicity on its own, the physiological effects of CO<sub>2</sub> potentiate the toxicity of other combustion by-products (40).

##### *1.4.1 Impact of Carbon Dioxide on Physiological Function*

Carbon dioxide is a much stronger stimulus to ventilation and is much more tightly regulated in the body compared to O<sub>2</sub> (41). Figure 5 illustrates the differences between regulation of CO<sub>2</sub> and O<sub>2</sub> in the body. Starting with O<sub>2</sub>, the green line demonstrates that despite relatively large changes in PO<sub>2</sub>, the oxygen content in the blood is maintained: between >100mmHg – 80mmHg PO<sub>2</sub>, blood oxygen content remains at ~175 mL/L. This is contrasted with carbon dioxide which shows a much steeper slope in the relationship between blood CO<sub>2</sub> content and partial pressure. Therefore, there is a more drastic change in CO<sub>2</sub> content in the blood for a relatively smaller change in the partial pressure of CO<sub>2</sub>. For example, as the partial pressure of CO<sub>2</sub> is increased by a small amount (30-40mmHg), the blood content of CO<sub>2</sub> largely increases

(~420 – 480 mL/L). This speaks to the sensitivity of the body to CO<sub>2</sub> inhalation and the regulation required to maintain an adequate and safe partial pressure in the range of 40 – 45mmHg CO<sub>2</sub> in the blood (41).

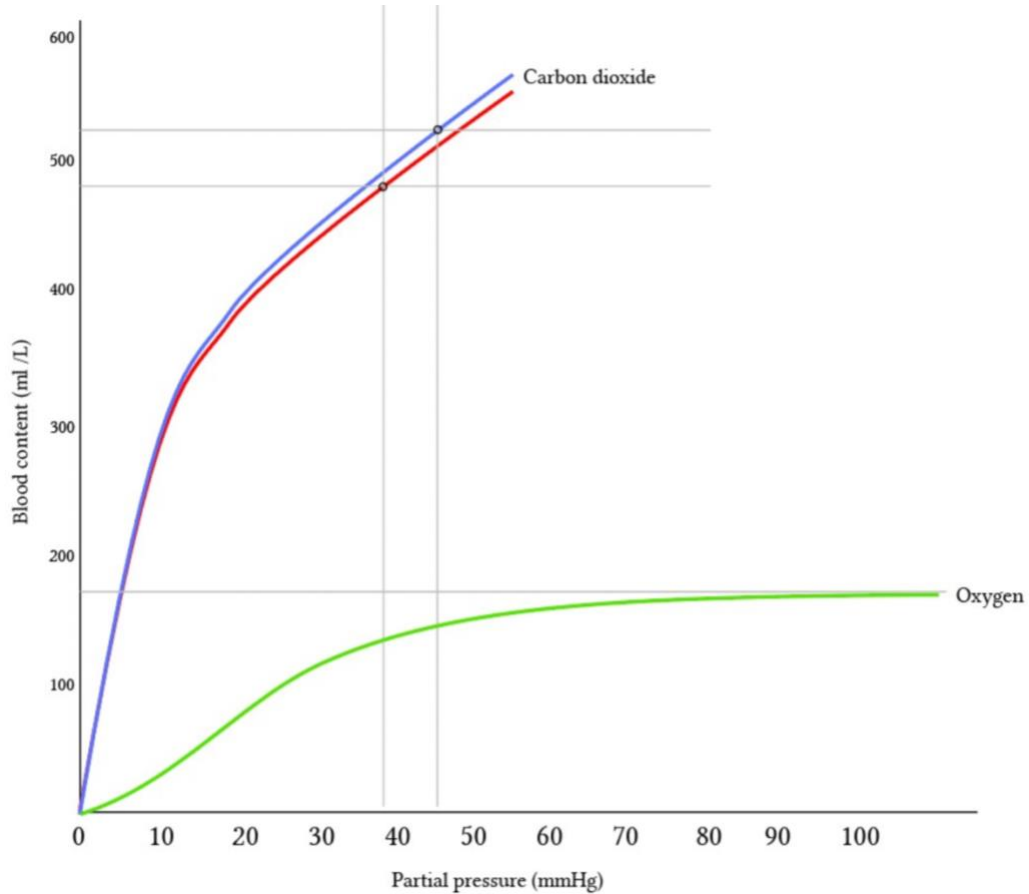


Figure 5: Carbon dioxide and oxygen disassociation curves. Red shows the arterial CO<sub>2</sub>, blue represents venous CO<sub>2</sub> and green represents oxygen. The grey lines signify the ideal regions of both CO<sub>2</sub> and O<sub>2</sub>.

Hypercapnia occurs following the onset of CO<sub>2</sub> retention, when arterial partial pressure of carbon dioxide (PaCO<sub>2</sub>) exceeds 45mmHg (42) and elicits both autonomic and ventilatory responses principally by an action within the central nervous system and a reduction in pH (17, 43). It is the lowering of pH that stimulates the drive to increase ventilation and therefore CO<sub>2</sub> clearance out of the blood, maintaining resting partial pressures (40 – 45mmHg). This process is

tightly regulated because very small changes in partial pressure of carbon dioxide ( $\text{PCO}_2$ ) can have drastic repercussions on the body and ventilation (41).

During exercise in normoxic conditions, when tissues are more active and producing more  $\text{CO}_2$  as the product of cellular respiration,  $\text{PCO}_2$  is maintained by expelling excess  $\text{CO}_2$  via increases in ventilation. Following the onset of constant exercise,  $\text{CO}_2$  concentration in the blood increases, this is coupled with increasing concentrations of hydrogen ions ( $\text{H}^+$ ), generated as a by-product of exercise, which lowers blood pH and making it more acidic. Changes in  $\text{PCO}_2$  in the blood are sensed by central chemoreceptors when increased amounts of  $\text{CO}_2$  crosses the blood brain barrier. Since this incoming blood crossing the blood brain barrier is more acidic with a higher concentration of  $\text{H}^+$ , it induces changes in the brain  $\text{H}^+$  concentration, effectively increasing  $\text{H}^+$  concentration in the cerebral blood (34). The increase of  $\text{CO}_2$  and  $\text{H}^+$  in the brain triggers further ventilatory and circulatory adjustments such as increasing dilation to increase blood flow (44, 45). Together these mechanisms promote  $\text{CO}_2$  clearance and allow for  $\text{PCO}_2$  to be maintained at below suprathreshold exercise intensities.

Fluctuations in  $\text{PCO}_2$  are highly regulated within the body, and if not maintained can cause disturbances in the human body such as respiratory acidosis (46). Increases to inhaled  $\text{CO}_2$  or during intense prolonged exercise, will cause  $\text{CO}_2$  to build up in the tissue. Increases to ventilation at rest is almost exclusively as a result of increasing tidal volume; whereas during exercise, both tidal volume and breathing frequency increase (47). When breathing hypercapnic gases, especially during exercise, the ventilatory response described above is exacerbated. Specifically, when only 3%  $\text{CO}_2$ , ventilation is approximately doubled, and at 5%  $\text{CO}_2$ , ventilation is tripled (43).

In the context of fire exposure, the uptake of asphyxiant gases is dependent on ventilation, which in turn highlights the important effects of inspired CO<sub>2</sub> and subsequent PCO<sub>2</sub> due to the mechanisms associated with increasing ventilation. When ventilation is stimulated during an egress scenario by both exercise and inhaling hypercapnic gas produced by the fire, the uptake of asphyxiant and irritant gases and soot will increase, effectively decreasing the time to incapacitation (10). Considering the ventilatory effect CO<sub>2</sub> has and the implication on the uptake of other toxic gases, it has been estimated that exposure to a 5% CO<sub>2</sub> fire environment, the time to incapacitation decreases to a third of what it would be without the stimulatory effects of CO<sub>2</sub> (48–50).

#### *1.4.2 Impact of Carbon Dioxide on Cognition*

Inhalation of carbon dioxide has been characterized in many species both at rest and during moderate exercise, outlining the numerous cardiorespiratory responses as well as physiological effects (48). These include physiological reactions such as impaired vision, diminished motor control, delayed reactions and disorientation (51); these impaired cognitive and motor abilities could decrease one's ability to safely recognize and escape a dangerous situation if needed (52, 53). As individuals within a given population have different tolerances, adaptations and reactions to partial pressures of CO<sub>2</sub>, the degree by which common symptoms are experienced will differ. These symptoms include but are not limited to difficulty breathing, headache, sweating, increased heart rate, restlessness, disorientation and declines in vision (40).

It has been found that inhaling low concentration of CO<sub>2</sub> causes difficulty in concentration resulting in lower cognitive performances (54–56). Inhalation of 7.5% CO<sub>2</sub> has been found to alter mood by inducing anxiety, feelings of breathlessness and increasing heart

rate (57). These negative impacts on cognitive functions from inhaling hypercapnic gas are exacerbated during exercise. At inhalation of 5%, there is a 50% increase in cerebral blood flow, resulting in an accentuation of the above impairments (44).

## **1.5 Acute Effects of Carbon Monoxide on Human Function**

Carbon monoxide is a toxic gas to humans commonly produced from the combustion of carbon containing compounds (i.e. hydrocarbons) and is produced in higher amounts during incomplete combustion (19). The production of CO is inversely proportional to the availability of O<sub>2</sub> in the combustion environment, as levels of oxygen declines, CO production is increased (19, 58). In terms of the impact on humans, hemoglobin has an affinity for CO that is over 200 times greater than that of O<sub>2</sub> (59). As CO is inhaled it binds to Hb in the red blood cell and forms carboxyhemoglobin (COHb). This formation of COHb decreases the carrying capacity of O<sub>2</sub> in the blood and impairs release of O<sub>2</sub> into the tissues (58, 60, 61). The “dose” of CO in the blood is expressed as percentage carboxyhemoglobin (% COHb) (62).

At rest, most non-smokers have a baseline COHb between 0-3%, depending on proximity to different environmental factors. Cigarette smokers have much higher baseline COHb, with baseline levels between 8-13%, due to prolonged exposure to combustion by-products (burning cigarettes) (63). As CO is inhaled, time is required for a fatal dose to be reached, approximately 40-50% COHb at rest in healthy young individuals (10). This dose was decreased to 30% COHb in cynomolgus monkeys during exercise when blood delivery and ventilation is increased, and similar saturations have been adapted for healthy young humans (19). However, symptoms are experienced even at low exposures ~10% COHb in non-smokers and these will be detailed below.

### *1.5.1 Impact of Carbon Monoxide on Physiological Function*

Acute exposure (less than 15 mins) to carbon monoxide has been characterized in both animals and humans (17, 64). The effects of CO exposure decrease the content of O<sub>2</sub> leading to a decreased fraction of O<sub>2</sub> being delivered to the tissue. The buildup of COHb at the alveolar-capillary interface shifts the oxygen disassociation curve (Figure 4) to the left, as CO binds to Hb, competitive inhibition prevents O<sub>2</sub> from binding to Hb. The shift in the oxygen disassociation curve prevents O<sub>2</sub> offloading into peripheral tissues as O<sub>2</sub> is less readily available and diffusion into the tissues is diminished (58, 65). Together CO and hypoxia have an additive effect to reduce SaO<sub>2</sub> and PaO<sub>2</sub> through competitive inhibition which decreases the concentration of O<sub>2</sub> available within the body (62).

The peripheral chemoreceptors, which sense decreases in PaO<sub>2</sub> are unable to detect hypoxia when it is caused by CO binding Hb, at 20% COHb or lower (66). Although CO binds to Hb and reduces O<sub>2</sub> carrying capacity in the blood, it does not interact with the O<sub>2</sub> sensing aspects in the carotid bodies and therefore does not stimulate the peripheral chemoreceptors (66). The peripheral chemoreceptors are stimulated by a fall in PaO<sub>2</sub>, which is not present following CO inhalation (lower than 20% COHb) (67). The increases in ventilation from peripheral chemoreceptors that we see with hypoxia are not commonly seen with acute carbon monoxide poisoning (67). As a result, there is a delayed hyperpnea response to CO inhalation. This delay is primarily due to the brain-cerebrospinal fluid acidosis: as the inhalation of CO leads to increasing saturation of COHb, there is a fall in blood pH and bicarbonate concentrations, along with a subsequent increase in lactate concentrations causing acidosis (67). The buildup of acidosis is sensed by central chemoreceptors, which then trigger the brain to increase ventilation.

Acute CO exposure can also target the cardiovascular system leading to an increase in cardiac output (Q); Q is a product of heart rate and stroke volume (volume of blood ejected with each heart beat). Cardiac output is seen to increase almost directly with increasing COHb saturation in rats (68). In humans, increases in cardiac output are shown following inhalation of CO up to 30% COHb. Following 30% COHb increases are no longer seen as intoxication is likely to occur (69, 70). At high levels of CO saturation, both heart rate and stroke volume increase in an attempt to maintain oxygen delivery (71–73). Anatomical limitations cause stroke volume to plateau, usually occurring once intensities of 40-60% of maximal oxygen consumption are reached. After stroke volume reaches a maximum, only increases in heart rate satisfy increases to Q.

In order to achieve adequate tissue oxygen delivery, along with increases to cardiac output, the human body will make changes in peripheral resistance and venous return to adapt to the effects of additional CO to ensure adequate circulation and oxygenation (68). Peripheral resistance is the resistance in the arteries to blood flow. Arteries will dilate to deliver more oxygenated blood to the active muscles and restrict in other parts of the body to optimize oxygen delivery (74). Similarly, venous return is the volume of deoxygenated blood transported back to the heart from the periphery, this will increase resulting in larger stroke volumes and ejections of blood from the heart (74). Despite these alterations by the body to combat CO saturation, there are still impacts to cognition that are seen at various levels of CO saturation as discussed in the section below.

### 1.5.2 Impact of Carbon Monoxide on Cognition

At a low acute exposure of carbon monoxide, the effects are minimal and include non-specific symptoms such as headaches and nausea. Low level exposure to CO (<5%) usually impact higher cognitive functions first, decrements include: choice discrimination with regards to letter and colours, changes in ability to perform mental arithmetic, visuomotor coordination, attention and concentration (18, 75).

Following exposure to higher concentrations of CO, the effects are more severe and the time to incapacitation occurs much faster. Studies on monkeys at rest by Purser *et al.* (19) found that the first signs of behavioral performance deficits occurred at concentrations of 15-20% COHb with effects that had a sudden onset and rapid loss of consciousness. Common symptoms to potent CO poisoning include confusion and incapacitation. These effects occur at 30% COHb in moderate exercising animals; the moderate exercise being completed is a similar intensity to what is commonly seen in humans during egress (19). At these higher %COHb, prior to incapacitation, cognitive impairments occur very rapidly, the unfortunate outcome being that people in a fire scenario may not realize they are in danger (75–77). During large-scale ventilation limited furniture fire tests (described above, see Figure 3), CO concentrations in a second storey compartment increased to approximately 2000ppm, 15 minutes after ignition. At this point %COHb was calculated to be 30% while using a breathing at a rate of 36L/min (with assumed parameters for blood volume, Hb mass using Lundby method ) (20, 78). Due to the physiological differences between males and females, sex differences are apparent between sexes, this will be further detailed below.

## 1.6 Sex Differences Between Males and Females

There is a difference in the cardiopulmonary anatomy, physiology and response to exercise between males and females. The ways that both sexes adapt to changes in ventilation and inspired gases have been quantified (24, 79, 80) however, this quantification has not been done in the context of egress wherein combinations of O<sub>2</sub>, CO<sub>2</sub>, and CO are manipulated and inhaled simultaneously.

### 1.6.1 Physiological Differences Between Males and Females

Physiological and anatomical differences between males and females have been characterized in multiple studies (24, 79). For example, when average body surface area (BSA) of North-American males and females are compared, females have an average BSA of 1.6m<sup>2</sup> whereas men have an average BSA of 1.9m<sup>2</sup> (81). Males are usually generally larger than females even when height matched and this is true with their respiratory physiology. To start, males have larger lungs and conducting airways compared to females (80). Females also have a more prismatic lung geometry with the base and apex of the lungs being smaller, whereas males have more pyramidal lung geometries with lung bases being larger than the apex (80). Females also have a smaller cross-sectional areas of the trachea and larger conducting airways when matched with males for height and lung size (80). Larger lungs and conducting airways allow for a higher volume of air to be inhaled and exhaled. These morphological and anatomical differences in the pulmonary system between males and females have minimal influence on the breathing mechanics or blood homeostasis at rest, however these differences have a significant effect on the integrative response to exercise between the sexes (79). Despite these anatomical differences, there is not a significant difference in the pulmonary diffusive capacity and

ventilation-perfusion mismatching between the sexes (82, 83); and at rest through to mild-intensity exercise, there are minimal differences in gas exchange between males and females (76,79, 80). Both males and females can match the oxygen demands in the active tissue.

The smaller airways seen in females leads to increased airway resistance and results in a relatively higher work of breathing (80, 84). To accommodate the increased work of breathing required to maintain  $PO_2$  during high intensity exercise, specifically in females, respiratory muscle blood flow is increased (80). This redirection of blood flow to the respiratory muscles results in a decrease in blood flow, and thus oxygen delivery, to the locomotive working muscles. This in conjunction with a relatively higher work of breathing experienced by females, indicates that a relatively larger percentage of an exercising female's  $VO_2$  max is used by the respiratory muscles (85). When the entire respiratory and locomotive muscle energetics were taken into account, it appears that females dedicate ~14% of their whole-body  $VO_2$  to their respiratory muscles compared to males (~9%) (85, 86). Redirecting blood flow away from the locomotive muscles may negatively impact mobility and walking, particularly if there is an increased metabolic demand of carrying a load. Similar trends can also be seen in the cardiovascular system, namely, females having smaller hearts, blood volumes and hemoglobin concentrations (84).

Majority of studies have not found a difference in the hypoxic ventilatory response between males and females. A caveat to this however is that studies have not controlled for the menstrual cycle. Sex hormones, specifically progesterone, estrogen and testosterone are known to have stimulatory effects on ventilation, which would also stimulate the hypoxic ventilatory response (87). Overall the effects of the menstrual cycle on ventilation are less clear as some studies show an impact (88) and others no impact (89), which is likely due to the variability and sensitivity of

the ovarian hormones. To enhance current tools used in egress and building design, accounting for sex differences is critical, particularly for cardiorespiratory parameters such as ventilation. Therefore, elucidating the effects of sex hormones on ventilation will allow for a more nuanced understanding and thus representation of the variability in ventilation within a given population.

To conclude, the number of studies examining the physiological response in females compared to males is drastically smaller. In exercise physiology, the number of male only studies vastly outweighs the number of female only studies ~4:1, with about a third of the studies including both sexes (90). By including both males and females in this study, we can quantify a dataset that more accurately represents the variability in the physiological response in a population, leading to more accurate and inclusive design tools.

## **2 Study Rationale**

The primary study rationale is to characterize the physiological response to the modern fire environment and identify any physiological sex differences which may explain why victims are unable to escape fire environments. With the trend towards ventilation-limited fires becoming more prevalent with modern building design, there is a need to further our understanding of physiological and cognitive responses under sub-incapacitating exposures representative of this modern fire environment. Additionally, enhancing the understanding of how exposure to a modern fire environment can impact various subsets of the population, in conjunction with the fact that there are known physiological cardiorespiratory differences between sexes, forms the basis for recruiting males and females. This study will aim to examine physiological responses under differing fire exposure conditions, as well as characterize differences in the response and overall ability to perform egress between healthy males and females.

### **3 Research Questions and Hypotheses**

Research Question: Do changes to ventilation, heart rate, tidal volume and fraction of oxygen bound to hemoglobin differ between the 4% COHb and 7% COHb egress protocol trials?

Hypothesis: The changes to the physiological response during the 4% COHb and 7% COHb trials will not differ as the combination of hypoxic and hypercapnic gases that participants are exposed to will cause the driving physiological responses.

Research Question: Does decreasing oxygen and increasing carbon dioxide in isolation vary from each other and from the normoxic control trial when comparing ventilation, heart rate, tidal volume and oxygen saturation?

Hypothesis: Increasing carbon dioxide will elicit a greater physiological response, specifically in ventilation, than hypoxia and control, and the response to hypoxia will be greater than control.

Research Question: Does the physiological response (ventilation, heart rate, tidal volume and fraction of oxygen bound to hemoglobin) and response times to the cognitive prompts during the worst-case condition (combination gases with 7%COHb saturation) during the egress protocol differ between sexes?

Hypothesis: Females will be more impacted than males and this will correlate with greater changes to adapt to the conditions during the trial and slower response times when completing the cognitive task. Males will be better able to adapt to the worst-case gas exposure than females.

#### **3.1 Ethics**

The experimental procedures were approved by the Office of Research Ethics at the University of Waterloo (ORE #43434) and conformed to TCPS2. The research methods and

protocols adhere to the recommendations outlined by the *Declaration of Helsinki* concerned with the use of human participants, except for registrations in a database.

## **3.2 Exposure to Fire Gases and Egress**

### *3.2.1 Mechanical Ventilator*

The gas concentrations used to develop the experimental egress protocol were collected by a mechanical ventilator, which was placed in the smaller upstairs bedroom of a two-storey structure (refer to building schematic in Figure 3 (20)) during a large-scale ventilation-limited fire conducted by the University of Waterloo Fire Research Facility (16). The mechanical ventilator was designed to simulate what an occupant would be experiencing in terms of inhaled gas concentrations as the structure fire progressed. The mechanical ventilator had two components, a ‘lung’ box and motor system. The ‘lung’ box had a 3D printed trachea, left and right bronchi of a 43-year-old female attached to two one-way valves (a mechanical nose), fastened to a plexiglass box that was 12L total volume. The ‘nose’ was placed 0.36m above the floor, assumed to be a similar head height to an occupant crawling close to the floor. A gas sensing unit was housed within this 12L ‘lung’ box, so the remaining volume was approximately 5L, similar to the lung volume of an adult. Attached to this box was the motor system that pumped a syringe to push (exhale) and pull (inhale) ambient air through the ‘lung’ box, 3D printed airway and valves. The ventilator was set to ‘breathe’ at a continuous rate of 36 L/min. This rate was chosen as it is similar to the rate of a moderately active female, with moderate activity being considered an accurate representation of egress. The gas sensing unit housed in the mechanical ventilator measured time-resolved changes of the inspired/expired gases as well as the accumulation of the gases that the occupant would be exposed to at that location during the

furniture fire (20). The gas concentrations of O<sub>2</sub>, CO<sub>2</sub> and CO measured by the mechanical ventilator are shown in Figure 6 below.

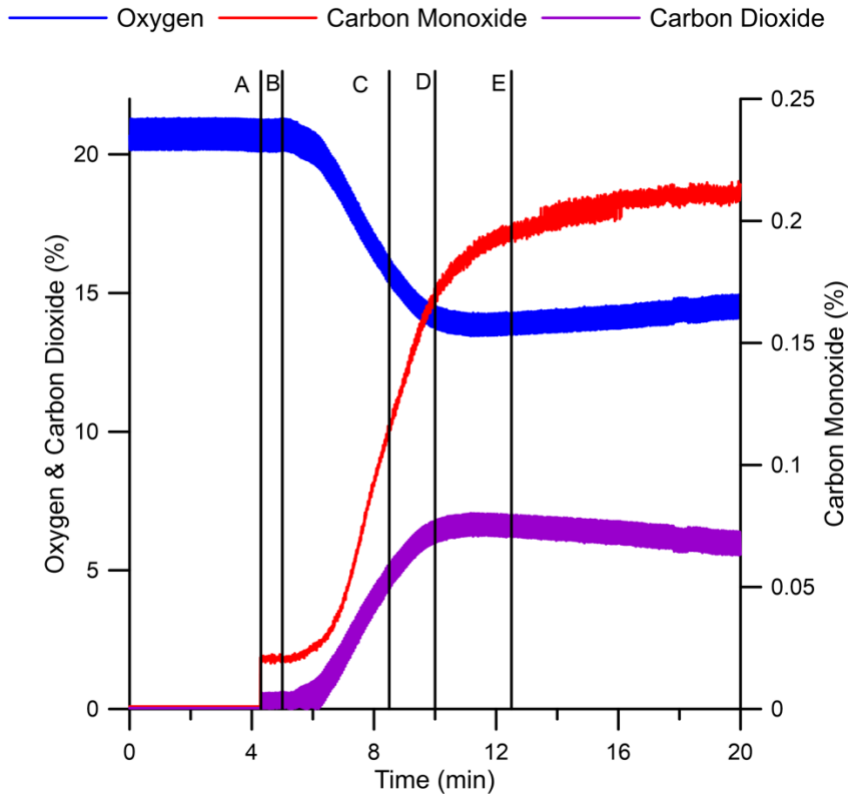


Figure 6: Time after ignition showing changes in CO, CO<sub>2</sub>, and O<sub>2</sub> from the mechanical ventilator placed in the upstairs bedroom during a furniture fire test conducted at the University of Waterloo Fire Lab. The vertical lines correspond to the egress events: A) 4.5 minutes, smoke detector in the bedroom alarms, B) 5 minutes, the occupant awakes from the alarm and begins pre-evacuation phase, C) 8.5 minutes, the occupant begins to egress D) 10 minutes, the occupant is able to escape or D) 12.5 minutes, the occupant is rescued by firefighting personnel (16).

### 3.2.2 Egress Timeline

The other component of the experimental egress protocol was the development of the egress timeline. This timeline paired with the measured gas concentrations from the mechanical ventilator comprises the experimental egress protocol used to simulate an occupant evacuating from the ventilation-limited fire. The letter markers in Figure 6 above correspond to key events in an egress timeline. Point A is the measured time after ignition for the smoke detector in the

upstairs bedroom with the mechanical ventilator to alarm (4 min 23 sec after ignition of the fire). Point B is the time for the occupant to wake to the alarm, 46 seconds, taken as an average from several studies (91). During the experimental egress protocol, the participants start sitting for 5 minutes, representing the time after ignition for the smoke detector to alarm and the occupant to wake up. Once an occupant is awake, they typically complete what is known as a pre-evacuation phase, which consist of behaviour such as confirming there is a fire, calling 911, collecting belongings and alerting other individuals in the home. The time of the pre-evacuation phase ranges extensively across studies (91), and in this study, a pre-evacuation phase of 3.5 minutes was considered representative (Point C). In the experimental protocol, participants began to walk 5 minutes after ignition, and they continued to walk until the end of the protocol (12.5 minutes total time, 7.5 minutes walking). After the pre-evacuation phase, the evacuation (egress) phase commences. It was assumed that it would be possible to egress the two-storey structure in 1.5 minutes (Point D). In a worst-case scenario, the occupant would not be able to successfully evacuate on their own, therefore they would stay in the fire environment attempting to find a way to escape until rescued by firefighting personnel. The experimental protocol followed this worst-case scenario. At the start of the evacuation phase (8.5 minutes from ignition, Point D), participants had to continue walking and were given a 20lb load to carry until then end of the protocol. This load was given to simulate evacuating with belongings or assisting an individual who was unable to evacuate on their own (i.e. small child, pet). The total protocol time was 12.5 minutes, based on the assumption that the occupant called 911 one minute after they woke up and confirmed there was a fire (6 minutes after ignition) and it took 6.5 minutes for the fire department to arrive. A detailed description of the experimental procedures used in this egress protocol are detailed in following sections below.

### 3.3 Participants

The sample size included 30 participants, 15 males and 15 females. Participants were all healthy young males and females between the ages of 18 and 40 who live active lifestyles, with a BMI less than 30kg/m<sup>2</sup>. Participants over the age of 40 were excluded due to the known impact of normative aging on the pulmonary system. Participants had no known cardiovascular or respiratory conditions to allow effective investigation of the normal physiological response to the simulated egress protocol. Participants were not colour-blind as that condition could impair their ability to complete the modified Stroop colour test. A physical activity questionnaire was given to, and completed by, all participants to ensure that they were within the inclusion criteria of an active lifestyle. Table 1 details the complete inclusion and exclusion criteria for the study.

Table 1: Inclusion and exclusion criteria to be a participant.

<b>Inclusion Criteria</b>	<b>Exclusion Criteria</b>
Age: 18-40 Sex: Male and female Lifestyle: Active	Obesity: BMI > 30kg/m <sup>2</sup> Cardiovascular or respiratory diseases Diabetes Arthritis Current smokers Pregnant or nursing females Colour blindness Cardiovascular, metabolic or respiratory conditions and taking prescribed medications for these conditions

## 4 Experimental Overview

All participants completed 3 days of testing (Figure 7 and 8). The first day of testing consisted of a familiarization day wherein participants performed the egress protocol and cognitive task under normal ambient conditions, further known as a control trial. The next two days of testing consisted of trials with changes to inspired gases to create hypoxic, hypercapnic and combination (hypoxic and hypercapnic in tandem) exposures. Inspired gases followed the temporal sequence measured by the mechanical ventilator (Figure 6) by using custom lab equipment and corresponded to a decrease in oxygen to 14%, and/or increase in carbon dioxide to 7%. On the second day of testing (Figure 7) participants completed 5 trials with changes to inspired air along with a mild carbon monoxide saturation. These trials were as follows: control, hypoxia at rest, egress protocol with combination exposure with 4% COHb, and the final two trials were randomized, egress protocol with combination exposure with 7% COHb, and combination exposure with 7% COHb at rest. On the third day of testing (Figure 8) participants completed 4 trials of the egress protocol with changes to inspired gases. Trials began with the control trial then the following 3 egress protocol were randomized between a hypoxic, hypercapnic and combination exposure. The second and third days of testing were randomized between participants.

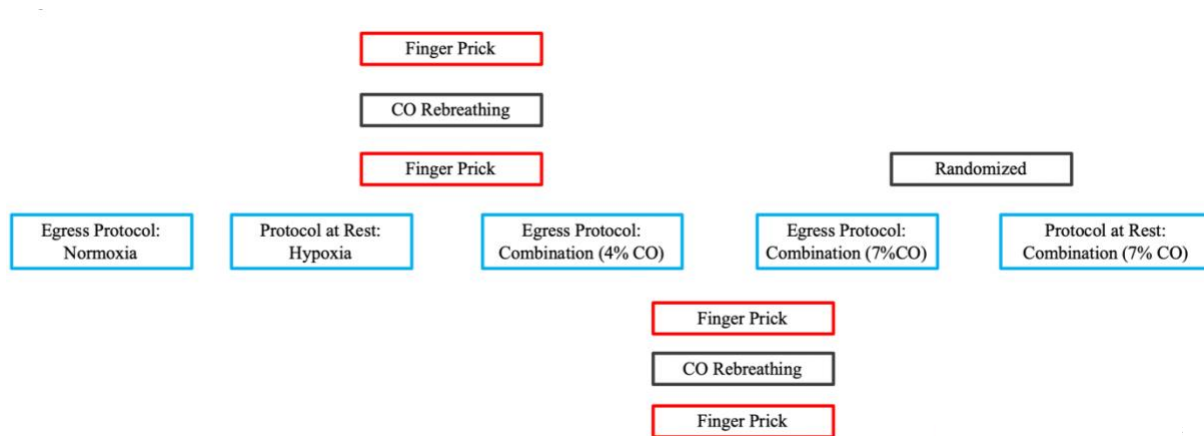


Figure 7: Schematic of Day 2 Study Protocol: Participants completed five trials with the CO rebreathing procedure occurring before trial 3 and again after trial 4.

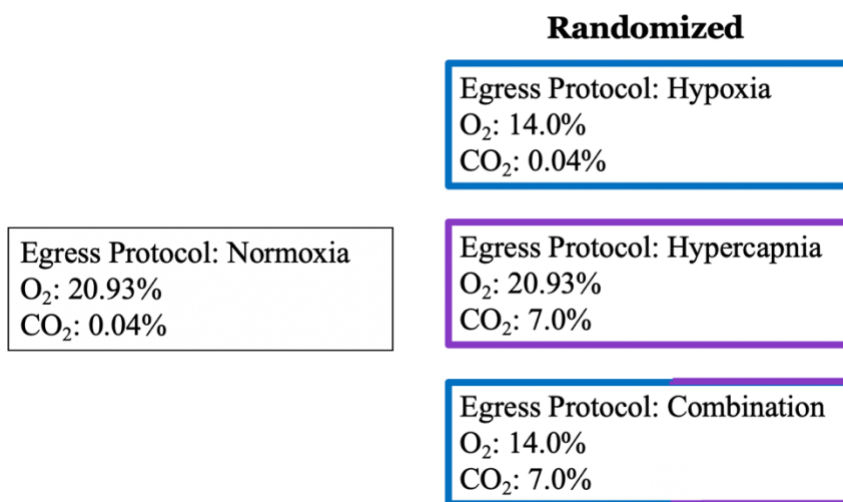


Figure 8: Schematic of Day 3 Study Protocol: Participants completed four trials of the egress protocol. Boxes outlined in blue signify changes in oxygen whereas boxes outlined in purple signify changes in carbon dioxide, boxes outlined with both blue and purple signify changes to oxygen and carbon dioxide in tandem. Final stage inspired fractions of oxygen and carbon dioxide are presented.

#### 4.1 Egress Protocol

The first study visit began with researchers answering any questions that participants had about the study and procedures. Participants then completed both the Get Active Questionnaire and Young Healthy Adult Screening Questionnaire to conform eligibility, before providing their signed consent. Participants were then asked to walk on the treadmill to determine the speed at

which they felt comfortable completing the egress protocol. Participants were guided to select a speed that felt akin to a casual walking pace ( $1.8 \pm 0.3$  miles), ensuring it did not feel as if their feet were lagging. Afterwards, participants were instrumented with a heart rate monitor, facemask and pulse oximeter. Each trial began seated on a chair placed on the treadmill. The cognitive task (more details in section 4.2) involved answering prompts on a tablet screen, as such, the tablet was placed within comfortable reach and viewing for the participant. Participants were required to answer prompts throughout the test, and as participants moved from sitting to standing, the height of the tablet was adjusted accordingly to ensure comfortable viewing and reach. A one-minute pre-test baseline was collected before the start of the test, and similarly at the end of the protocol, a 2-3-minute post-test baseline was collected to ensure participants' heart rate, oxygen saturation and end-tidal CO<sub>2</sub> returned to within 10% of their pre-test baseline values. A schematic overview of this egress protocol in normoxia including the sequence of events: 5-minutes of sitting (simulating sleeping and waiting for the smoke detector to alarm), 3.5 minutes of walking (pre-evacuation phase), and 4 minutes of walking while carrying the 20lb load (evacuation) can be seen in Figure 9.

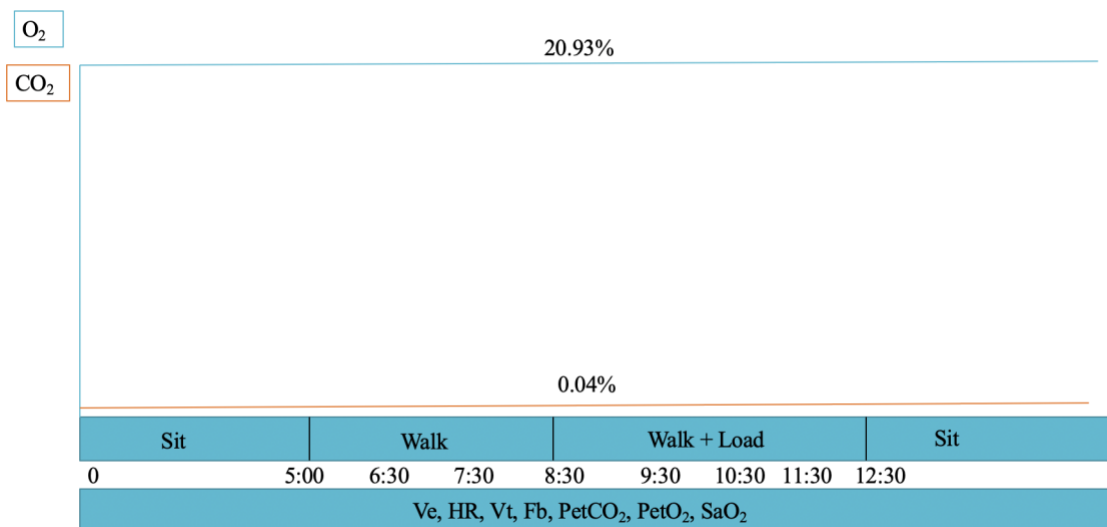


Figure 9: Schematic of the egress protocol in normoxia.

Each testing day included a control trial performed in normoxia, O<sub>2</sub> and CO<sub>2</sub> 20.93% and 0.04% respectively. Table 2 below outlines the temporal changes to the inspired gases measured by the mechanical ventilator (Figure 6) that participants were exposed to during the hypoxic, hypercapnic and combination (hypoxic and hypercapnic in tandem) trials.

Table 2: Exposures of inspired oxygen and carbon dioxide and physical task at each time point during the egress protocols

Time (min:sec)	Inspired Oxygen (%)	Inspired Carbon Dioxide (%)	Activity
0:00	20.93	0	Sitting (begin test)
5:00	20.93	0	Stand
6:30	19	1	
7:30	17.5	3	
8:30	15.5	5	20kg Weight
9:30	14	7	
12:30	20.93	0	Sitting (end test)

For the hypoxic exposure trial, only oxygen was changed while carbon dioxide was held constant; during the hypercapnic exposure trial only carbon dioxide was changed as oxygen was held constant. For the combination exposure trail, both gases changed in tandem, shown schematically in Figure 10 below.

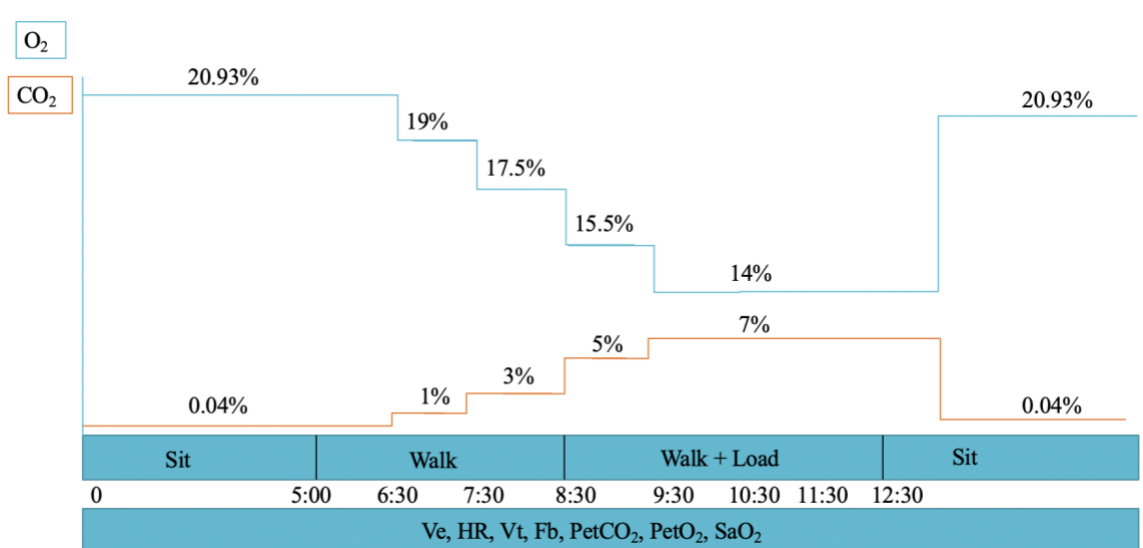


Figure 10: Schematic diagram of the egress protocol and changing inspired gas concentrations at each time point. Changes in CO<sub>2</sub> are depicted in red and changes in O<sub>2</sub> are in blue.

If during any point of testing the participant was too uncomfortable and they wished to terminate the trial, they were assisted in sitting down and their inspired gases were immediately returned to room air. Participants were not required to redo the trial as the inability to complete the protocol was a potential research outcome. Additionally, following each trial, participants were asked to rate their mental and physical rate of perceived exertion (RPE) following Borgs modified scale (92) (Table 3). To determine mental RPE, participants were asked open ended questions such as how difficult it was to complete the cognitive task and were there any changes to mental state, i.e. anxiety or loss of focus. Similarly, to determine physical RPE participants were asked how difficult was it to complete the walking and loaded walking. The purpose of asking the participant these questions, along with open-ended recall of symptoms or sensations experienced during the trial, was to collect qualitative and anecdotal information with respect to participants' experiences with the exposures.

Table 3: Borgs modified rate of perceived exertion scale (92).

Numerical Value	Rating of Perceived Exertion
0	Nothing at all
0.5	Just noticeable
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
7	Very severe
9	Very, very severe (almost maximal)
10	Maximal

#### 4.2 Cognitive Task Protocol

Throughout the egress protocol, participants were asked to complete a cognitive task. This cognitive task was a combination of an egress-specific task which consisted of identifying the directional arrow and an EXIT sign and a modified version of the Stroop Colour test used to assess executive functioning. During the EXIT sign prompt, participants were asked to select the appropriate directional arrow button that corresponded with the EXIT sign displayed on the screen. During the modified Stroop Colour test, colours were written in various ink colours that may or may not have corresponded to the name of the colour. Participants were asked to select the ink colour that the word was written in by selecting the corresponding colour button on the bottom of the screen. EXIT sign and modified Stroop prompts are shown in Figure 11. This custom code was designed to provide a prompt every 15 seconds that alternated between the EXIT sign and modified Stroop test. The code recorded the answer selected by the participant as well as the time taken to answer the prompt after it populated on the screen.

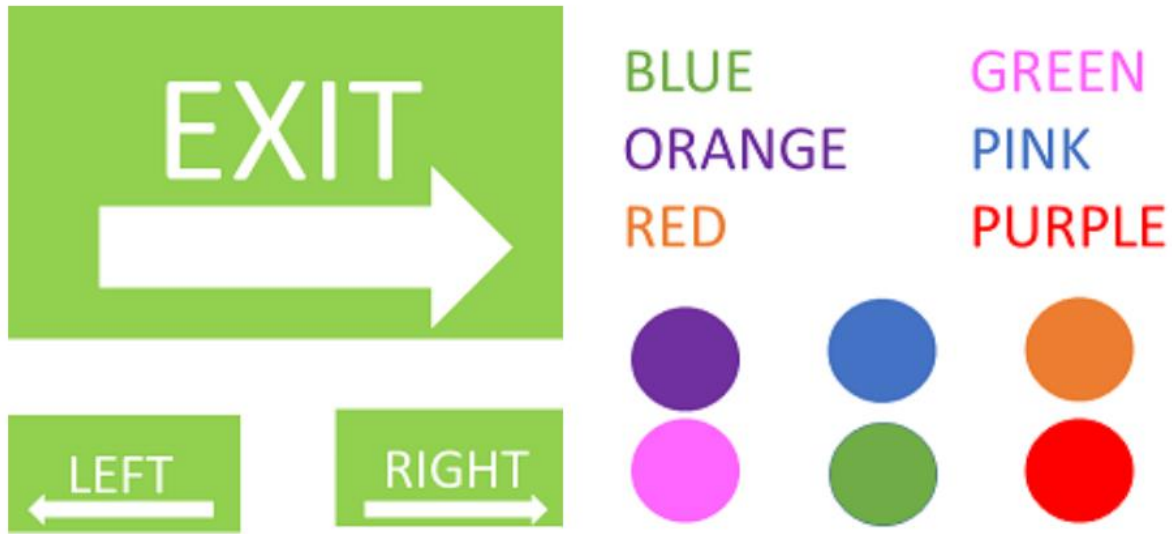


Figure 11: Cognitive task of the EXIT sign and modified Stroop Colour test. The cognitive task is a combination of an egress- specific task which consists of identifying the appropriate directional arrow of an EXIT sign, and a modified version of the standardized cognitive test for executive function, known as the Stroop test. The ‘LEFT’, ‘RIGHT’ and coloured circle images represent the buttons participants used to select their answers.

### 4.3 Carbon Monoxide Saturation Procedure

Calculated doses of CO to administer to participants were done using the Lundby method, which required participant-specific input parameters (78). To start, the participant was weighed (kg) and ambient room temperature, pressure and humidity were recorded. A finger prick (retractable lance) and blood sample (single 100 µl capillary sample) was taken and processed by a blood gas analyzer (ABL80 FLEX, Radiometer, Mississauga, ON, Canada). This provided researchers with the participants baseline %COHb and a measure of their hemoglobin (Hb) mass. The final input parameter needed to calculate the participants CO dose was the blood volume of the participant, which was assumed to be 70-75 mL/kg for males and 60 mL/kg for females (93). The Lundby is outlined in equations 2-6 and was the method selected to determine how much CO to administer to raise the participants baseline %COHb up to the target saturation, either 4% or 7% COHb.

$nHb\ total = Hb\ mass\ in\ the\ body / 6.44 \times 10^4\ g/mol\ (Hb\ molar\ Mass)\ (equation\ 2)$

$nHb\ tagged = nCO\ absorbed / 4\ (equation\ 3)$

$PV = nRT\ (equation\ 4)$

$\%COHb = (nHb\ tagged / nHb\ total) \times 100\% (equation\ 5)$

$Total\ \%COHb\ theoretical = baseline\ \%COHb + \%COHb\ (equation\ 6)$

Measured Hb mass from the baseline finger prick sample was converted from g/dL to g/L and multiplied by an assumed blood volume to get the total Hb mass in the body. The Hb mass in the body was divided by the molar mass of Hb to get the total moles of hemoglobin in the body, nHb total (equation 2). It is known that 1 mol of Hb binds 4 moles of CO, therefore moles of CO absorbed can be divided by 4, to get the nHb tagged, the number of Hb molecules bound to CO (equation 3). nCO (moles of CO) absorbed is calculated based on the ideal gas law (equation 4) where P is the room pressure in atm, V is the estimated volume of the CO dose in L, R is a gas constant in atm•L/mol•K and T is the temperature in Kelvin. The percentage of COHb is equal to nHb tagged divided by nHb total, multiplied by 100% (equation 5). The volume of CO was estimated based on the bodyweight of the participant, which typically ranged between 40-70 mL/kg. This calculated %COHb from the dose of CO (mL) in summation with the original baseline %COHb measured by the blood gas analyzer, should equal the target %COHb saturation (equation 6), and this was verified with another blood sample. The volume of CO to administer was repeated accordingly to ensure the appropriate target saturation was achieved.

Once the correct dose of CO was determined, participants were instrumented with a pulse oximeter (model 7500FO, Nonin, Plymouth, MN, USA) and high acuity patient monitor to allow

for continuous measures of both oxygen and carbon monoxide in the blood. Participants wore a face mask, connected to a rebreathing apparatus that consisted of a 3-way valve connected to room air and four 3L balloons filled with room air. A syringe containing the calculated dose of CO was connected via the sampling port in the face mask to optimize the amount of CO inhaled during the inhalation breathing maneuver done by the participant. Once ready, the participant was instructed to exhale completely as best as possible before taking a slow, controlled deep inhale while researchers administered the dose of CO. Following the CO administration, participants were asked to hold their breath for up to 30 seconds before they continued to breathe normally while remaining connected to the rebreathing circuit for 2.5 minutes. A post-rebreathing finger prick and blood sample analysis was then conducted to ensure that the target COHb saturation was reached. The experimental uncertainty of 4% COHb saturation was 20%, and for 7% COHb saturation was 36.67%. This procedure was repeated as required to reach the target saturation before the 4% COHb and 7% COHb egress trials.

## 5 Data Collection

### 5.1 Cardiorespiratory Responses

Raw data was recorded at a rate of 200 Hz with a 16-channel analog-to-digital data acquisition system (PowerLab/16SP model ML 795; ADInstruments, Colorado Springs, CO). Expiratory flow was continuously measured by having participants breathe through the mouthpiece, which was attached to a pneumotachometer located on the breathing circuit. The pneumotachometer (Hans Rudolph 800 L/min Heated Pneumotachometer, ADInstruments, Colorado Springs, CO, USA) was heated to 37°C and calibrated before each participant using room air and a 3-L syringe. Calibrated O<sub>2</sub> and CO<sub>2</sub> analyzers (AEI Technologies S-3-A/I; Applied Electrochemistry, Bastrop, TX, USA) were used to sample mixed expired gases during exercise. End-tidal gases were sampled at the mouth using a sample line connected to the analyzers. During the experimental protocol, expired gases were sampled by a set of calibrated O<sub>2</sub> and CO<sub>2</sub> analyzers. The O<sub>2</sub> analyzer was used to sample end-tidal oxygen and the CO<sub>2</sub> analyzer for end-tidal CO<sub>2</sub>. All collected gases were dried using nafion tubing inside a sealed glass jar filled with Drierite to ensure the gases contain 0% humidity prior to entering the gas analyzers. Heart rate (HR) was measured using a telemetric sensor (Polar T34; Polar Electro, Kempele, Finland), and oxygen saturation (SpO<sub>2</sub>) and carbon monoxide saturation (SpCO) was estimated using a finger-pulse oximeter (model 7500FO, Nonin, Plymouth, MN, USA). Manipulation of inhaled gases was completed with the use of customized software described below in section 5.2.

Associated error/uncertainty with this equipment is detailed as follows: sampling is done at the mouth of the face mask, however, there is a slight delay from this collection due to the length of the sample line. During exercise this is not a concern as breathing rate is accelerated.

The pneumotachometer is based on the assumption of linear flow and was calibrated with room air, therefore large changes in gas density could alter the results of the pneumotachometer. This was assumed unlikely to occur during these experiments and thus assumed negligible. The CO<sub>2</sub> analyzer had an accuracy of  $\pm 0.02$  and sensitivity of  $\pm 0.001\%$  over the range of 0-15% CO<sub>2</sub> and the O<sub>2</sub> analyzer had an accuracy of  $\pm 0.01\%$  and sensitivity of  $\pm 0.001\%$  at all O<sub>2</sub> concentrations from 0-100% O<sub>2</sub>. The gas analyzers were calibrated at the beginning of each testing day with a calibrated gas cylinder tank with known concentrations to ensure accurate measurements during testing.

## **5.2 Inhaled Gas Manipulation**

Manipulation of inspired gases was completed using customized hardware (Airforce 6.1) and software (Pneumologixs, Consulting Ltd., 2019) This system is a custom-built gas mixing system that allowed researchers to change the fractions of inspired air on a breath-by-breath basis. Gases flowed directly from medical grade gas cylinders (99% pure oxygen, 99% pure carbon dioxide and 100% pure nitrogen) into a mixing chamber and through the inspired side of the breathing circuit, based on the desired volume fractions inputted by the researcher. The researcher controlled the inspired fractions of O<sub>2</sub> and CO<sub>2</sub> as well as volumes via manual inputs into the software. Prior to testing each day, this system underwent a multi-step calibration process.

## 6 Data Analysis

### 6.1 Cardiorespiratory Responses

The measured flows from the pneumotachometer were integrated to determine tidal volume ( $V_T$ ) and calculate breathing frequency ( $F_b$ ). Tidal volume was measured as the change in pressure across the pneumotachometer with each breath being identified following each change in pressure. Inspiratory ventilation ( $V_I$ , equation 7) was calculated as the product of  $V_T$  and  $F_b$ , and was converted into expiratory ventilation ( $V_E$ , equation 8) using the Haldane transformation (94). Ventilation was corrected for temperature, humidity and barometric pressure, and expressed in body temperature pressure saturated (BTPS).  $F_{eO_2}$  and  $F_{eCO_2}$  are the fractions of expired oxygen and carbon dioxide respectively that are collected during exercise.

$$V_I = V_T \times F_b \text{ (equation 7)}$$

$$V_E = V_I / ((1 - (F_{eO_2}/100)) - (F_{eCO_2}/100)) / (1 - 20.93/100 - (0.03/100)) \text{ (equation 8)}$$

The fraction of  $O_2$  bound to hemoglobin ( $FO_2Hb$ ) was determined by subtracting the fraction of CO bound to hemoglobin ( $FCOHb$ , determined from the blood-gas analyzer results of measured %COHb using the CO saturation procedure described above) from the oxygen saturation ( $SpO_2$ ) measured by the pulse oximeter (equation 9).

$$SpO_2 = FO_2Hb + FCOHb \text{ (equation 9)}$$

Analysis of these measures was done as follows: each stage of a trial was averaged into fifteen-second increments, including a pre- and post-test baseline. Statistical analysis (described in the next section) focussed on five different time points of interest: pre-trial baseline (PrB,

4:30-4:45 minutes), unloaded exercise (ULE, 7:00-7:15 minutes) loaded exercise (LE, 9:15-9:30 minutes), worst-case loaded exercise (WcLE, 12:15-12:30 minutes) and post-trial baseline (PoB, 14:00-14:15). If a participant was unable to complete the full egress protocol during a trial, the data up until the point they stopped was included in the analysis. Unloaded exercise was the walking phase on the treadmill (pre-evacuation phase) and the loaded exercise was the walking while carrying the 20lb load phase (evacuation phase). Finally, the worst-case loaded exercise phase was the final fifteen-seconds of the egress protocol wherein participants walked on the treadmill, carrying the 20lb load while exposed to the most severe inspired gases.

## **6.2 Statistical Analysis**

Statistical analyses were conducted using GraphPad Prism 8. For inferential tests, a significance level of  $p < 0.05$  was set and all tests were two-sided. Normality tests were completed for all statistical tests using Shapiro-Wilks tests, and when normality failed, the non-parametric statistics tests were employed. A statistic was deemed significant if  $p < 0.05$ .

The time variable was continuous (interval) and was measured during each trial completed by the participant. The primary outcomes compared between sexes and trials were the cardiorespiratory variables including heart rate (HR), ventilation ( $V_I$ ), fraction of oxygen bound to hemoglobin ( $FO_2Hb$ ), oxygen saturation ( $SpO_2$ ), tidal volume ( $V_T$ ), as well as rate of perceived exertions both mental and physical, and the response time of the cognitive task. The cardiorespiratory and cognitive task response time variables were measured continuously throughout each trial and significant differences were assessed using repeated measures mixed-effects models between different conditions and trials. The categorical data from the self-reported mental and physical RPEs was analyzed using independent t-tests between conditions.

To compare COHb saturation, a 2 (4% COHb and 7% COHb) by 5 (PrB, ULE, LE, WcLE and PoB) repeated measures ANOVA was completed between the two egress protocol trials with 4% COHb and 7% COHb. Comparisons made between the hypoxic, hypercapnic and control exposures were completed using a 3 by 5 (PrB, ULE, LE, WcLE and PoB) repeated measures ANOVA to compare significance between conditions at different time points. This allowed for interpretations to be made between the effects of changing O<sub>2</sub> and CO<sub>2</sub> independently. A 2 (male and female) by 5 (PrB, ULE, LE, WcLE and PoB) repeated measures ANOVA was used to compare between sex and different time points during the 7% COHb egress protocol. Another percent change analysis was made within a condition between ULE and WcLE within a condition (control, hypoxia, hypercapnia, 7% COHb) and compared between males and females. These percent change values were analyzed between sexes using a 2 (male and female) by 4 (control, hypoxia, hypercapnia, 7% COHb) ANOVA. A percent change analysis was made between conditions (hypoxia, hypercapnia, 7% COHb) and control trials during the WcLE time point between males and females. These percent change values were analyzed between sexes using a 2 (male and female) by 3 (hypoxia, hypercapnia, 7% COHb) ANOVA. All percent change comparisons were also made between males and the 6 taller female participants (heights greater than or equal to 1.7m) to determine if sex differences were based off physiological sex differences or size differences. To compare mental and physical RPE between conditions, independent t-tests were completed between the 4% COHb and 7% COHb conditions as well as between males and females during the 7% COHb condition. A one-way ANOVA was used to compare the mental and physical RPE between the control, hypoxia and hypercapnia conditions. The success at completing the entire 12.5 min egress protocol was analyzed between males and females using a Fisher Exact Test.

Cognitive task data was analyzed by test type (EXIT sign and Stroop) and separated into 1-minute bins to determine the average response times per participant. Comparisons were done between conditions during ULE in ambient conditions (5:30-6:30) and during the last minute of testing during WcLE (11:30-12:30). Comparisons of interest were done between the hypoxic, hypercapnic and control conditions as well as between the 4% COHb and 7% COHb conditions. Analysis was done using a 2 (ULE and WcLE) by 3 (hypoxia, hypercapnia, control) and 2 (ULE and WcLE) by 2 (4% COHb and 7% COHb) repeated measures ANOVAs. Each ANOVA was completed for the EXIT sign and for the modified Stroop test results. Comparisons were also completed between all five trials (control, hypoxia, hypercapnia, 4% COHb and 7% COHb) during the WcLE conditions with 5 (exposure conditions) by 2 (EXIT sign and Stroop) repeated measures ANOVA. A sex differences comparison was completed on the 7% COHb trial comparing response times between males and females during WcLE during the last minute of testing (11:30- 12:30). EXIT and Stroop response times were compared using a 2 (males and females) by 2 (Stroop and EXIT sign) ANOVA. Participant summary data and CO saturations were analyzed between males and females using independent t-tests. Participant comparisons were done on participants heights (m), weights (kg), treadmill speed (miles/hour), age (years) and BMI ( $\text{kg}/\text{m}^2$ ).

All independent t-tests were only completed if they passed assumptions of normality using Shapiro-Wilks. The non-parametric Wilcoxon Signed Rank test was completed if assumptions of normality failed as the data was not normally distributed. Multiple comparisons were corrected for using the Bonferroni-Dunn method and if significant F ratios were detected, a Tukey post hoc test was completed. In the case where the data set was non-normally distributed, repeated measures mixed-effects models were used in place of ANOVAs and the Tukey post hoc

testing was completed. Post hoc testing was completed to identify exactly which groups differed from each other. Repeated measures testing was completed to determine the relationship between trial condition for a given time point of interest throughout the egress protocol. Repeated measures testing was also completed with the added variable of sex, timepoint of interest and condition for the control and 7% COHb trials. Summary statistics (mean and standard deviation) were used to describe baseline characteristics and other outcomes of interest.

## 7 Results

### 7.1 Participant Summary Data

A total of 15 males and 15 females completed all 3 days of testing. A summary table of the physical characteristics of the participants are listed in Table 4. Males were significantly taller ( $p=0.0006$ ) and weighed more ( $p=0.002$ ) than female participants.

Table 4: Participant summary data (n=30, females=15).

	<b>Average</b>	<b>Average Male</b>	<b>Average Female</b>
<b>Treadmill Walk Speed (miles)</b>	1.8±0.3	1.9±0.2	1.7±0.3
<b>Age (years)</b>	25±3.7	25±3.8	25±3.7
<b>Height (m)</b>	1.7±0.1	1.8±0.1 *	1.7±0.9
<b>Weight (kg)</b>	75±17	84±17 *	66±11
<b>Body Max Index (kg/m<sup>2</sup>)</b>	25±3.3	26±4	24±3

\* indicates significantly different than females ( $p<0.05$ ). Data are means ± SD.

### 7.2 4% COHb and 7% COHb Egress Trials

#### 7.2.1 4% COHb and 7% COHb Egress Trials: Carbon Monoxide Saturation

Participants were saturated to  $3.8±0.6\%$  COHb and  $6.7±0.6\%$  COHb (Table 6). Males had significantly higher baseline %COHb levels ( $p=0.04$ ) and Hb concentrations ( $p=0.0006$ ). During the 4% COHb trial, females were saturated to a higher CO saturation ( $p=0.002$ ). Males received a significantly higher dose of CO to reach 7% COHb ( $p=0.007$ ) however there was no difference between the degrees of saturation at 7% COHb between sexes ( $p=0.12$ ).

Table 5: Individual baseline carboxyhemoglobin percentages and hemoglobin mass, individual CO doses and the percent of carbon monoxide bound to hemoglobin that participants completed trials with. Participants 001-015 are female and 016-030 are males.

Participant Number	Baseline COHb (%)	Hemoglobin Concentration (g/dL)	CO dose (mL)	4% measured COHb (%)	CO dose (mL)	7% Measured COHb (%)
001	1.1	13.9	50	4.6	30	6.6
002	1.2	14.5	80	5.1	45	7.2
003	1.0	14.8	35	3.8	45	6.2
004	1.2	15.2	35	4.0	40	6.9
005	1.0	16.8	45	3.6	65	6.1
006	1.3	14.6	30	4.6	35	6.9
007	1.2	15.2	40	4.5	45	7.1
008	0.5	15.7	45	4.9	60	6.7
009	0.8	15.2	40	3.3	58	6.7
010	1.1	12.6	58	4.8	40	6.4
011	0.7	14.8	45	3.3	55	8.5
012	1.1	12.2	45	3.6	35	6.3
013	1.0	13.8	40	4.2	70	6.9
014	0.7	15.8	32	4.2	35	7.3
015	0.9	13.7	30	4.2	46	6.8
<b>Female Average</b>	1.0±0.2	15±1.2	43±13	4.2±0.6	47±12	6.8±0.6
<b>Males</b>						
016	1.0	15.6	65	4.2	65	5.8
017	1.0	17.4	55	3.4	105	6.7
018	1.1	17.4	45	3.7	92	7.7
019	1.1	17.5	50	3.0	60	6.0
020	1.3	15.4	30	3.2	50	6.3
021	1.3	17.5	36	3.4	55	6.9
022	1.5	15.9	30	3.0	52	6.3
023	1.3	14.5	35	2.4	60	7.0
024	1.3	15.3	45	3.6	105	7.0
025	1.3	15.7	40	3.3	50	6.9
026	1.3	15.7	55	4.3	43	7.0
027	1.2	16.4	55	3.7	55	6.6
028	0.9	17.2	60	3.7	90	5.9
029	0.7	16.7	50	3.3	60	5.2
030	1.1	14.6	40	4.1	45	6.0
<b>Male Averages</b>	1.2±0.2 *	16±1 *	46±10	3.5±0.5*	64±21 *	6.5±0.6
<b>All Participant Averages</b>	1.1±0.2	15±1.4	46±14	3.8±0.6	56±20	6.7±0.6

Abbreviations: COHb, carbon monoxide bound to hemoglobin. \* indicates significantly different than females (p<0.05). Data are means ± SD.

### 7.2.2 4% COHb and 7% COHb Egress Trials: Cardiorespiratory Variables

There was a main effect of time during all cardiorespiratory variables ( $p < 0.001$ ), and an interaction effect was seen between time and %COHb when comparing only the fraction of oxygen bound to hemoglobin ( $p < 0.001$ ). Fraction of oxygen bound to hemoglobin was significantly greater during the 4% COHb compared to the 7% COHb trials during the pre-trial baseline ( $p < 0.001$ ), unloaded exercise ( $p = 0.0037$ ), and post-trial baseline ( $p < 0.001$ ) (Figure 12, D). Post hoc testing revealed no other significant differences between time points and the 4% COHb and 7% COHb conditions (HR: all  $p > 0.6$ ),  $V_I$ : all  $p > 0.98$ ,  $V_T$ : all  $p > 0.99$ ,  $SpO_2$ : all  $p > 0.7$ ).

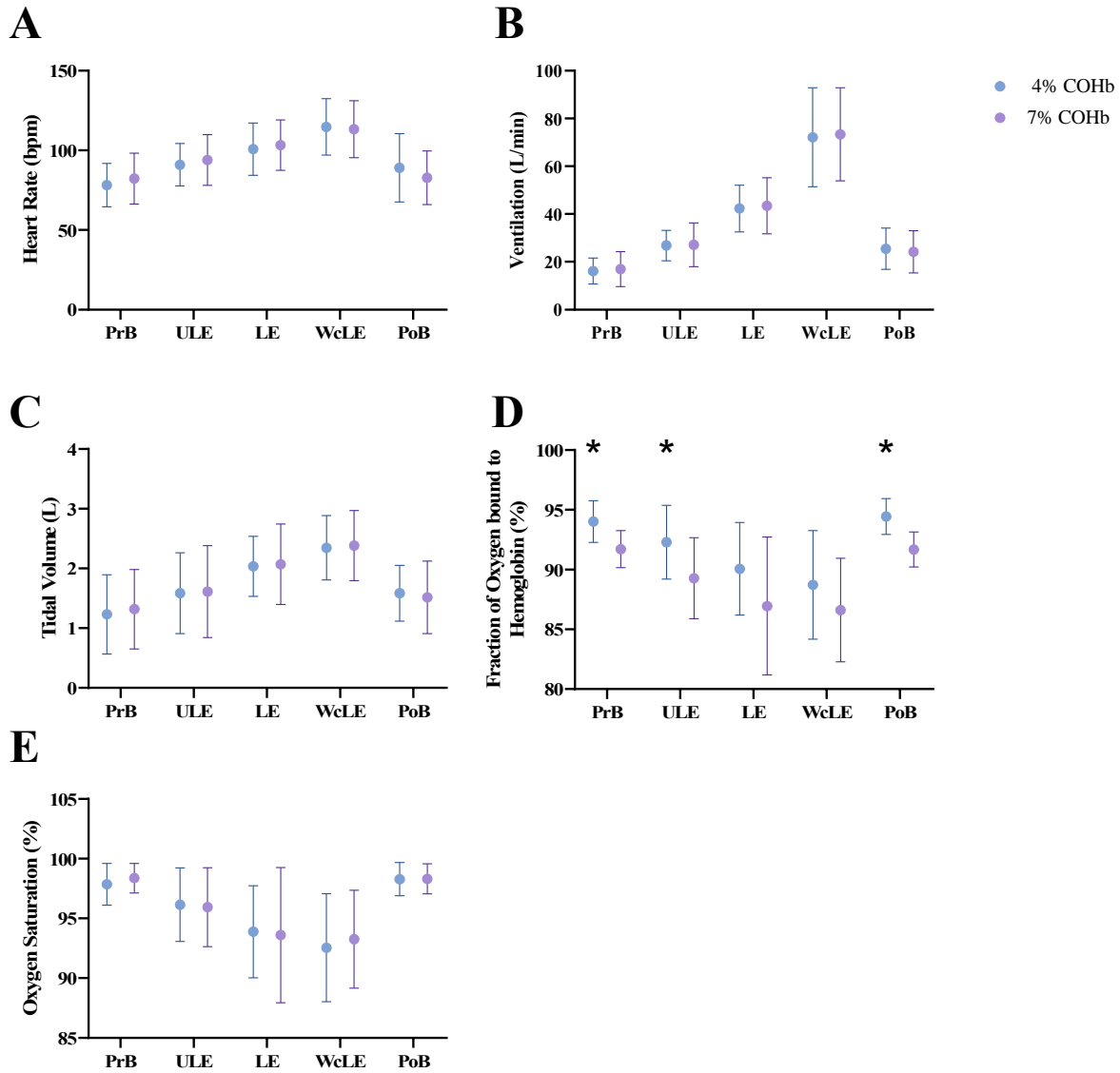


Figure 12: Cardiorespiratory variables during the 4% COHb and 7% COHb egress trials. Comparisons made at 5 timepoints: pre-baseline rest (PrB), unloaded exercise (UL), loaded exercise (LE), worst-case loaded exercise (WcLE) and post-test baseline (PoB). Cardiorespiratory variables include heart rate (A), ventilation (B), tidal volume (C), fraction of oxygen bound to hemoglobin (D) and oxygen saturation (E). \* indicates measurements that were significantly different than 7% COHb ( $p < 0.05$ ). Data are means  $\pm$  SD.

Table 6: Cardiorespiratory variables during pre-baseline (PrB), unloaded exercise (ULE), loaded exercise (LE), worst-case loaded exercise (WcLE) and post-baseline (PoB) during the 4% and 7% COHb egress trials.

	Condition	PrB	ULE	LE	WcLE	PoB
<b>HR (bpm)</b>	4% COHb	78±14	91±13	102±19	110±25	89±22
	7% COHb	82±16	94±16	105±15	115±19	85±20
<b>V<sub>I</sub> (L/min)</b>	4% COHb	16±5.5	27±6	46±12	72±21	26±9
	7% COHb	17±7.3	27±9	47±14	73±19	24±9
<b>V<sub>T</sub> (L)</b>	4% COHb	1.2±0.7	1.6±0.7	2.0±0.5	2.4±0.5	1.6±0.5
	7% COHb	1.3±0.7	1.6±0.8	2.1±0.7	2.4±0.6	1.5±0.6
<b>FO<sub>2</sub>Hb (%)</b>	4% COHb	94±1.8*	92±3.1*	91±5.7	89±4.5	95±1.5*
	7% COHb	92±1.5	89±3.5	88±5.0	87±4.5	92±1.4
<b>SpO<sub>2</sub> (%)</b>	4% COHb	98±1.8	96±3.1	94±5.7	93±4.5	98±1.4
	7% COHb	98±1.2	96±3.3	95±4.8	93±4.1	98±1.3

Abbreviations: HR, heart rate. V<sub>I</sub>, ventilation. V<sub>T</sub>, tidal volume. FO<sub>2</sub>Hb, fraction of oxygen bound to hemoglobin. SpO<sub>2</sub>, oxygen saturation. \* indicates measurements that were significantly different than 7% COHb (p<0.05). Data are means ± SD.

### 7.2.3 4% COHb and 7% COHb Egress Trials: Rate of Perceived Exertion

There were no significant differences between the 4% COHb and 7% COHb trials when comparing mental and physical RPE (p=0.9 and p=0.8 respectively) (Figure 13). The 4% COHb trial had an average mental rating of 3.9±2.4 and physical rating of 5.3±2.2. The 7% COHb trial had an average mental rating of 4.0±2.3 and physical rating of 5.1±2.3.

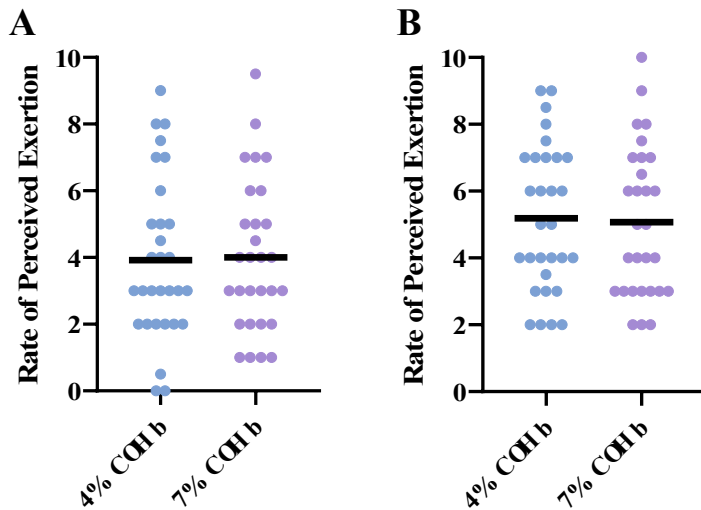


Figure 13: Mental (A) and physical (B) ratings of perceived exertion by participants following completion of the 4% COHb and 7% COHb egress trials. Ratings were completed based on Borg modified scale. Abbreviations: RPE, rating of perceived exertion. COHb, carbon monoxide bound to hemoglobin. Data are means  $\pm$  SD.

#### 7.2.4 4% COHb and 7% COHb Egress Trials: Cognitive Task

Cognitive task response time for the EXIT sign and modified Stroop tests were not significantly different between the 4% COHb and 7% COHb egress trials. During the EXIT Sign test, response time during WcLE during the last minute of testing for both 4% and 7% COHb was significantly longer compared to ULE in normoxia (4% COHb:  $p=0.003$ , 7% COHb:  $p=0.02$ ). Significant differences were not seen between response times during the modified Stroop test (all  $p>0.29$ ). On average, the response time during WcLE for the 4% COHb was  $1.4\pm 0.4$ s and  $1.6\pm 0.5$ s for EXIT sign and modified Stroop test prompts respectively (Figure 14). During the 7% COHb trial during WcLE, the average response times for EXIT sign and modified Stroop test prompts were  $1.5\pm 0.5$ s and  $1.7\pm 1.0$ s respectively. During ULE the average response time for the EXIT sign and modified Stroop test were  $1.2\pm 0.3$ s and  $1.4\pm 0.3$ s.

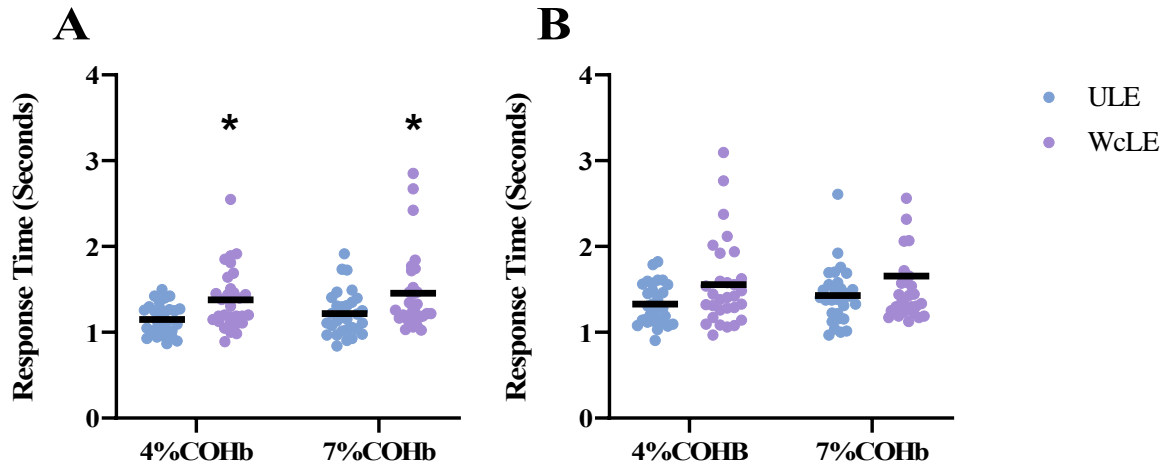


Figure 14: Average cognitive task response times during the EXIT sign (A) and modified Stroop colour (B) tests between the 4% COHb and 7% COHb egress trials during unloaded exercise in normoxia (ULE, 5:30-6:30) and worst-case loaded exercise during the last minute of testing (WcLE, 11:30-12:30). \* indicates measurements that were significantly longer during WcLE. Data are means  $\pm$  SD.

### 7.3 Hypoxia, Hypercapnia and Control Trials

#### 7.3.1 Hypoxia, Hypercapnia and Control Trials: Cardiorespiratory

A summary of the cardiorespiratory data between the control, hypoxia and hypercapnia trials is presented in Table 7. Heart rate had a main effect for time and an interaction effect between time and condition ( $p < 0.001$ ) (Figure 15, A). An interaction effect was seen during WcLE with hypercapnia and hypoxia being greater than control ( $p = 0.027$  and  $p = 0.034$ ). Ventilation presented both a time and condition main effect as well as an interaction effect ( $p < 0.001$  for all). During both LE and WcLE,  $V_I$  was increased during hypercapnia compared to hypoxia and control (all  $p < 0.001$ ) (Figure 15, B). Tidal volume showed a main effect for time as well as an interaction effect between the hypercapnia and hypoxia trials and hypercapnia and control trials ( $p < 0.001$ ) (Figure 15, C). These interaction effects were seen during the LE (hypercapnia vs hypoxia:  $p = 0.0016$  and hypercapnia vs control:  $p < 0.001$ ) and WcLE trials (hypercapnia vs hypoxia:  $p < 0.001$ , hypercapnia vs control:  $p < 0.001$ ). Oxygen saturation had main effects for both time and condition as well as an interaction effect during the hypoxia,

hypercapnia and control trials ( $p < 0.001$ ) (Figure 15, D). During LE, a greater desaturation was seen during the hypoxia trial compared to the hypercapnia trial ( $p = 0.035$ ). During WcLE, oxygen desaturation was seen in the hypoxia condition compared to hypercapnia and control (all  $p < 0.001$ ).

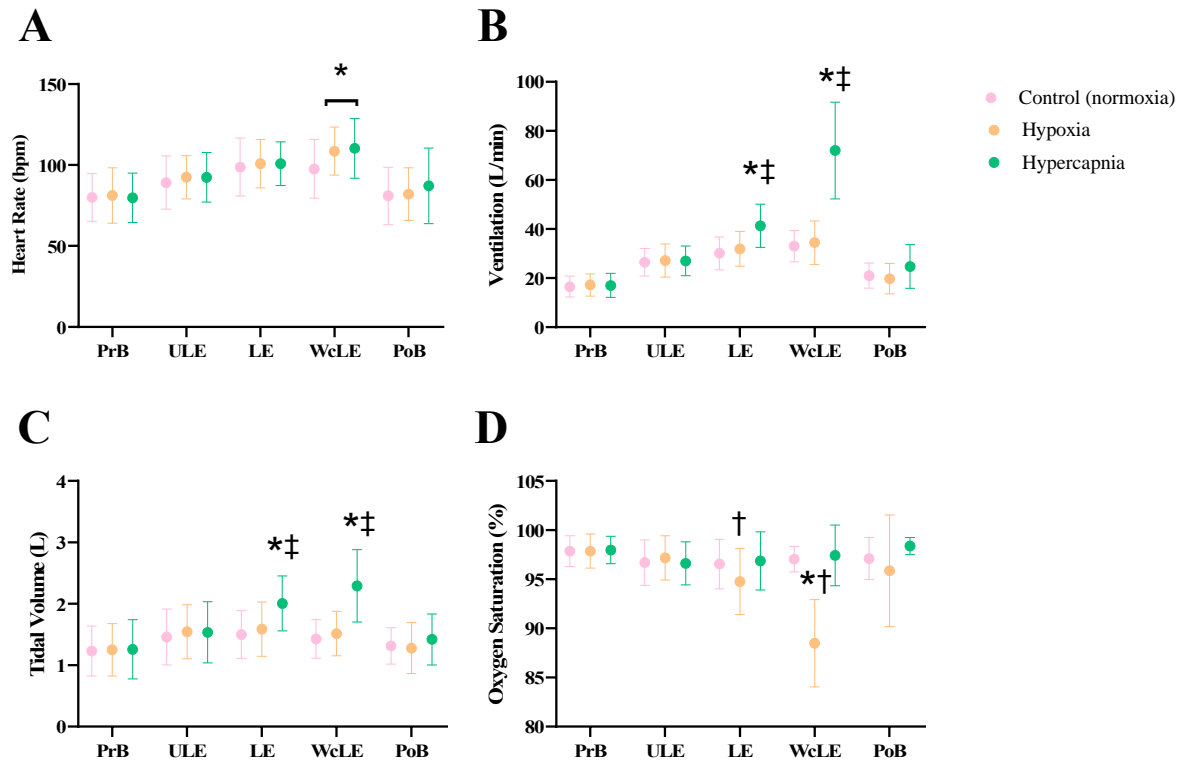


Figure 15: Cardiorespiratory variables during the control, hypoxia and hypercapnia egress trials. Comparisons made at 5 timepoints: pre-baseline rest (PrB), unloaded exercise (UL), loaded exercise (LE), worst-case loaded exercise (WcLE) and post-test baseline (PoB). \* indicates a significant difference than control, † indicates a significant difference than hypercapnia and ‡ indicates significant difference than hypoxia. For all significant differences  $p < 0.05$ . Data are means  $\pm$  SD.

Table 7: Cardiorespiratory variables during pre-baseline (PrB), unloaded exercise (ULE), loaded exercise (LE), worst-case loaded exercise (WCLE) and post-baseline (PoB) during the control, hypoxia and hypercapnia egress trials.

	Condition	PrB	ULE	LE	WcLE	PoB
<b>HR (bpm)</b>	Control	80±15	90±15	101±16	98±18	81±18
	Hypoxia	81±17	92±13	103±15	107±15 *	82±16
	Hypercapnia	80±15	92±15	98±16	110±18 *	87±23
<b>V<sub>I</sub> (L/min)</b>	Control	17±4	27±6	31±7	33±6	21±5
	Hypoxia	17±5	27±7	33±7	34±8.9	19±7
	Hypercapnia	17±5	27±6	44±10 *‡	72±20 *‡	25±9
<b>V<sub>T</sub> (L)</b>	Control	1.2±0.4	1.5±0.5	1.5±0.4	1.4±0.3	1.3±0.3
	Hypoxia	1.3±0.4	1.5±0.4	1.6±0.4	1.5±0.4	1.3 ±0.4
	Hypercapnia	1.3±0.5	1.5±0.5	2.0± 0.5 *‡	2.3±0.6*‡	1.4±0.4
<b>SpO<sub>2</sub> (%)</b>	Control	98±1.6	97±2.3	97±2.9	97±1.3	97±2.1
	Hypoxia	98±1.7	97±2.3	94±3.7 †	89±4.4*†	96±5.7
	Hypercapnia	98±1.4	97±2.2	97±2.7	97±3.1	98±0.9

Abbreviations: HR, heart rate. V<sub>I</sub>, ventilation. V<sub>T</sub>, tidal volume. FO<sub>2</sub>Hb, fraction of oxygen bound to hemoglobin. SpO<sub>2</sub>, oxygen saturation. \* indicates measurements that were significantly different than control. † indicates measurements that were significantly different than hypercapnia. ‡ indicates measurements that were significantly different than hypoxia. For all significant differences p<0.05. Data are means ± SD.

### 7.3.2 Hypoxia, Hypercapnia and Control Trials: Rate of Perceived Exertion

Between all three conditions, hypercapnia was rated significantly higher, both mentally and physically than hypoxia (p<0.001) and control (p<0.001). Hypoxia was rated more challenging than control (mentally: p<0.001, and physically: p=0.009) (Figure 16). Hypercapnia was rated the highest for both mental and physical RPE between the three conditions with an average rating of 3.1±1.9 and 4.3±2.3 respectively. The control trial was rated 1.3±0.2 for mental

and  $1.5 \pm 0.2$  for physical, and similarly the hypoxia trial was  $1.9 \pm 1.5$  for mental and  $2.3 \pm 1.6$  for physical.

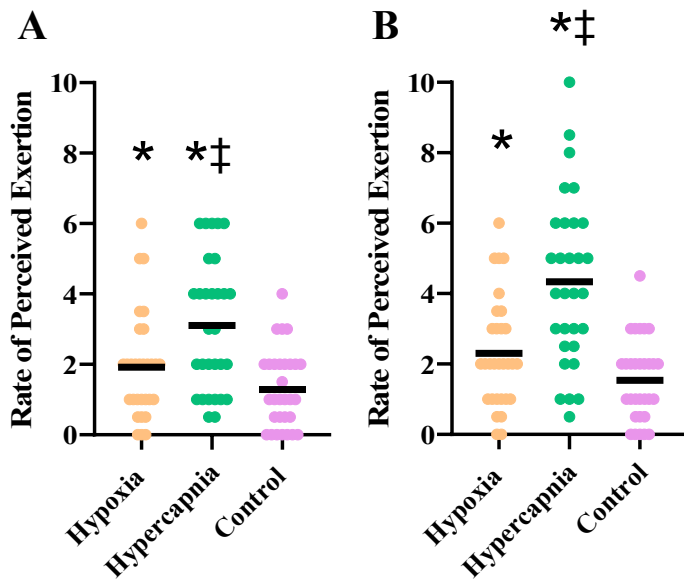


Figure 16: Mental (A) and physical (B) ratings of perceived exertion by participants following completion of the hypoxia, hypercapnia and control egress trials. Ratings were completed based on Borg modified scale. \* indicates measurements that were significantly different than control. ‡ indicates measurements that were significantly different than hypoxia. For all significant differences  $p < 0.05$ . Data are means  $\pm$  SD.

### 7.3.3 Hypoxia, Hypercapnia and Control Trials: Cognitive Task

Cognitive task response times for both the EXIT sign and modified Stroop tests presented main effects for time ( $p=0.035$  and  $p=0.011$ ) (Figure 17). Neither cognitive task prompt showed significant differences between conditions during the ULE or WcLE time points (EXIT sign:  $p > 0.2$ , modified Stroop:  $p > 0.3$ ).

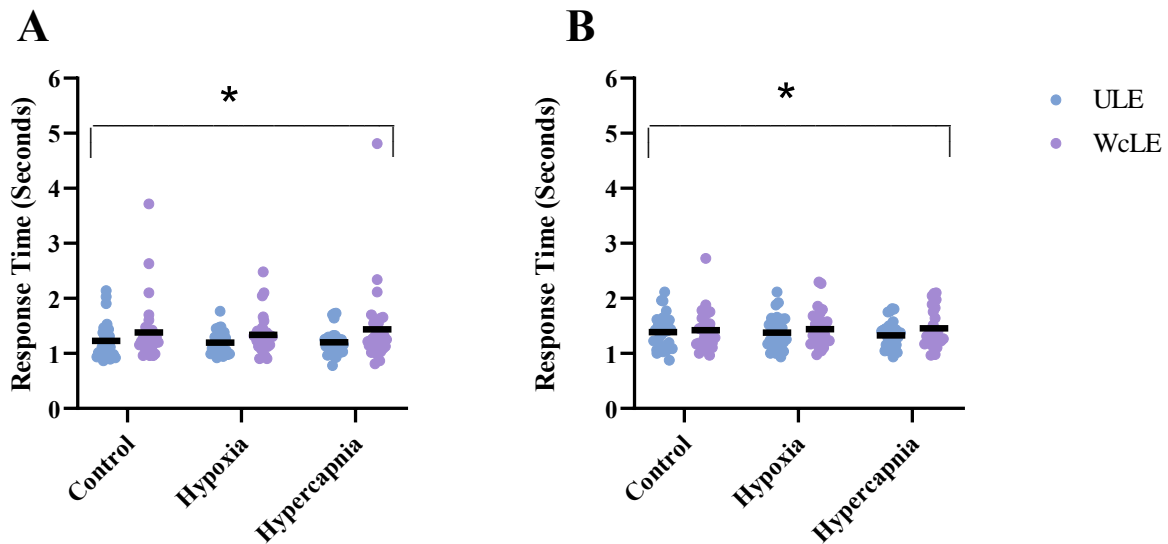


Figure 17: Average cognitive task response times during the EXIT sign (A) and modified Stroop colour (B) tests between the control, hypoxia and hypercapnia egress trials during unloaded exercise in normoxia (ULE, 5:30-6:30) and worst-case loaded exercise during the last minute of testing (WcLE, 11:30-12:30). \* indicates a main effect for time across all conditions. Data are means  $\pm$  SD.

## 7.4 Sex Differences during 7% COHb Trial

### 7.4.1 Sex Differences during 7% COHb Trial: Cardiorespiratory Variables

A summary table of the absolute sex differences data between males and females during the 7% COHb trial is present in Table 8. When comparing HR within the 7% COHb condition, a main effect for time ( $p < 0.001$ ) as well as an interaction effect between time and sex ( $p = 0.015$ ) was seen. However, there were no significant differences between males and females during any of the five time points (all  $p > 0.3$ , range 0.3-0.99) (Figure 18, A). During PrB and ULE, males had higher HR than females, this then switches from LE to PoB as female heart rates are consistently higher than males. Ventilation had a main effect for time ( $p < 0.001$ ) when comparing between males and females. Post hoc testing revealed that there was no significant difference between males and females ( $p = 0.07$ ) (Figure 18, B). Tidal volume presented a main effect for both time and sex ( $p < 0.001$  and  $p = 0.045$ ). A significant difference was seen between sexes with

males having a greater  $V_T$  during the WcLE ( $p=0.006$ ). Males displayed an average tidal volume of  $2.7\pm 0.5L$  compared to  $2.1\pm 0.5L$  in females (Figure 18, C). There were no differences in the 7% COHb saturations between males and females, with average saturations of  $6.6\pm 1.3\%$  COHb and  $6.8\pm 0.6\%$  COHb respectively (Table 5). Fraction of oxygen bound to hemoglobin had a main effect for time ( $p<0.001$ ) as well as an interaction effect between time and sex ( $p=0.048$ ). Post hoc testing revealed no significant differences between sexes during any time point for both saturations ( $p>0.4$ ) (Figure 18, D). Oxygen saturation had a main effect for sex ( $p<0.0001$ ), however between time points no differences were seen ( $p>0.2$ ) (Figure 18, E). Females were carrying a significantly greater percentage of their body weight while carrying the 20lb load compared to males ( $p=0.002$ ). The 20lb load was  $14\pm 2.3\%$  and  $11\pm 2.1\%$  of females and males body weight respectively.

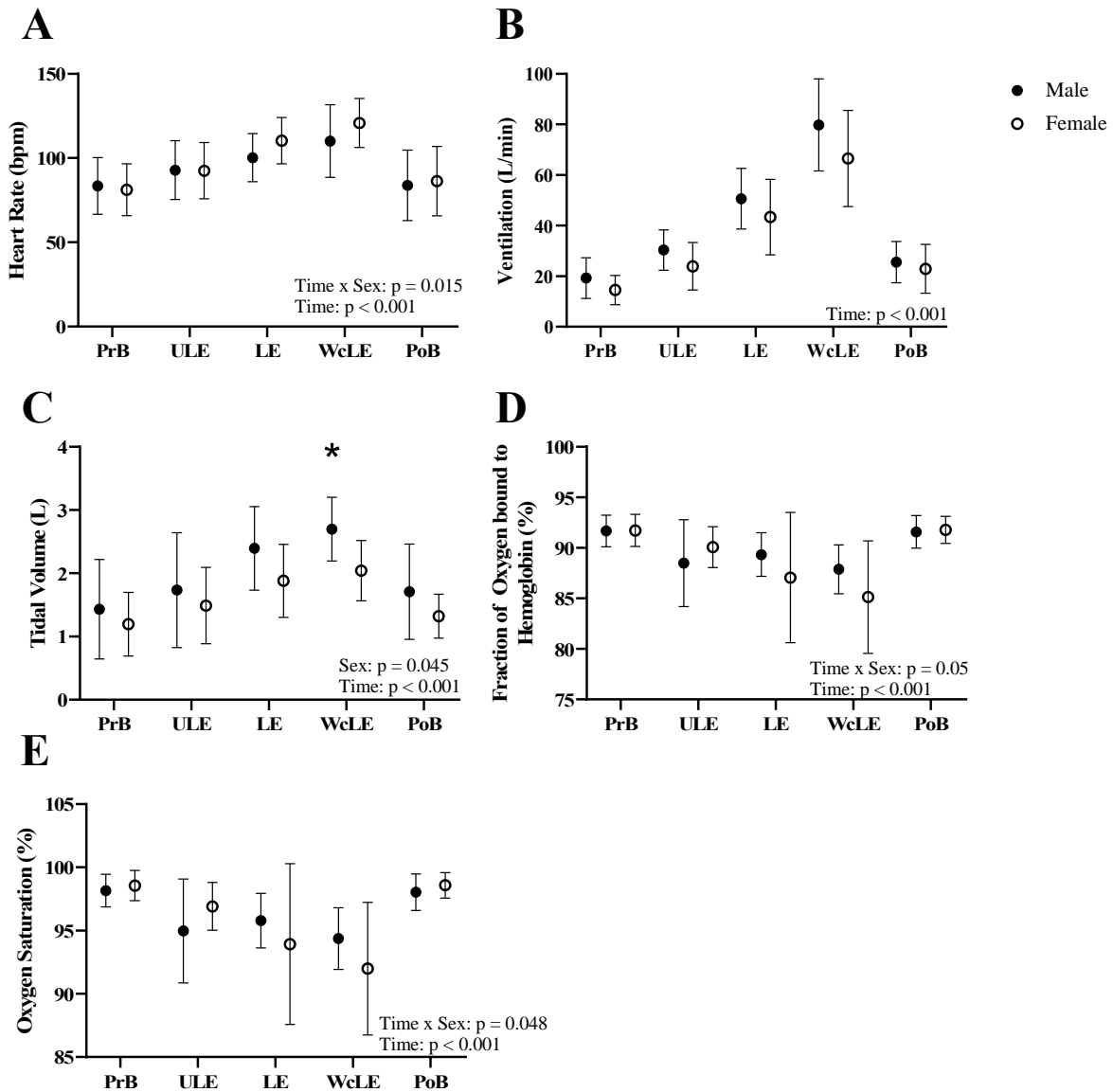


Figure 18: Cardiorespiratory variables between males and females during the 7% COHb egress trial. Comparisons made at 5 timepoints: pre-baseline rest (PrB), unloaded exercise (UL), loaded exercise (LE), worst-case loaded exercise (WcLE) and post-test baseline (PoB). Cardiovascular variables include heart rate (A), ventilation (B), tidal volume (C), fraction of oxygen bound to hemoglobin (D) and oxygen saturation (E). \* indicates measurements that were significantly different than females ( $p < 0.05$ ). Data are means  $\pm$  SD.

Table 8: Cardiorespiratory variables during pre-baseline (PrB), unloaded exercise (ULE), loaded exercise (LE), worst-case loaded exercise (WCLE) and post-baseline (PoB) during the 7%COHb egress trials between males and females.

	Condition	Sex	PrB	ULE	LE	WcLE	PoB
<b>HR (bpm)</b>	7% COHb	Male	83±17	93±17	100±14	110±22	84±21
		Female	78±14	92±11	106±10	118±11	82±12
<b>V<sub>T</sub> (L)</b>	7% COHb	Male	1.4±0.8	1.7±0.9	2.4±0.7	2.7±0.5*	1.7±0.8
		Female	1.2±0.5	1.5±0.7	1.9±0.6	2.1±0.5	1.3±0.4
<b>V<sub>I</sub> (L/min)</b>	7% COHb	Male	19±8	30±8	51±12	80±18	26±8.2
		Female	15±6.1	24±9.9	43±15	67±20	23±9.9
<b>FO<sub>2</sub>Hb (%)</b>	7% COHb	Male	92±1.5	88±4.4	90±1.6	88±2.3	91±1.5
		Female	92±1.8	90±2.3	87±7.3	85±6.1	92±1.3
<b>SpO<sub>2</sub> (%)</b>	7% COHb	Male	98±1.3	95±4.1	96±2.2	94±2.5	98±1.5
		Female	99±1.3	97±2.0	94±6.8	92±5.5	99±0.9

Abbreviations: HR, heart rate. V<sub>I</sub>, ventilation. V<sub>T</sub>, tidal volume. FO<sub>2</sub>Hb, fraction of oxygen bound to hemoglobin. SpO<sub>2</sub>, oxygen saturation. \* indicates measurements that were significantly different than females (p<0.05). Data are means ± SD.

#### 7.4.2 Completion of Egress Trials

Of the 30 participants that completed all 10 trials, 2 females were unsuccessful in completing the entirety of the 12.5min egress protocol for all ten trials. The ability to complete the egress protocol was not significant between males and females (p=0.4828).

#### 7.4.3 Sex Differences during 7% COHb Trial: Rate of Perceived Exertion

There were no significant differences between ratings for males and females when comparing mental and physical RPE (p=0.47 and p=0.86 respectively). Average ratings by males and females were 4.3±2.4 and 3.7±2.1 for mental RPE and 5.1±2.4 and 5.0±2.2 for physical RPE (Figure 19).

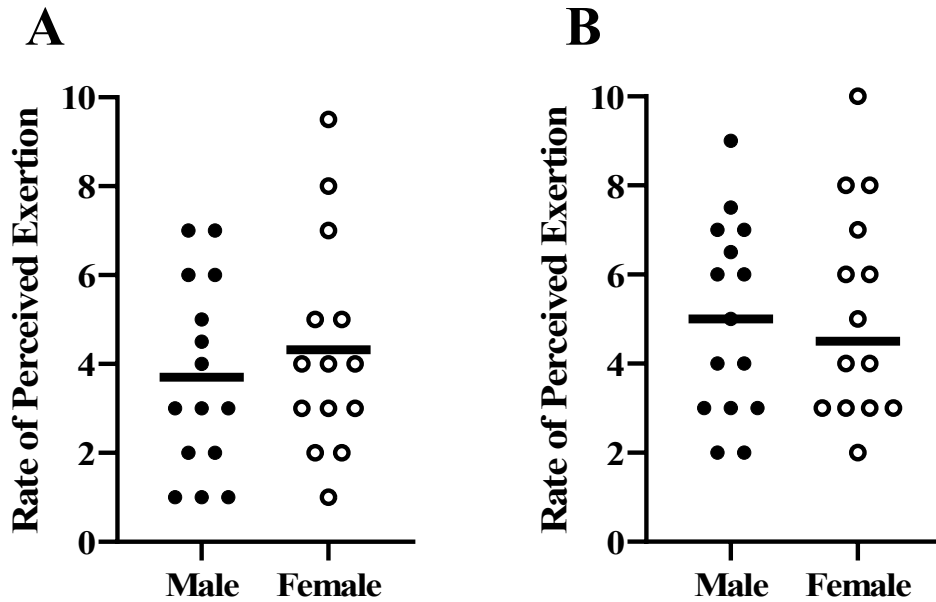


Figure 19: Mental (A) and physical (B) ratings of perceived exertion by males and females following completion of 7% COHb egress trial. Ratings were completed based on Borg modified scale. Data are means  $\pm$  SD.

#### 7.4.4 Sex Differences during 7% COHb Trial: Cognitive Task

Average response times to the EXIT sign and modified Stroop tests were recorded between males and females during the last minute of egress during the 7% COHb trial (Figure 20). There were no significant differences between male and female response times or between response times to either the EXIT sign or modified Stroop test ( $p > 0.17$  and  $p > 0.99$  respectively). The average response times for males and females during the EXIT sign tests were  $1.4 \pm 0.5$ s and  $1.5 \pm 0.5$ s and for the modified Stroop tests were  $1.4 \pm 0.2$ s and  $1.9 \pm 1.4$ s.

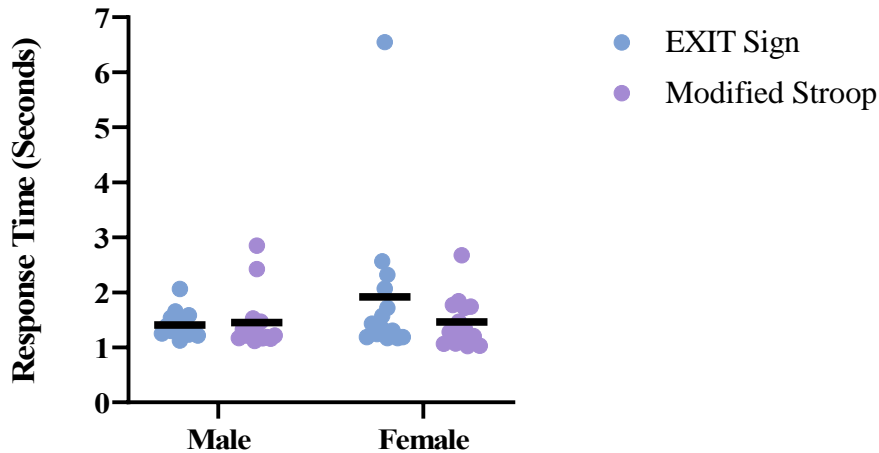


Figure 20: Average cognitive task response times during the EXIT sign (A) and modified Stroop colour (B) tests between males and females during worst-case loaded exercise during the last minute of testing (WcLE, 11:30-12:30), while completing the 7% COHb combination egress trial. Data are means  $\pm$  SD.

## 7.5 Relative Sex-based Comparisons

### 7.5.1 Relative Change Sex Differences: Within Conditions

Comparisons were made at two time points, ULE and WcLE within a condition between males and females. Females exhibited greater percent changes in HR than males as a main effect for sex was seen ( $p < 0.0001$ ) (Figure 21, A). Ventilation had a main effects for both sex and condition ( $p < 0.0001$ ), as well as an interaction effect ( $p = 0.002$ ) (Figure 21, B). Females had a relatively greater change in  $V_I$  than males during the hypoxia ( $p < 0.0001$ ), hypercapnia ( $p = 0.008$ ) and 7% COHb combination trials ( $p < 0.0001$ ). Main effects for sex, condition and an interaction effect were all seen for tidal volume (all  $p < 0.0001$ ) (Figure 21, C). Males had greater relative changes in  $V_T$  during the control, hypercapnia and 7% COHb combination trials (all  $p < 0.0001$ ). Fraction of oxygen bound to hemoglobin had main effects for both sex and condition ( $p < 0.0001$ ,  $p = 0.002$ ) (Figure 21, D) and an interaction effect ( $p = 0.005$ ). Greater relative changes were seen with females desaturating more than males during the 7% COHb combination trial ( $p < 0.0001$ ).

When sample size was corrected for between males and tall females (n=6), results did not change.

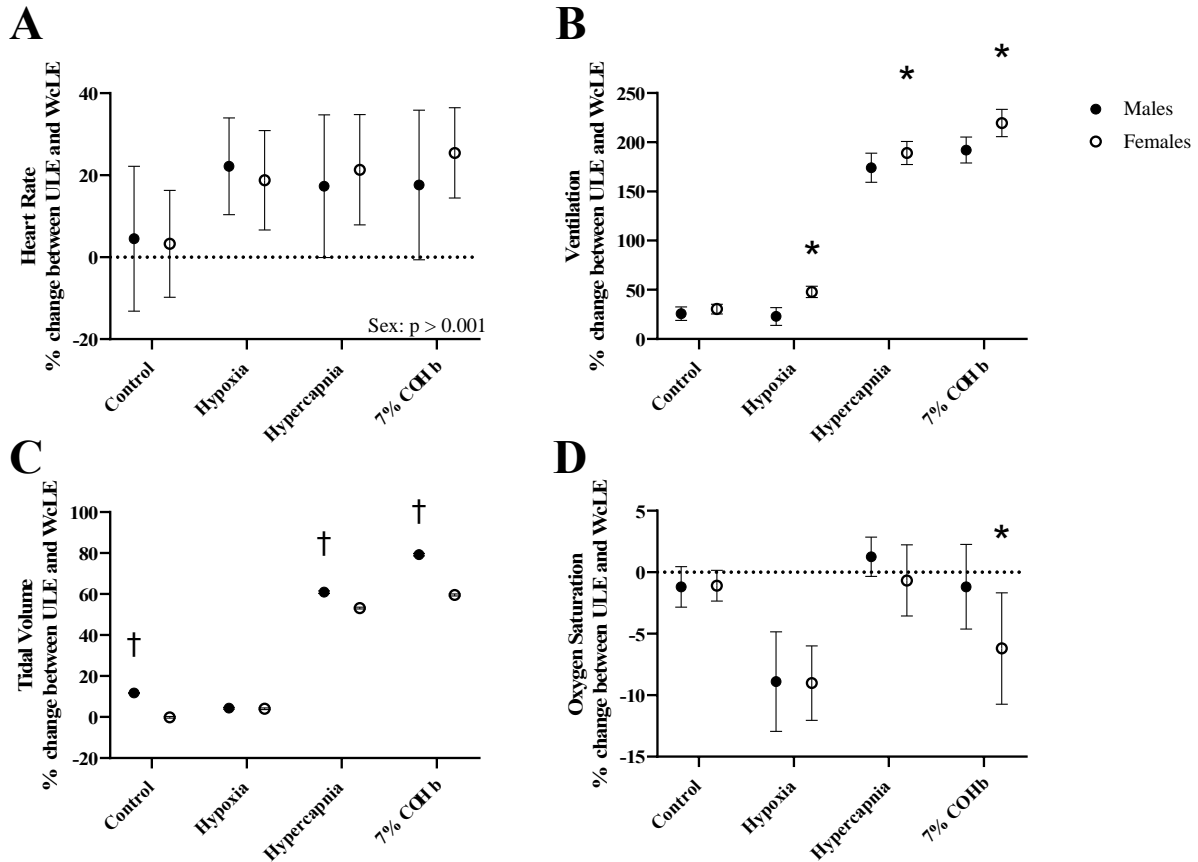


Figure 21: Percent change between unloaded exercise (6-6:15 minutes) and worst case loaded exercise (12:15-12:30) within each trial between sexes. Positive values represent positive percent changes (increase) between time points whereas negative values represent negative percent changes (decreases). Percent change comparisons were made on heart rate (A), ventilation (B), tidal volume (C) and fraction of oxygen bound to hemoglobin (D). \* indicates that females had a greater relative (percent change) than males ( $p < 0.05$ ). † indicates that males had a greater relative (percent change) than females ( $p < 0.05$ ). Data are means  $\pm$  SD.

### 7.5.2 Relative Change Sex Differences: Between Condition and Control Trials

Comparisons were made during the WcLE time point between conditions and control trials between males and females. Heart rate showed a main effect for condition ( $p = 0.006$ ) (Figure 22, A), and post hoc testing did not reveal any significant differences ( $p > 0.46$ , range 0.47-0.99). Ventilation displayed a main effect for sex ( $p < 0.0001$ ) (Figure 22, B) and an

interaction effect between sex and condition ( $p=0.006$ ). Males displayed a greater relative percent change during the 7% COHb combination trial ( $p=0.0002$ ). Tidal volume displayed main effects for sex and condition and an interaction effect (all  $p<0.000$ ) (Figure 22, C). Males had a greater relative percent change in  $V_T$  during all three conditions (all  $p<0.0001$ ). Fraction of oxygen bound to hemoglobin displayed main effects for sex and condition and an interaction effect ( $p=0.003$ ,  $p<0.0001$ ,  $p=0.03$ ) (Figure 22, D). During the 7% COHb condition females exhibited a greater change in  $FO_2Hb$  than males ( $p=0.0006$ ). When sample size was corrected for between males and tall females ( $n=6$ ), results did not change.

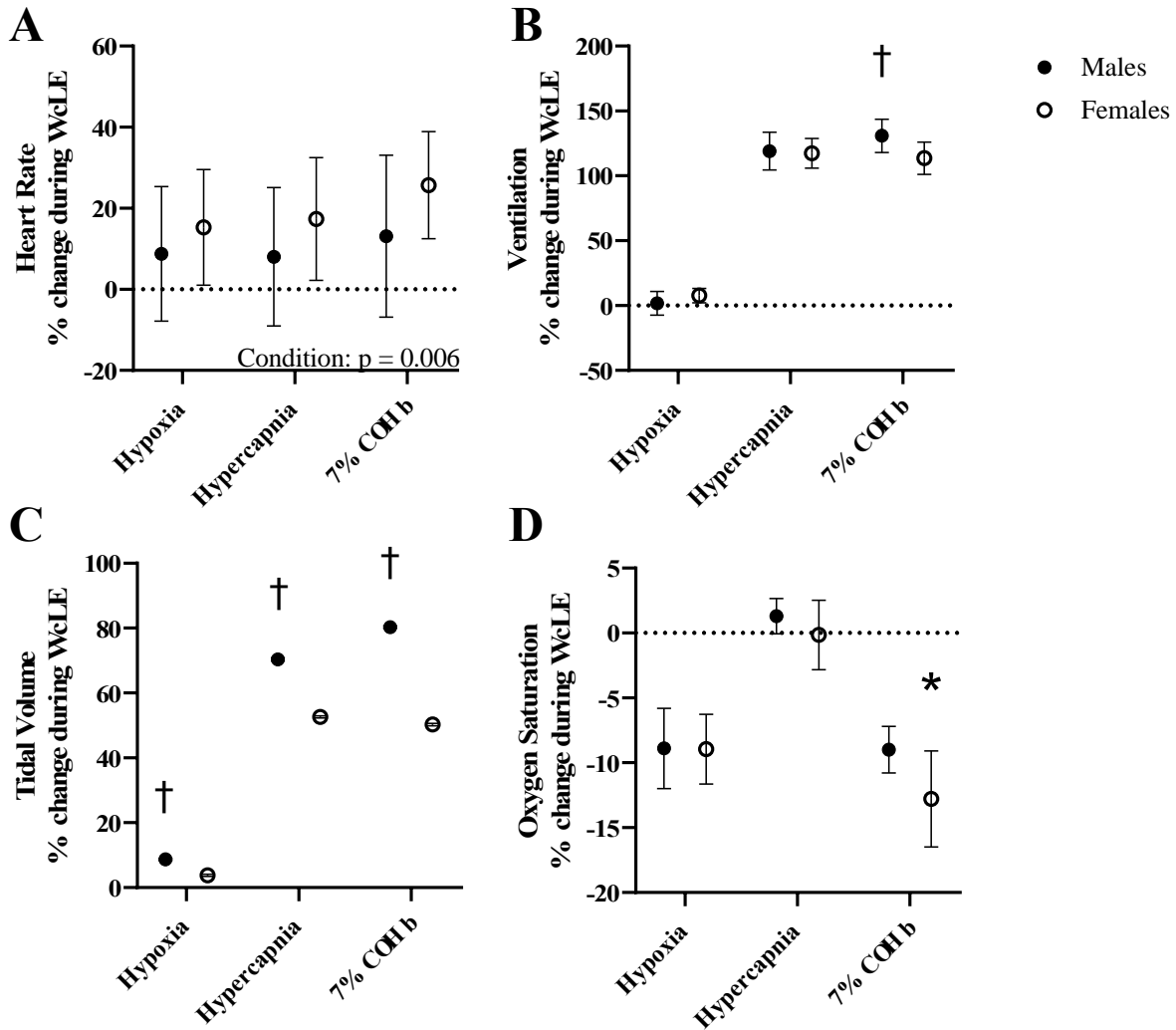


Figure 22: Percent change between the condition indicated and the control trial during worst case loaded exercise (12:15-12:30) of each condition between sexes. Positive values represent positive percent changes (increase) between time points whereas negative values represent negative percent changes (decreases). Percent change comparisons were made on heart rate (A), ventilation (B), tidal volume (C) and fraction of oxygen bound to hemoglobin (D). \* indicates that females had a greater relative (percent change) than males ( $p < 0.05$ ). † indicates that males had a greater relative (percent change) than females ( $p < 0.05$ ). Data are means  $\pm$  SD.

## 7.6 Relative Sex-based Comparisons with Taller Female Participants

### 7.6.1 Relative Change Sex Differences with Taller Female Participants: Within Conditions

Comparisons were made at two time points, ULE and WcLE within a condition between males and the significantly taller female participants, heights greater than or equal to 1.7m ( $n=6$ ,

p=0.002 between groups of females, p=0.22 between males and taller females). Taller females exhibited relative greater percent changes in HR than males as a main effect for condition was seen (p=0.001). Ventilation displayed main effects for both sex, condition and an interaction effect (all p<0.0001). Taller females exhibited a relatively greater change than males during the control, hypoxia and hypercapnia trials (all p<0.0001). Tidal volume exhibited main effects for sex, condition and an interaction effect (all p<0.0001) and males had greater relative changes in  $V_T$  during all conditions compared to taller females (all p<0.0001). Fraction of oxygen bound to hemoglobin displayed a main effect for condition (p<0.0001), however no significant differences were seen between males and taller females (p>0.36, range 0.36-0.99).

#### 7.6.2 *Relative Change Sex Differences with Taller Female Participants: Between Conditions*

Comparisons were made during the WcLE time point between conditions and control trials between males and the taller female participants (n=6, p=0.002 between groups of females, p=0.22 between males and taller females). Heart rate showed a main effect for sex (p=0.01), and post hoc testing did not reveal any significant differences (p>0.24, range 0.24-0.86). Ventilation had a main effect for sex and condition (p=0.003, p<0.0001) and an interaction effect (p<0.0001). Males displayed a greater percent change during the 7% COHb combination trial (p<0.0001). Tidal volume had main effects for sex and condition and an interaction effect (all p<0.0001). Males had a greater percent change in  $V_T$  during all three conditions (all p<0.0001). Fraction of oxygen bound to hemoglobin had main effects for sex and condition (p=0.01 and p<0.0001), however no significant differences were seen (p>0.1).

## 7.7 Multiple Conditions Cognitive Task

No significant differences were seen between all five conditions, control, hypoxia, hypercapnia, 4% COHb and 7% COHb, when comparing response times between EXIT sign and modified Stroop test during WcLE (Figure 23). On average, the 7% COHb had the longest response times to both the EXIT sign and modified Stroop tests however this value was not significant ( $p>0.8$  and  $p>0.36$  respectively).

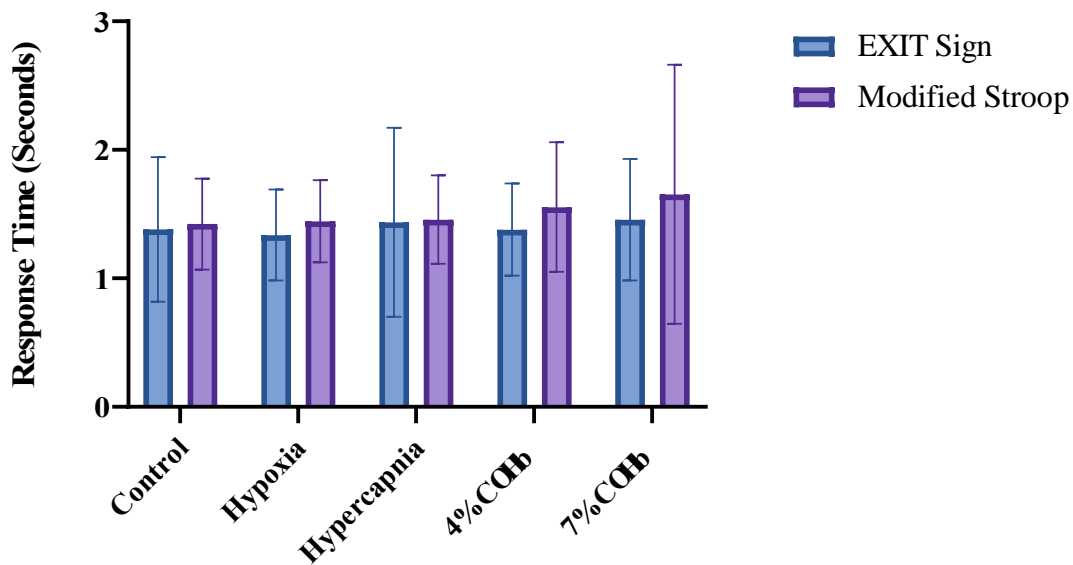


Figure 23: Cognitive task response times during the EXIT sign and modified Stroop tests taken during WcLE during the last minute of exercise (11:30-12:30) of each egress trial; control, hypoxia, hypercapnia, 4% COHb and 7% COHb. Data are means  $\pm$  SD.

## 8 Discussion

The aim of this study was to utilize the modern ventilation-limited fire environment to characterize the response to individual and combined gases and identify any physiological sex differences that may explain why victims are unable to escape fire environments. The primary finding was seen between the role of the different individual inspired gases, where the addition of carbon dioxide evoked the largest change to both physical and mental performance. Compared to the hypoxia and control trials, the hypercapnia trial had the greatest impact to cardiorespiratory variables which imposed the largest challenge during egress. The hypercapnia trials were also rated the highest in terms of both mental and physical RPE. The secondary finding was that when comparing percent change within condition between males and females, females exhibited a greater change in HR,  $V_T$  and  $FO_2Hb$ . When comparing percent change between condition and control during WcLE, males displayed a greater percent change in  $FO_2Hb$ ,  $V_I$  and  $V_T$  than females. In terms of cognitive test response times during the worst-case 7% COHb condition, no differences between sexes were seen. Overall, during an egress trial, females were relatively more affected than males from a physiological standpoint, but this did not result in differences in ratings of perceived exertion or ability to answer the cognitive prompts (indicating likely minimal differences in cognitive functioning). The third finding of the study was that the physiological response to 4% COHb and 7% COHb saturations did not differ between participants. Cardiorespiratory variables, cognitive response times and RPE were very similar and were not different between the trials regardless of the increase in CO saturations that were present. In conclusion, it appears that the addition of inhalation of  $CO_2$  to egressing trials had the greatest decrement in performance and ability to complete the egress protocol.

## 8.1 Hypoxia, Hypercapnia and Control Trials

Investigating the physiological responses to hypoxia and hypercapnia in isolation compared to an ambient control trial targeted a fundamental research question regarding the body's adaptive mechanisms under different environmental conditions. The main finding between these three conditions was that addition of CO<sub>2</sub> elicited the greatest increase to HR, V<sub>I</sub>, V<sub>T</sub> and SpO<sub>2</sub>, highlighting the body's sensitivity and response mechanisms to hypercapnia.

### 8.1.1 Hypoxia

Although participants were made to be hypoxic through inhalation of 14% O<sub>2</sub> during the worst-case phase of the egress trial, participants were likely not hypoxic enough to experience the typical symptoms associated with hypoxia. Oxygen desaturation during the hypoxia trial was greater than the hypercapnic condition during LE and WcLE stages and was greater than the control trial during the WcLE stage (Figure 15, D). On average during the hypoxia condition at the WcLE stage, oxygen saturation only dropped ~9% (to 90%) compared to baseline levels. Participants were still saturated at 89±4.4% O<sub>2</sub> and individuals do not usually experience symptoms of hypoxia until between 75-90% O<sub>2</sub> (95). The hypoxic ventilatory response is usually activated when PaO<sub>2</sub> is ~ 60mmHg, most participants remained above this PO<sub>2</sub> (PetO<sub>2</sub> during WcLE: 68±12mmHg) (96). Therefore, it is likely that during the hypoxia trial, participants did not desaturate enough to trigger this response, and would explain why during the hypoxia trial V<sub>I</sub> and V<sub>T</sub> did not differ from control trials. This study selected 14% O<sub>2</sub> as it was the minimum oxygen level measured in the upstairs bedroom during the large scale fire experiment (Figure 3). Future trials could look to trigger the hypoxic ventilatory response by decreasing the inspired oxygen content below 14% O<sub>2</sub>, thus having participants desaturate closer to the 70% SaO<sub>2</sub> range.

By making participants more hypoxic, they would be further experiencing a modern fire environment in other locations throughout the structure (i.e. along an egress route). In terms of a fire context, modern tightly sealed homes usually have ventilation-limited fires which have globally low levels of O<sub>2</sub>, specifically in the room of the fire (10, 11). In the large-scale fire experiment done by the UW fire lab, minimum O<sub>2</sub> levels were measured at 3% in the room of the fire (20). At less than 8% O<sub>2</sub>, individuals would experience an inability to move along with loss of consciousness occurring very quickly (23), if not removed from the environment. Future study designs could be completed at lower fractions of inspired O<sub>2</sub>, to target the hypoxic ventilatory response and further specify the role of hypoxia during egress in a fire environment.

### 8.1.2 *Hypercapnia*

During exercise, tissues are more metabolically active and will increase volume of CO<sub>2</sub> produced (VCO<sub>2</sub>) as a by-product of cellular respiration. Therefore, not only is a larger fraction of CO<sub>2</sub> being inspired, it is also being generated. The body wants to remain at homeostasis with a PCO<sub>2</sub> of ~40 - 45mmHg, and therefore ventilation increases to expel the excess CO<sub>2</sub> that may begin to build up. Even without the added CO<sub>2</sub> inhalation, ventilation will increase in proportion with VCO<sub>2</sub>. The CO<sub>2</sub> disassociation curve is steep and linear, thus increases to PCO<sub>2</sub> will result in increased contents of CO<sub>2</sub> in the blood. Unlike with O<sub>2</sub>, the content of CO<sub>2</sub> in the blood will not plateau. Exercising while inhaling CO<sub>2</sub> exacerbates the ventilatory response, as such V<sub>I</sub> and V<sub>T</sub> are seen to be significantly higher during the intense exercise stages during the hypercapnic trials compared to during the hypoxia or control trials (Figure 15, B and C). Increasing ventilation requires an increased work of breathing and therefore both respiratory and locomotor muscles need to be delivered oxygen (24). Carbon dioxide is a ventilatory stimulant, sensed by

the central chemoreceptors when increased amounts of CO<sub>2</sub> cross the blood brain barrier. Due to the increased production of H<sup>+</sup> generated as a by-product of exercise, the blood crossing the blood brain barrier is also more acidic and increases the H<sup>+</sup> concentration in the cerebral blood. The increased CO<sub>2</sub> and H<sup>+</sup> concentrations cause both circulatory and ventilatory adjustments, dilation in the cerebral vasculature to increase blood flow and increasing HR and ventilation to promote CO<sub>2</sub> clearance (44). During the hypercapnia trials, HR is significantly higher compared to both the control and hypoxia trials (Figure 15, A). Carbon dioxide is a much stronger ventilatory stimulant than oxygen and therefore the greatest response to HR, V<sub>I</sub> and V<sub>T</sub> are seen during the hypercapnia trials (Figure 15, A, B, and C). Ventilation during the WcLE stage of hypercapnia trial is more than double compared to the hypoxia and control trials (72±20L/min vs 34±9L/min and 33±6L/min, Table 7), as such, it appears that the addition of carbon dioxide had the greatest influence on egress.

### 8.1.3 *Application to Egress*

In the context of egress and fire exposure, CO<sub>2</sub>, a known stimulant to ventilation would increase the uptake of asphyxiant and irritant gases. As the combustion process transitioned into more incomplete combustion, CO<sub>2</sub> generation would continue and the production of CO and other harmful by-products would start to increase. In the large-scale fire experiment used to generate the egress timeline, ventilation was held to a breathing rate of 36L/min. However, during the hypercapnia trial, specifically during WcLE, V<sub>I</sub> was an average of 72±20L/min (Table 7); approximately double what was used to generate the timeline. Asphyxiant gases such as hydrogen cyanide (HCN) and irritant gases like nitric oxides (NO<sub>x</sub>) are gases produced during a fire and are fatal at very low concentrations (20). To ensure participants' safety, they could not

be administered during the present study. However, the effect of hypercapnia on the ventilation and the resulting time to toxicity of these gases should be explored. Low levels of HCN (0.018%) are normally fatal to humans at rest within 10 minutes (97). During the residential fire experiment by the University of Waterloo Fire Lab, NO<sub>x</sub> and HCN were measured at 0.012% and 0.0225% respectively, in the room of the fire (20). Being in this environment while experiencing the ventilatory stimulus of CO<sub>2</sub> would lead to much sooner times to incapacitation as greater uptakes of toxic gases would be consumed. The discrete gas concentrations used in this study only begin to show the severity that an egressing occupant would be experiencing during a modern fire environment, and future studies should take these results into consideration.

#### *8.1.4 Rate of Perceived Exertion*

Notably, hypercapnia elicited the highest RPE ratings for both mental and physical exertion among the three conditions. This finding is likely due to the increases in  $V_I$  and respiratory drive that are associated with increases in CO<sub>2</sub> inhalation. Recognizing the impact of CO<sub>2</sub> on RPE is very important when applying these findings to egress and future studies, as it emphasizes the severity of modern-fire environment. Although the experiments conducted were much more conservative than a true modern fire environment, individuals on average rated the hypercapnic trial  $3.1 \pm 1.9$  and  $4.3 \pm 2.3$  for mental and physical respectively. These ratings are very high and don't encompass the more severe changes to inspired gas concentrations or some of the more uncomfortable environmental stressors that occur during egress, such as heat, particulate matter and reduced visibility. In a residential fire environment, even when not directly in the room of the fire, participants would experience warmer temperatures, reduced visibility and irritation from the smoke and particulate matter. Warmer body temperatures also increase

ventilation, known as hyperthermia-induced hyperventilation (98). In the upstairs bedroom where the mechanical ventilator was placed temperatures increased to about 80°C, however in the room of the fire these temperatures can be much more severe exceeding 1000°C (3, 9, 99). These temperatures can radiate throughout the home, creating hot, but not as thermally severe environments in surrounding rooms (100). Smoke production can also cause airway irritation, leading to coughing and choking, which would be exacerbated while inhaling hot air. These highly uncomfortable symptoms would likely further impair occupants and prevent them from successfully evacuating.

## **8.2 Sex Differences during 7% COHb Trial**

The physiological and cognitive response was compared during the 7% COHb egressing trial between males and females to parse out any sex differences that may impact ability to egress. Due to the smaller size of females both in terms of their respiratory systems and overall stature, it was hypothesized that females would have a greater physiological response to maintain egress, especially during the more physically strenuous conditions where CO<sub>2</sub> is an added stimulus. Although it was hypothesized that females would have a greater physiological response than males, specifically while completing the 7% COHb egress protocol, this does not appear to be the case. Although participants were completing exercise, the exercise intensity of egress can be classified as moderate exercise. Most cardiorespiratory sex differences are seen at suprathreshold exercise, and so, it is likely that the exercise intensity associated with egress is not intense enough to parse out these differences.

### 8.2.1 *Differences between Participants*

In terms of participants, six females were much taller (average height of 1.76m) compared to the remaining nine females (average height of 1.46m); this should be considered when looking at generalizability of a population (Table 4). The height differences between the two groups of female participants was statistically significant ( $p=0.002$ ), however, a difference was not seen between the taller females and male groups ( $p=0.22$ ). In terms of a within condition relative percent change response, when comparisons were made between males and all female participants compared to just the taller female participants, several differences were seen. A main effect for condition was displayed for HR with taller females having greater percent changes in HR than males. When comparing percent change in HR between males and all female participants a main effect was displayed for sex, with a greater change seen in males during the control and hypoxia conditions and in females during the hypercapnia and 7% COHb conditions (Figure 21, A). This could show that physiological changes in heart rate during egress is more size dependent instead of sex dependent as larger individuals generally have slower heart rates (101). In terms of  $V_I$ , the same main effects were seen with both groups of females. However, the taller female group revealed greater changes in  $V_I$  than males across all trials except for the 7% COHb combination trial. When all females and males were compared, females displayed a greater change than males for all trials. The lack of significance during the worst-case trial with the larger females reveals that the physiological response to egress, specifically HR and  $V_I$ , may be tied to participant's size and less to do with sex.

Within the group of 15 female participants, 3 participants were considerably less-fit (completed exercise less than 90 minutes a week) compared to the others (on average completed 243 minutes of exercise a week) in the study. These less-fit participants did find the protocol the

most challenging, and in the case of these 3 less-fit females, 2 were not able to finish the entire 12.5 minute egress protocol with 7% COHb saturation. These participants provided average mental and physical RPE scores of 8.8 and 9.5, and commented on the intense feelings of breathlessness and physicality associated with carrying the load during the trial. Although both participants that were unable to complete the egress protocol were female, this was not significant compared to the male participants completion. Future research should consider the RPE rankings and results of these three less physically fit participants as they are more generalizable to a population with a lower fitness level and may be representative of more at-risk groups of individuals.

Though walking speeds were self-selected and described as a comfortable ‘could walk forever’ pace ( $1.8 \pm 0.3$  miles), the weight of the load used was standardized across all participants. For smaller participants, carrying the 20lb load while completing the egress protocol was relatively more taxing, especially while inhaling CO<sub>2</sub>. The weight of 20lb was selected as it is the weight of a small child or pet who may not be able to egress on their own; it could also be an estimate of the weight of an individual’s belongings that they are taking with them as they egress. These smaller participants, most of which were females, were carrying the same absolute load, and females were carrying a significantly larger percentage of their body weight than males ( $p=0.002$ ). The added physicality of carrying a greater relative load may explain why females had greater percent change than males within a condition, however not between conditions.

### 8.2.2 *Cardiorespiratory Differences between Males and Females*

It is known that females dedicate a larger percentage of their whole body VO<sub>2</sub> to their respiratory muscles than males, specifically during high intensity exercise. During egress,

especially while carrying the 20lb load, females are unable to dedicate as much available O<sub>2</sub> to locomotor muscles. In a fire environment, when concentrations of O<sub>2</sub> are continuing to decline and CO saturation is rising, females, specifically smaller and less fit individuals, may have a more difficult time egressing, especially if they are carrying a load. These results suggest that it may be less of a sex difference and more of a size and fitness comparison that impacts individuals' abilities to egress. From our intergroup analysis, we are to a degree able to parse out that: ability to complete egress does appear to be based on relative size and fitness level as opposed to a sex difference.

Significant differences were only seen between males and females when comparing tidal volumes during the WcLE phase; this is likely due to differences in anatomical size. Research has shown that even when matched for size, female respiratory anatomy is smaller than males (79). Although not significant, average V<sub>I</sub> in males was notably higher than in females (80±18L/min vs 67±20L/min during WcLE) (Table 8). Compared to males, females do have smaller lungs and airways however these morphological differences have little impact on breathing mechanics; specifically, during moderate exercise as seen with egress as individuals are not flow-limited. Although significant differences were not seen between sexes, when examining percent changes within a condition, it appears that the duration of egress impacted females more than males, with greater percent changes within conditions at different time points.

### 8.2.3 *Relative Percent Change Differences between Males and Females*

When comparing V<sub>I</sub> within a condition at different time points, a greater percent change was seen in females during all trials except control (Figure 21, B). However, when comparing WcLE between control and hypoxic, hypercapnic and 7% COHb conditions a greater percent

change is seen in males and only during the 7% COHb combination trial (Figure 22, B). Since males have larger respiratory systems, they are able to increase ventilation to a greater degree. This can be seen with males having a larger percent change of  $V_T$  within a condition for the control, hypercapnic and 7% COHb combination trials (Figure 21, C) and between conditions during the hypoxia, hypercapnia and 7% COHb combination trials (Figure 22, C). Ventilation is the product of  $V_T$  and  $F_b$ , so when  $V_T$  reaches a maximum and plateaus, only increases to  $F_b$  remain. Males are able to satisfy the necessary increases to ventilation following increased exercise and inhalation of  $CO_2$  with greater percent changes to  $V_T$ . Females have smaller respiratory systems and during the egress protocols had smaller  $V_I$  and  $V_T$  than males. Within a condition, a larger percent change in  $V_I$  is seen in females compared to males, and this is seen during the hypoxia, hypercapnia and 7% COHb combination trials (Figure 21, B). Throughout the egress protocol,  $O_2$  demand is increased via loaded exercise (carrying the weight) and the changing degree of inspired gases, females need to increase  $V_I$  to a greater degree to supply adequate oxygenation.

Hypercapnia trials elicited a greater within condition percent change in HR among females compared to males (Figure 21, A). Females need to increase blood flow to a greater degree than males to ensure adequate oxygenation of both locomotor and respiratory muscles. Sized matched females do have smaller hearts and blood volumes as well as Hb concentrations and thus  $O_2$  carrying capacities than males (81). Moreover, greater increases in HR, specifically following the onset of exercise or a ventilatory stimulant, are required to match the  $O_2$  demand in the active muscle. Females had a greater negative percent change in terms of  $FO_2Hb$  within conditions during the control trial (Figure 21, D) and between conditions during the 7% COHb combination trial (Figure 22, D) compared to males, meaning that females were desaturating to a

greater degree. However, the level of desaturation for both sexes was minimal and likely not severe enough to illicit the hypoxic ventilatory response. In terms of a circulatory response to hypoxia, HR is increased, and dilation occurs to critical organs (i.e. heart, brain) and constriction to peripheral vasculature to redistribute oxygen delivery (102). In conclusion, while there are notably physiological differences between males and females, these physiological differences did not appear to have an effect when completing the egress protocol during the study.

#### *8.2.4 Rate of Perceived Exertion*

In a fire environment, occupants are unable to prepare for the stress and surprise that may be experienced during a fire evacuation. The collected mental and physical rate of perceived exertion may not be sufficiently representative of an occupant evacuating from a fire, as the element of surprise and associated stress cannot be mimicked. Participants were blinded and randomized to what condition they would be receiving, but they were aware that they were in a safe and controlled environment. Ratings of perceived exertion were similar between sexes; however, it was only two females that were unsuccessful in completing all 10 egress trials. Both males and females rated the 7% COHb trial the highest, mentally  $4.3 \pm 2.4$  and physically  $5.1 \pm 2.4$  for females and mentally  $3.7 \pm 2.1$  and physically  $5.0 \pm 2.2$  for males. During the WcLE phase of the trial, participants would occasionally miss prompts on the cognitive task as the physical toll of the weight and hypercapnic stimulation to  $V_I$  remained their sole focus. When asked about RPE ratings, females appeared to comment on and be further impacted by the weight of the load and the drastic increase to ventilation than males. In a fire environment, cognitive ability, such as the ability to focus and make sound decisions, could be hindered in females as the physical demand associated with egress, increased ventilation and carrying a load, takes the forefront.

Future studies could use more quantitative measures of perceived exertion or ask participants throughout the study to provide ratings. This would allow researchers to parse out what point of egress is most difficult, whether that be the increased to ventilation or loaded exercise.

#### *8.2.5 Sex Differences During Cognitive Task*

The average response times to the EXIT sign and modified Stroop tests during the last minute of egress during the 7% COHb condition did not differ between males and females. The lack of significance in response times suggests that the cognitive processing speeds as assessed by response times were comparable between sexes. Under the specific tests used, cognitive function did not appear to be more inhibited by one sex than the other. It is important to note that the COHb saturation of 7% is much milder than what is seen in a fire environment. At saturation levels closer to 15% COHb, impacts to cognition are much more severe and, if exposure persists, loss of consciousness (19). Studies have not been done at these high saturations to compare cognitive abilities between males and females. At these higher saturations of CO, it would be very difficult to safely test participants, however, sex differences could potentially be observed. Future studies should consider having participants complete more complex tasks in a fashion wherein a more isolated measure of cognition is taken while completing the 7% COHb egress trial to identify any higher cognitive function sex differences.

### **8.3 4% COHb and 7% COHb Egressing Trials**

The main objective of comparing two different COHb saturations was to determine if a higher CO saturation would make the ability to egress more difficult both mentally and physically for occupants. Saturations of 4% and 7% COHb were chosen as two threshold saturations to compare between participants, while ensuring the safety of the participants yet still

representing a realistic early exposure to CO during a fire. Similar to the hypothesis, the physiological response was not different between the two levels of CO exposure. The physiological response to exercise, including an increase to HR,  $V_I$  and  $V_T$ , were shown to have a main effect of time during both CO saturation conditions. Following the onset of exercise and changes to inspired gases, the body must adapt to maintain the physiological demands of exercise by continuing to oxygenate the active tissues, especially when physiological demands increase, such as during LE and WcLE.

### *8.3.1 Fraction of Hemoglobin Bound to Oxygen*

The main effect for decreasing  $FO_2Hb$  during the CO saturation trials was as a direct result of the increase in CO administered between the two trials. During the pre- and post-trial baselines, the difference in  $FO_2Hb$  was as a result of the differences in CO saturation that was administered prior to beginning the trial. During the unloaded exercise phase, participants were completing moderate exercise while in normoxic conditions and the increased  $V_I$  seen at this phase were not enough to overcompensate for the initial desaturation caused by the CO saturation.

As the egress protocol progressed, the percentage of inspired  $O_2$  gradually declined as participants were receiving the combination of hypoxic and hypercapnic gases (Table 2). With a lower  $PO_2$  present, participants gradually became more hypoxic, resulting in a decrease in  $FO_2Hb$  regardless of the presence of CO. Recall, CO has a much higher affinity for Hb than  $O_2$ , therefore when both molecules are present Hb is much more likely to bind CO (103). Despite this, the degree to which participants desaturated was very minor, and this is likely due to the ventilatory stimulation of the inspired hypercapnic gas. Although participants were breathing in a

lower concentration of O<sub>2</sub>, V<sub>I</sub> was much higher during the 4% COHb (72±21L/min) and 7% COHb (73±20L/min) egress trials compared to during the isolated hypoxia trial (34±8.9L/min), specifically during the WcLE phase. It appears that increases in V<sub>I</sub>, both from exercise and inhalation of the hypercapnic gas, were able to overcompensate for any potential O<sub>2</sub> desaturation caused by the initial offset of administered CO saturation.

### 8.3.2 *Application to the Modern Fire Environment*

In a fire environment, there is a compounded effect of COHb saturation as continuous inhalation of CO occurs while an occupant remains in the burning structure. Throughout the 4% and 7% COHb trials, as V<sub>I</sub> was increased, participants would desaturate by approximately 1% COHb as CO was naturally expelled throughout the trial via ventilation. During the study protocol, participants were not held at a constant level of CO saturation due to the dangerous risks associated with potential CO poisoning and the feasibility of safely increasing saturation to maintain a constant level of CO saturation. However, in reality, this is not the case in a fire environment. Due to the increase in ventilatory drive that is known to occur following inhalation of CO<sub>2</sub>, throughout the exposure during the fire, occupants would continually be further saturated with CO if they remained in the burning structure. The mechanical lung placed in the structure during the fire experiment by the UW fire lab, which was used to determine the target levels of CO saturation, was set at a ventilation rate of 36 L/min (99). However, when looking at the ventilations measured from this participant cohort during the hypercapnic and combination trials (Table 6 and 7), this breathing rate is grossly underestimated, and in fact, ventilation is almost doubled. At the ventilatory rates measured from the participants during these trials, over the duration of a 12.5min exposure to the fire, an occupant would be continuously saturated and

begin to approach ~17-23% COHb levels. If the occupant remained in the environment, after 15 minutes, their COHb would approach the dangerous level of 30%-40% COHb in which incapacitation is likely (10, 19). The conditions of the current study, though more conservative, allowed participants a glimpse into the dangerous and all-encompassing fire environment. Overall, these results contribute to our understanding of how CO exposure impacts cardiorespiratory variables and highlights the complex interplay between CO saturation, physical demand and physiological responses.

The observed differences between the 4% and 7% COHb conditions imply that higher levels of CO exposure would elicit distinct effects on O<sub>2</sub> transport and potentially other cardiorespiratory variables compared to lower levels examined in this work. In a fire environment, studies have predicted that in young healthy individuals, the mental and physical effects of CO are not usually felt until exercising individuals reach 15% COHb with incapacitation occurring closer to 30% COHb (19). During this study participants were only saturated to a maximum of 7% COHb and therefore it is likely that participants were not saturated enough to experience the symptoms associated with CO poisoning. Despite the potential physiological difference induced by the varying COHb levels, participants subjectively reported similar levels of mental and physical exertion. This suggests that the extent of COHb saturation within the ranges studied, 4% and 7% COHb, may have not been high enough to induce meaningful changes in the rate of perceived exertion.

### *8.3.3 Saturation Differences During the Cognitive Task*

Results indicated no significant differences between cognitive task response times when comparing the 4% and 7% COHb trials for both EXIT sign and modified Stroop colour test

prompts. These findings suggest that a CO exposure under 7% may not have a significant impact on cognitive task performance. As stated above, previous research have measured deficits in decision making and choice discrimination at CO levels of approximately 15% COHb (19). The lack of significant differences in cognitive task response times seen in this study are therefore likely a result of the selected CO saturation exposure being too low to elicit any measured changes. It is essential to note that while response times were not significantly different between the two CO exposure conditions, other cognitive factors such as attention, memory, and executive function were not assessed in this study. Further research is warranted to explore the effects of varying CO saturation levels on a broader range of cognitive functions and to investigate potential short- and long-term implications for cognitive health and performance when exposed to a fire environment.

To ensure participant safety, these high exposures that would result in measured differences in cognitive performance (15% COHb and above) cannot and should not be used during testing. The findings of this study suggest that the relationship between %COHb and effect on cardiorespiratory and response times to cognitive test prompts may not be dose related, but instead a saturation threshold (~15% COHb in healthy individuals) is likely to exist. When evaluating the impact of CO saturation on human health and performance, the findings of this study should be taken into consideration, especially in scenarios such as emergency egress where accurate understanding of cardiorespiratory function is critical.

## 8.4 Considerations and Limitations

### 8.4.1 Carbon Monoxide Saturation

The differences in the achieved CO saturations across the participants were mainly due to human differences. The variation between the ability to breath hold, baseline Hb mass concentrations (hydration was found to impact this measurement) and the researcher's estimation of blood volume were highly influential in ability to reach the target level of COHb and administration of the CO dose (mL). During the COHb saturation procedure, individuals were asked to inhale slowly and deeply as the CO was administered, then hold their breath for up to 30 seconds before staying connected to the rebreathing circuit for an additional 2-minutes. Some participants were less efficient at this task, leading to levels of COHb that were under the target saturation as these participants had less CO uptake than predicted. On average, males have higher Hb level than females (1-2 g/dL) (104). Therefore, the significant difference between Hb mass concentrations in males and females is likely due to a physiological sex difference. Higher Hb concentration required a larger dosage of CO (mL) to reach the appropriate COHb saturation as there are more molecules available for binding. Thus, males also received significantly larger volumes of CO to reach 7% COHb than females. When determining volumes of CO, the Lundy equation requires an estimation of blood volume (93). Researchers used an assumed blood volume of 70-75 mL/kg for males and 60mL/kg for females (93) however, larger and/or trained participants tend to have larger blood volumes. Without knowing a given individuals blood volume, the administered dose of CO was at times underestimated, requiring an additional dose of CO to reach 7% COHb. To conclude, although participants may have received different doses of CO (mL), all were eventually saturated to the same target COHb saturation and thus all

participants completed the egress trials with relatively the same saturation of CO, allowing for direct comparisons to be made.

#### 8.4.2 *Methodological Limitations*

Although the study was designed to mimic egress from a ventilation-limited fire, there were several limitations to creating this environment. In order to accurately represent the environmental exposure during egress from a ventilation-limited fire environment, in addition to the manipulation of inspired gases carried out in this study, participants would also have to be subjected to increasing temperatures, other asphyxiant and irritant gases, as well as particulate matter and smoke. As previously mentioned (Section 1.1.2), temperatures in modern fire environments can reach upwards of 1000°C within 10 minutes in areas close to the fire (9). Although occupants in an upstairs bedroom would not experience the same increase in temperatures, areas further away from the fire room would still increase above the ambient temperature in a controlled laboratory (~22°C). For example, in the large-scale ventilation-limited fire used to inform this egress protocol, temperatures increased to roughly 80°C in the upstairs bedroom where the mechanical ventilator was placed. This temperature would be expected to not only elicit a ventilatory response, but cause burns (when the junction between the top and second layer of human skin reached 44°C, burn injury occurs (105)). Asphyxiant gases such as HCN and irritants such as NO<sub>x</sub> can also be produced during large-scale ventilation-limited fires fuelled by nitrogen containing materials (such as the furniture used in the large-scale fire experiment). Measured concentrations of these products (20) would be fatal to healthy active humans within 10 minutes (97). These gases along with the particulate matter that is generated during a fire can cause serious problems to human health both acutely and long-term such as

cardiovascular events, difficulty breathing and premature death. Due to the dangers of potentially simulating these health conditions, these parameters could not safely be used as part of the study design, as such, care should be taken when extrapolating the results of the study. Future studies can be aimed at examining these added parameters in a safe and controlled fashion to further examine the combined impacts of the fire environment on occupants.

Participants were given all the information and full context with respect to the study protocol and outcomes (no forms of deception were used). Participants were also in a safe and controlled laboratory environment wherein the research team was continuously monitoring their vitals and physiological data throughout the duration of each trial. Although some trials were randomized and the testing days were randomized, participants were aware as to when they would undergo the CO saturation protocol. Additionally, participants were instructed on how to signal to the research team if they wished to stop the trial for any reason as well as how to disconnect themselves from the breathing circuits (CO rebreathing circuit as well as the breathing circuit used in the egress protocol) if they felt too uncomfortable. This was necessary for safety, and combined with the decision to not use deception. This likely diminished any stress and mental toll associated with experiencing an unplanned fire evacuation in reality, as the study did not allow for the 'element of surprise' and thus examination of any decrements in performance as a result of this induced stress and anxiety could not be examined. Overall, despite the fact that this experimental design did not encompass all the environmental parameters associated with a modern ventilation-limited fire environment, the data collected from the manipulation of inspired gases does accurately represent the physiological response to hypercapnia, hypoxia and the combination of both gases with CO saturation. The administered gases are in fact representative of an occupant's exposure during egress in a modern ventilation-limited fire environment.

## 9 Conclusions

The aim of this study was to characterize the physiological response to the modern ventilation-limited fire environment, and along with this identify any potential sex differences that may affect an occupant's ability to egress. The primary finding was that the researchers were able to successfully characterize the physiological response and further highlight the impact that hypercapnia has on the ventilatory response, which appeared to have the greatest hinderance to egress abilities. Along with the highest mental and physical RPE ratings, trials that involved CO<sub>2</sub> administration also had the greatest percent changes to V<sub>I</sub>, HR and V<sub>T</sub> within both males and females. When comparing the sexes, females appeared to be more affected than males during the egress trials, as evident by females having greater increases to HR, V<sub>T</sub> and desaturation of FO<sub>2</sub>Hb within a trial. Moreover, this could be further explored to reveal a potential sex difference at higher intensity egress. However, this study did not encompass all the aspects associated with egress, as it was limited by feasibility and the importance of keeping participants safety in the forefront. As such, future studies should continue to explore the impact of heat, asphyxiant and toxic gas exposure as well as particulate matter that are associated with fire exposure and could potentially reveal further sex differences in egress-ability and performance. As discussed, the saturations of 4% COHb and 7% COHb used in this study were much more conservative than possible levels of COHb saturation that can occur during exposure to a ventilation-limited fire. Further research investigating egress-ability should be carried out with higher levels of CO saturation as this would allow for further characterization of this dangerous environment. In conclusion, the research from this study forms a strong basis in characterizing the physiological response to the modern-ventilation limited fire environment in males and

females, however results should be used with caution as not all aspects of the fire environment were included.

## 10 Timeline

Milestone	Fall 2022	Winter 2023	Spring 2023	Fall 2023	Winter 2024	Spring 2024
Coursework						
Data Collection						
Data Analysis						
Thesis Writing						
Thesis Defense						

## References

1. **Kerber S.** Analysis of Changing Residential Fire Dynamics and Its Implications on Firefighter Operational Timeframes. *Fire Technol* 48: 865–891, 2012. doi: 10.1007/s10694-011-0249-2.
2. **McKenna S, Birtles R, Dickens K, Walker R, Spearpoint M, Stec AA, Hull TR.** Authors' response to comments on "Flame retardants in UK furniture increase smoke toxicity more than they reduce fire growth rate." *Chemosphere* 232: 512–515, 2019. doi: 10.1016/j.chemosphere.2018.10.178.
3. **Bwalya AC, Kashaf A.** Results of Fire Experiments to Quantify Residential Design Fires [Online]. *ASHRAE Trans* 120: 1–8, 2014. <https://libraryresources.columbiasouthern.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=a9h&AN=108334517&site=ehost-live&scope=site>.
4. **(NAHB) NA of HB.** New Single-Family Homes Characteristics and Trends: 2019 Edition. 2020.
5. **Rein G, Zhang X, Williams P, Hume B, Heise A, Jowsey A, Lane B, Torero JL.** Multi-story Fire Analysis for High-Rise Buildings [Online]. *11th Interflam* : 605–616, 2007. <https://www.researchgate.net/publication/277237623>.
6. **Statistics Canada.** *Incident-based fire statistics, by type of fire incident and type of structure.* 2023.
7. **Statistics Canada.** *Circumstances surrounding unintentional fire-related deaths, 2011-2020.* 2022.
8. **Forrest B, Weckman E, DiDomizio M, Senez P, Ryder N.** Smoke development and movement during ventilation-limited fires in a multi-storey house. *Fire Mater* 45: 1063–1074, 2021.
9. **Kodur V, Kumar P, Rafi MM.** Fire hazard in buildings: review, assessment and strategies for improving fire safety. *PSU Res Rev* 4: 1–23, 2020. doi: 10.1108/PRR-12-2018-0033.
10. **Purser DA.** Toxic product yields and hazard assessment for fully enclosed design fires. *Polym Int* 49: 1232–1255, 2000. doi: 10.1002/1097-0126(200010)49:10<1232::AID-PI543>3.0.CO;2-T.
11. **Blais MS, Carpenter K, Fernandez K.** Comparative Room Burn Study of Furnished Rooms from the United Kingdom, France and the United States. *Fire Technol* 56: 489–514, 2020. doi: 10.1007/s10694-019-00888-8.
12. **Peatross M, Beyler C.** Ventilation Effects On Compartment Fire Characterization. *Fire Saf Sci* 5: 403–414, 1997. doi: 10.3801/iafss.fss.5-403.
13. **Kerber S.** Impact of Ventilation on Fire Behavior in Legacy and Contemporary Residential Construction. .
14. **Boehmer H, Floyd J, Gottuk D.** Fire Dynamics and Forensic Analysis of Limited Ventilation Compartment Fires Volume 2: Modeling [Online]. *Analysis* 2: 165, 2009. [http://www.haifire.com/Resources/publications/NIJ\\_Compartment\\_Fires\\_Vol\\_2\\_Modeling\\_Final.pdf](http://www.haifire.com/Resources/publications/NIJ_Compartment_Fires_Vol_2_Modeling_Final.pdf).
15. **Hull TR, Stec AA.** Polymers and fFre. *R Soc Cambridge* : 1–14, 2009.
16. **Morikawa T, Yanai E, Nishina T.** Toxicity evaluation of fire effluent gases from experimental fires in a building. 5: 248–271, 1987.

17. **Hurley MJ, Gottuk D, Hall JR, Harada K, Kuligowski E, Puchovsky M, Torero J, Watts JjM, Wieczorek C.** SFPE handbook of fire protection engineering, fifth edition. 2016.
18. **Purser DA, Woolley W.** Biological Studies of Combustion Atmospheres. *J Fire Sci* 1: 118–145, 1983.
19. **Purser DA, Berrill K.** Effects of Carbon Monoxide on Behaviour in Monkeys in Relation to Human Fire Hazard. *Arch Environ Health* 38: 308–305, 1983.
20. **Forrest B, DiPaola A, Ibrahimli V, Lakhani A, Weckman E.** Towards characterizing full-scale furniture fires in a two-storey house: Gaseous species concentrations during a ventilation-limited fire. *Fire Saf J* 141: 103963, 2023. doi: 10.1016/j.firesaf.2023.103963.
21. **Woolley W., Raftery M.** Smoke and toxicity hazards of plastics in fires. *J Hazard Mater* 1: 215–222, 1975.
22. **UK Government.** Fire statistics monitor: April 2015-March 2016 [Online]. [date unknown]. <https://www.gov.uk/government/statistics/fire-statistics-monitor-april-2015-to-march-2016>.
23. **Shaw DM, Cabre G, Gant N.** Hypoxic Hypoxia and Brain Function in Military Aviation: Basic Physiology and Applied Perspectives. *Front Physiol* 12, 2021. doi: 10.3389/fphys.2021.665821.
24. **Sheel AW, Romer LM.** Ventilation and Respiratory Mechanics. *Compr Physiol* 2: 1093–1142, 2012. doi: 10.1002/cphy.c100046.
25. **Frisancho A.** Functional adaptation to high altitude hypoxia. *Science (80- )* 187: 313–319, 1975.
26. **Areza-Fegyveres R, Kairalla RA, Carvalho CRR, Nitrini R.** Cognition and chronic hypoxia in pulmonary diseases. *Dement e Neuropsychol* 4: 14–22, 2010. doi: 10.1590/S1980-57642010DN40100003.
27. **Collins JA, Rudenski A, Gibson J, Howard L, O’Driscoll R.** Relating oxygen partial pressure, saturation and content: The haemoglobin–oxygen dissociation curve. *Breathe* 11: 194–201, 2015. doi: 10.1183/20734735.001415.
28. **Komiyama T, Katayama K, Sudo M, Ishida K, Higaki Y, Ando S.** Cognitive function during exercise under severe hypoxia. *Sci Rep* 7: 1–11, 2017. doi: 10.1038/s41598-017-10332-y.
29. **Ando S, Hatamoto Y, Sudo M, Kiyonaga A, Tanaka H, Higaki Y.** The Effects of Exercise Under Hypoxia on Cognitive Function. *PLoS One* 8, 2013. doi: 10.1371/journal.pone.0063630.
30. **Dominelli PB, Wiggins CC, Baker SE, Shepherd JA, Roberts K, Roy TK, Curry TB, Hoyer JD, Oliveira JL, Joyner MJ, Medicine P, Clinic M, Clinic M.** The Oxygen Cascade During Exercise in Health and Disease. *Mayo Clin Proc* 598: 1475–1490, 2021. doi: 10.1113/JP279161.Influence.
31. **Cruickshank S, Hirschauer N.** The alveolar gas equation. *Contin Educ Anaesthesia, Crit Care Pain* 4: 24–27, 2004. doi: 10.1093/bjaceaccp/mkh008.
32. **Verges S, Bachasson D, Wuyam B.** Effect of acute hypoxia on respiratory muscle fatigue in healthy humans. *Respir Res* 11, 2010.
33. **McMorris T, Hale BJ, Barwood M, Costello J, Corbett J.** Effect of acute hypoxia on cognition: A systematic review and meta-regression analysis. *Neurosci Biobehav Rev* 74: 225–232, 2017. doi: 10.1016/j.neubiorev.2017.01.019.
34. **O’Regan RG, Majcherczyk S.** Role of peripheral chemoreceptors and central

- chemosensitivity in the regulation of respiration and circulation. *J Exp Biol* 100: 23–40, 1982. doi: 10.1242/jeb.100.1.23.
35. **Dominelli PB, Wiggins CC, Baker SE, Shepherd JRA, Roberts SK, Roy TK, Curry TB, Hoyer JD, Oliveira JL, Joyner MJ.** Influence of high affinity haemoglobin on the response to normoxic and hypoxic exercise. *J Physiol* 598: 1475–1490, 2020.
  36. **Wang X, Cui L, Ji X.** Cognitive impairment caused by hypoxia: from clinical evidences to molecular mechanisms. *Metab Brain Dis* 37: 51–66, 2022. doi: 10.1007/s11011-021-00796-3.
  37. **Ando S, Kokubu M, Yamada Y, Kimura M.** Does cerebral oxygenation affect cognitive function during exercise? *Eur J Appl Physiol* 111: 1973–1982, 2011. doi: 10.1007/s00421-011-1827-1.
  38. **Nakata H, Miyamoto T, Ogoh S, Kakigi R, Shibasaki M.** Effects of acute hypoxia on human cognitive processing: A study using ERPs and SEPs. .
  39. **Rice GM, Snider D, Drollinger S, Greil C, Bogni F, Phillips J.** Dry-EEG manifestations of acute and insidious hypoxia during simulated flight. *Med Hum Perform* 90: 92–100, 2019.
  40. **Busby D.** Carbon dioxide toxicity. *Sp Clin Med* 1: 381–419, 1968.
  41. **Defares J., Visser B.** On the Form of the Physiological CO<sub>2</sub> Dissociation Curve, the Physiological O<sub>2</sub> Dissociation Curve, and the Diffusion Curves of O<sub>2</sub> and CO<sub>2</sub> Along the Capillary Path. *Ann New York Acad Sci* 96: 939–955, 1962.
  42. **King BG.** High Concentration–Short Time Exposures and Toxicity. *J Ind Hyg Toxicol* 31: 365–375, 1949.
  43. **Somers VK, Mark AL, Zavala DC, Abboud FM.** Contrasting effects of hypoxia and hypercapnia on ventilation and sympathetic activity in humans. *J Appl Physiol* 67: 2101–2106, 1989. doi: 10.1152/jappl.1989.67.5.2101.
  44. **Cipolla MJ.** *The Cerebral Circulation*. San Rafael (CA): Morgan & Claypool Life Sciences, 2009.
  45. **Lewis BM.** Measurement of arterial blood gases at the transition from exercise to rest. *J Appl Physiol Respir Environ Exerc Physiol* 54: 1340–1344, 1983. doi: 10.1152/jappl.1983.54.5.1340.
  46. **Patel P, Zwibel H.** Physiology, Exercise. .
  47. **Askanazi J, Milic-Emili J, Broell JR.** Influence of exercise and CO<sub>2</sub> on breathing pattern of normal man. *J Appl Physiol Respir Environ Exerc Physiol* 47: 192–196, 1979. doi: 10.1152/jappl.1979.47.1.192.
  48. **Purser D.** *Chapter 4: Asphyxiant components of fire effluents*. Woodhead, Cambridge, UK: 2010.
  49. **Gibbs FA, Gibbs EL, Lennoc W., Nims L.** The Value of Carbon Dioxide in Counteracting the Effects of Low Oxygen. *J Aviat Med* 14: 250–261, 1943.
  50. **Karl, A., McMillan G., Ward S., Kissen A., Souder M.** Effects of Increased Ambient CO<sub>2</sub> on Brain Tissue Oxygenation and Performance in the Hypoxic Rhesus. *Aviat Space Environ Med* 44: 984–989, 1978.
  51. **Vercruyssen M, Kamon E, Hancock PA.** Effects of Carbon Dioxide Inhalation on Psychomotor and Mental Performance during Exercise and Recovery. *Int J Occup Saf Ergon* 13: 15–27, 2007. doi: 10.1080/10803548.2007.11076705.
  52. **Weitzman DO, Kinner JS, Luria SM.** Effects on vision of repeated measure to carbon dioxide (Technical Report No. 6–8). .

53. **Weybrew B.** An exploratory study of the psychological effects of intermittent exposure to elevated carbon dioxide levels (Technical Report No. 647). .
54. **Vehviläinen T, Lindholm H, Rintamäki H, Pääkkönen R, Hirvonen A, Niemi O, Vinha J.** High indoor CO<sub>2</sub> concentrations in an office environment increases the transcutaneous CO<sub>2</sub> level and sleepiness during cognitive work. *J Occup Environ Hyg* 13: 19–29, 2016. doi: 10.1080/15459624.2015.1076160.
55. **Daniels R.** Guidelines on ventilation, thermal comfort and indoor air quality in schools: building Bulletin 101, Draft for Public Consultation. .
56. **Allen JG, MacNaughton P, Satish U, Santanam S, Vallarino J, Spengler JD.** Associations of cognitive function scores with carbon dioxide, ventilation, and volatile organic compound exposures in office workers: A controlled exposure study of green and conventional office environments. *Environ Health Perspect* 124: 805–812, 2016. doi: 10.1289/ehp.1510037.
57. **Garner M, Attwood A, Baldwin DS, Munafò MR.** Inhalation of 7.5% carbon dioxide increases alerting and orienting attention network function. *Psychopharmacology (Berl)* 223: 67–73, 2012. doi: 10.1007/s00213-012-2690-4.
58. **Hartzell G.** Overview of combustion toxicology. *Toxicology* 115: 7, 1996.
59. **Commins BT, Lawther PJ.** A Sensitive Method for the Determination of Carboxyhaemoglobin in a Finger Prick Sample of Blood. *Br J Ind Med* 22: 139–143, 1965.
60. **Norris J., Ballantyne B.** Toxicology and implications of the products of combustion. In: *General and Applied Toxicology*, edited by Ballantyne B, Marrs T, Syversen T. 1999, p. 1915–1933.
61. **Maynard R., Waller R.** Carbon Monoxide. In: *Air Pollution and Health*, edited by Holgate S., Samet J., Koren H., Maynard R. Academic Press, 1999, p. 749–796.
62. **W.S R.** Carbon Monoxide. In: *Handbook of Physiology, American Physiology Society.* Washington, DC: 1985, p. 1087–1098.
63. **Castleden CM, Cole P V.** Carboxyhaemoglobin levels of smokers and non smokers working in the City of London. *Br J Ind Med* 32: 115–118, 1975. doi: 10.1136/oem.32.2.115.
64. **Purser D.** A Bioassay Model for Testing the Incapacitating Effects of Exposure to Combustion Product Atmospheres Using Cynomolgus Monkeys. *J Fire Sci* 2: 20–26, 1984.
65. **Prien T, Traber D.** Toxic smoke compounds and inhalation injury--a review. *Burns* 14: 451–460, 1988.
66. **Vesely A., Somogyi RB, Sasano H, Sasano N, Fisher J., Duffin J.** The effects of carbon monoxide on respiratory chemoreflexes in humans. *Environ Res* 94: 227–233, 2004.
67. **Santiago T V., Edelman NH.** Mechanism of the ventilatory response to carbon monoxide. *J Clin Invest* 57: 977–986, 1976. doi: 10.1172/JCI108374.
68. **Penney DG.** Review: Hemodynamic Response to Carbon Monoxide. *Environ Health Perspect* 77: 121–130, 1988.
69. **Chiodi H, Dill D., Consolazio F, Horvath S.** Respiratory and circulatory responses to acute CO poisoning. *Am J Physiol* 134: 683–693, 1941.
70. **Asmussen E, Chiodi H.** The effect of hypoxemia on ventilation and circulation in man. *Am J Physiol* 132: 426–436, 1941.
71. **Klausen K, Rasmussen B, Gjellerod H, Madsen H, Peterson E.** A comparison of

- prolonged exposure to carbon monoxide and hypoxia in man. *Scand J Clin Lab Inven* 22: 26–38, 1968.
72. **Vogel J., Glesner M.** Effect of carbon monoxide on oxygen transport during exercise. *J Appl Physiol* 32: 234–239, 1972.
  73. **Stewart RD, Peterson JE, Fisher TN, Hosko MJ, Baretta ED, Dodd HC, Herrmann A.** Experimental human exposure to high concentrations of carbon monoxide. *Arch Env Heal* 26: 1–7, 1973.
  74. **Young D.** Venous Return. In: *Control of Cardiac Output*. San Rafael (CA): Morgan & Claypool Life Sciences, 2010.
  75. **Amitai Y, Zlotogorski Z, Golan-Katzav V, Wexler A, Gross D.** Neuropsychological impairment from acute low-level exposure to carbon monoxide. *Arch Neurol* 55: 845–848, 1998. doi: 10.1001/archneur.55.6.845.
  76. **Horvath S, Dahms T, O’Hanlon J.** Carbon monoxide and human vigilance: a deleterious effect of present urban concentration. *Arch Env Heal* 23: 343–347, 1971.
  77. **Ramsey J.** Carbon Monoxide, tissue hypoxia and sensory psychomotor response in hypoxaemic subjects. *Clin Sci* 42: 619–625, 1972.
  78. **Siebenmann C, Keiser S, Robach P, Lundby C.** CORP: The assessment of total hemoglobin mass by carbon monoxide rebreathing. *J Appl Physiol* 123: 645–654, 2017. doi: 10.1152/jappphysiol.00185.2017.
  79. **Molgat-Seon Y, Peters CM, Sheel AW.** Sex-differences in the human respiratory system and their impact on resting pulmonary function and the integrative response to exercise. *Curr Opin Physiol* 6: 21–27, 2018. doi: 10.1016/j.cophys.2018.03.007.
  80. **Dominelli PB, Molgat-Seon Y, Sheel AW.** Sex Differences in the Pulmonary System Influence the Integrative Response to Exercise. *Exerc Sport Sci Rev* 47: 142–150, 2019. doi: 10.1249/JES.0000000000000188.
  81. **Levin H.** Re-constructing Thermal Comfort. *Netw Comf Energy Use Build* , 2016.
  82. **Olfert M, Balouch J, Kleinsasser A, Knapp A, Wagner H, Wagner P., Hopkins S.** Does gender affect human pulmonary gas exchange during exercise? *J Physiol* 557: 529–541, 2004.
  83. **Bouwsema M., Tedjasaputra V, Stickland MK.** Are there sex differences in the capillary blood volume and diffusing capacity response to exercise? *J Appl Physiol* 122: 460–469, 1985.
  84. **Rascon J, Trujillo E, Morales-Acuña F, Gurovich A.** Differences between Males and Females in Determining Exercise Intensity. *Int J Exerc Sci* 13: 1305–1316, 2020.
  85. **Dominelli P., Render J., Molgat-Seon Y, Foster G., Romer L., Sheel A.** Oxygen cost of exercise hyperpnoea is greater in women compared with men. *J Physiol* 593: 1965–1979, 2015.
  86. **Dominelli P., Molgat-Seon Y, Griesdale DE., Peters C., Blouin J., Sekhon M, Dominelli G., Henderson W., Foster G., Romer L., Koehle M., Sheel A.** Exercise-induced quadriceps muscle fatigue in men and women: effects of arterial oxygen content and respiratory muscle work. *J Physiol* 595: 5227–5244, 2017.
  87. **Teppema LJ, Dahan A.** The ventilatory response to hypoxia in mammals: Mechanisms, measurement, and analysis. *Physiol Rev* 90: 675–754, 2010. doi: 10.1152/physrev.00012.2009.
  88. **Itoh M, Ueoka H, Aoki T, Hotta N, Kaneko Y, Takita C, Fukuoka Y.** Exercise hyperpnea and hypercapnic ventilatory responses in women. *Respir Med* 101: 446–452,

- 2007.
89. **MacNutt MJ, De Souza MJ, Tomczak SE, Homer JL, Sheel AW.** Resting and exercise ventilatory chemosensitivity across the menstrual cycle. *J Appl Physiol* 112: 737–747, 2012. doi: 10.1152/jappphysiol.00727.2011.
  90. **Ansdell P, Thomas K, Hicks K., Hunter S., Howatson G, Goodall S.** Physiological sex differences affect the integrative response to exercise: acute and chronic implications. *Exp Physiol* 105: 2007–2021, 2020.
  91. **Society of Fire Protection Engineers.** *SFPE guide to human behavior in fire.* Springer, 2018.
  92. **Borg G.** *Borg's Perceived Exertion And Pain Scales.* 1998.
  93. **Oberholzer L, Montero D, Robach P, Siebenmann C, Ryrsoe CK, Bonne TC, Breenfeldt Andersen A, Bejder J, Karlsen T, Edvardsen E, Rønnestad BR, Hamarsland H, Cepeda-Lopez AC, Rittweger J, Treff G, Ahlgrim C, Almquist NW, Hallén J, Lundby C.** Determinants and reference values for blood volume and total hemoglobin mass in women and men. *Am J Hematol* 99: 88–98, 2024. doi: 10.1002/ajh.27162.
  94. **Wilmore JH, Costill D.** Adequacy of the Haldane transformation in the computation of exercise VO<sub>2</sub> in man. *J Appl Physiol* 35, 1973.
  95. **West JB.** *Respiratory Physiology: The Essentials".* Wolters Kluwer Health, 2016.
  96. **Gozal D, Kheirandish-Gozal L.** Hypoxic ventilatory response. In: *Kryger, M., Roth, T., & Dement, W.C. (Eds.), Principles and Practice of Sleep Medicine.* Elsevier Saunders, 2008, p. 255–266.
  97. **Gidlow D.** Hydrogen cyanide-an update. *Occup Med (Chic Ill)* 67: 662–663, 2017. doi: 10.1093/occmed/kqx121.
  98. **Hayashi K.** Ventilatory response to increasing body temperature: Characteristics and effect on central fatigue. *J Phys Fit Sport Med* 4: 143–149, 2015. doi: 10.7600/jpfsm.4.143.
  99. **Forrest B, DiPaola A, Ibrahimli V, Lakhani A, Weckman E.** Towards characterizing full-scale furniture fires in a two-storey house: gaseous species concentrations during a ventilation-limited fire. *Fire Saf J* 141, 2023.
  100. **Nystedt F.** Deaths in Residential Fires-an Analysis of Appropriate Fire Safety Measures [Online]. <http://lup.lub.lu.se/record/642092>.
  101. **Smulyan H, Marchais SJ, Pannier B, Guerin AP, Safar ME, London GM.** Influence of body height on pulsatile arterial hemodynamic data. *J Am Coll Cardiol* 31: 1103–1109, 1998. doi: 10.1016/S0735-1097(98)00056-4.
  102. **Heinonen IHA, Boushel R, Kalliokoski KK.** The circulatory and metabolic responses to hypoxia in humans - with special reference to adipose tissue physiology and obesity. *Front Endocrinol (Lausanne)* 7: 1–6, 2016. doi: 10.3389/fendo.2016.00116.
  103. **Mairbäurl H, Weber RE.** Oxygen Transport by Hemoglobin. *Compr Physiol* 2, 2012.
  104. **Murphy WG.** The sex difference in haemoglobin levels in adults — Mechanisms, causes, and consequences. *Blood Rev* 28: 41–47, 2014.
  105. **Martin N., Falder S.** A review of the evidence for threshold of burn injury. *Burns* 43: 1624–1639, 2017.