EXERCISE-INDUCED ARTERIAL HYPOXAEMIA IN FEMALE MASTERS ATHLETES

by

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submitted by Viviana Shiffman in partial fulfillment of the requirements for

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Abstract

The pulmonary system can maintain arterial blood gas homeostasis during exercise in healthy, young adults. However, some endurance athletes demonstrate a significant reduction in arterial oxygenation during exercise, a phenomenon termed exercise-induced arterial hypoxemia (EIAH). EIAH has been previously observed in young adults, and male masters athletes but there are no reports of gas exchange impairment in female masters athletes. It was hypothesized the majority of female masters athletes will develop EIAH during submaximal, near maximal, and maximal treadmill exercise. Pulmonary function was assessed followed by an incremental exercise test to determine maximal O_2 uptake ($\dot{V}O_2max$). Participants were instrumented with a radial arterial catheter, an oesophageal balloon-tipped catheter, and temperature probe. Arterial samples were drawn while participants exercised at 60-70, 75, 90-95, and 100% $\dot{V}O_2max$ for 2-4 minutes. Participants (n=6, 48-57 years) had an average $\dot{V}O_2max$ of 47±2 ml/kg/min (range 40-55 ml/kg/min, 135-186% predicted). During submaximal, near maximal, and maximal exercise the arterial partial pressure of O_2 (PaO_2) decreased from rest by 14±2 mmHg (range 6-21), 13±4 (range -6-24), and 11±7 mmHg (range -7-21), respectively. The arterial partial pressure of CO_2 ($PaCO_2$) decreased from rest by 1.8±1 mmHg (range -2-6), 4±1 mmHg (range 0.3- 8), and 5±2 mmHg (range 2-5) at submaximal, near maximal, and maximal exercise, respectively. There was a reduction in oxyhemoglobin saturation 2.5± 0.3% (range 1.9-3.4) and arterial O_2 content 1.2± 0.2 mL O_2/100 mL of blood (range 0.7-1.8) at all intensities. Participants with a minimal change to $PaCO_2$ tended to have a greater reduction in PaO_2 ($r = -0.85$, $R^2 = 0.73$, $p< 0.05$). The alveolar to arterial oxygen ($A\text{-}aDO_2$) gradient increased during submaximal (range 7-34 mmHg), near maximal (range 7-47 mmHg) and maximal (range 7-48 mmHg) exercise. The decrease in PaO_2 and increased $A\text{-}aDO_2$ gradient indicates an inadequate ventilatory response to exercise. There

was no relationship between $\dot{V}O_2max$ and PaO_2. These results suggest that female masters athletes develop EIAH at submaximal and maximal exercise intensities and a high level of aerobic fitness is not a requisite for the development of EIAH.

Lay Summary

Exercise-induced arterial hypoxaemia (EIAH) is defined as a decrease in partial pressure of oxygen during exercise. It was previously thought to only develop in highly-trained male endurance athletes. However, EIAH has been shown to occur in endurance trained and untrained females. There is controversy on whether or not females have a higher occurrence of EIAH relative to males. Male masters athletes have been shown to develop EIAH at a higher occurrence than their younger counterparts due to the effects of healthy aging on the pulmonary system, but female masters athletes have yet to be tested. The purpose of this thesis was to characterize EIAH in female masters athletes at submaximal, near maximal and maximal exercise levels. It was found that female masters athletes experience EIAH during light and heavy exercise, however there was considerable variability in terms of severity.

Preface

The current research study was designed myself, Viviana Shiffman, with the assistance of my supervisor (Dr. William Sheel), committee members (Drs. Michael Koehle, Donald McKenzie, and James McKinney) and members of the Health and Integrative Physiology Lab at the University of British Columbia (Mick Leahy and Shalaya Kipp). Testing was performed by myself with the assistance of Michael Leahy, Shalaya Kipp, Dr. William Sheel, Dr. Peter Rose, and Dr. Bevan Hughes. Scheduling and analysis were done myself. Interpretation of results was done myself with the assistance of Dr. William Sheel and members of the Health and Integrative Physiology Lab at the University of British Columbia. All methods executed in this thesis was approved by the University of British Columbia's Research Ethics Board (H20-00446).

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List of Abbreviations

a	arterial
A	alveolar
A-aDO_2	Alveolar to arterial oxygen difference
ATPS	Atmospheric temperature pressure saturated
bpm	Beats per minute
BTPS	Body temperature pressure saturated
CaO_2	Oxygen content of arterial blood
$cHCO_3^-$	Concentration of bicarbonate
Cl^-	Chloride
CO	Cardiac output
DLCO	Lung diffusion capacity for carbon monoxide
EFL	Expiratory flow limitation
EIAH	Exercise-induced arterial hypoxaemia
Fb	Breathing frequency
FiO_2	Fraction of inspired oxygen
FRC	Functional residual volume
FV	Flow-volume
$FEV_{1.0}$	Forced expiratory volume in 1 second
FVC	Forced vital capacity
Hct	Hematocrit
HR	Heart rate
Hb	Hemoglobin

IC	Inspiratory capacity
IVC	Inspiratory vital capacity
K^+	Potassium
MFVC	Maximal flow-volume curve
Na^+	Sodium
NEIAH	No exercise-induced arterial hypoxaemia
ODC	Oxygen dissociation curve
P_B	Barometric pressure
P_{H20}	Water vapor pressure
PaO_2	Partial pressure of oxygen in arterial blood
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
PAO_2	Partial pressure of oxygen in alveolar gas
$P_{ET}CO_2$	Mixed end-tidal carbon dioxide tension
PEF	Peak expiratory flow
pH	potential Hydrogen
pKp	negative log base of acid dissociation
PV	Pressure-volume
RER	Respiratory exchange ratio
RV	Residual volume
SaO_2	Arterial oxyhemoglobin saturation
STPD	Standard temperature pressure dry
TLC	Total lung capacity
$\dot{V}A$	Alveolar ventilation

V_D	Deadspace
V_{DV}	Breathing valve deadspace
$\dot{V}O_2$	Oxygen uptake
$\dot{V}O_2$ max	Maximal oxygen uptake
$\dot{V}CO_2$	Carbon dioxide output
VC	Vital capacity
WOB	Work of breathing

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Special thank you Mick Leahy and Shalaya Kipp for always being there for me. Thank you to my lab mates for the continuous support.

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Dedication

To my family,

Laura Horwitz

Claude Shiffman

Michael Horwitz

Vittorio Shiffman

Alexandre Shiffman

Jordana Horwitz

Sasha Horwitz

Viviane Galante

Chapter 1: Introduction

It is generally accepted that the pulmonary system is able to maintain arterial blood gas homeostasis during exercise in healthy young adults. With increasing exercise intensity the demand of oxygen to the working muscles increases and therefore a greater cardiac output (CO) is required. When exercising, the respiratory system responds by oxygenating blood through an increase in alveolar ventilation ($\dot{V}A$) that is proportional to metabolic demand. The rise in ventilation increases the partial pressure of oxygen (PaO_2) while decreasing the partial pressure of carbon dioxide ($PaCO_2$) and a widening of the alveolar-to-arterial PO_2 difference ($A\text{-}aDO_2$) is minimized. Oxyhemoglobin saturation (SaO_2) and thus the arterial oxygen content (CaO_2) are both maintained. Therefore, the respiratory system can be described as highly ordered, serving to ensure arterial blood gases are maintained at near-resting levels even during strenuous exercise.

1.1 Defining exercise-induced arterial hypoxaemia

The pulmonary system can generally be considered 'overbuilt' for exercise in healthy young humans (Dempsey, 1986). However, there is evidence that this is not necessarily the case in some highly-trained male athletes where hypoxaemia is developed during heavy and submaximal exercise (Dempsey et al., 1984; Rice et al., 1999) – termed exercise-induced arterial hypoxaemia (EIAH). The definition of EIAH is a decrease in arterial oxygenation which may result from i) a fall of PaO_2 and (SaO_2), ii) a rightward shift of the O_2 dissociation curve without a fall in PaO_2 or, iii) a combination of these processes (Dempsey & Wagner, 1999). EIAH can be categorized into three severities: mild which corresponds to an SaO_2 of 93-95%; moderate which corresponds to an SaO_2 of 88-93%; and severe which corresponds to SaO_2 values of less than 88% (Dempsey & Wagner, 1999). The definition based on SaO_2 better defines the consequences

of EIAH to the systemic O_2 transport and maximum oxygen uptake ($\dot{V}O_2max$). SaO_2 may also be reduced owing to a reduction in PaO_2 and a rightward shift of the HbO_2-dissociation curve via reductions in pH and increase in temperature. Categorizing EIAH can be based on the widening of the A-aDO_2 where excessive EIAH corresponds to an A-aDO_2 of 25-30 mmHg and severe EIAH corresponds to an A-aDO_2 of 35-40 mmHg (Dempsey & Wagner, 1999). This definition better defines EIAH as an indicator of inadequate ventilation. For the purpose of the study, EIAH will be defined as a decrease in PaO_2 >10 mmHg from the resting value (Dempsey et al., 1984).

1.2 Exercise-induced arterial hypoxaemia

The "Demand vs. Capacity" relationship put forward by Dempsey (1986) explains EIAH occurring at maximal exercise such that there is a mismatch between 'organ systems'. There is a general consensus that the metabolic and cardiovascular systems respond to chronic exercise training such that the delivery and utilization of O_2 during exercise is increased (Dempsey & Wagner, 1999). However, the respiratory system shows very little to no adaptation to exercise training (Saltin et al., 1968). As such, the improvements in O_2 transport across organ systems exceed the capacity of the respiratory system and it may become a limiting factor during exercise in some athletic populations. However, many highly-trained athletes exhibit EIAH during moderate levels of exercise and the alveolar-to-arterial oxygen difference (A-aDO_2) widens excessively with a minimal hyperventilatory response even though the respiratory system has the capacity to increase $\dot{V}A$ and offset hypoxemia (Dempsey et al., 1984; Préfaut et al., 1994, Dominelli et al., 2013). There are two main mechanisms causing EIAH: widening of A-aDO_2 and the absence or minimal hyperventilatory response (Dempsey et al., 1984). The extent to which each contributes to the development of EIAH varies and is not fully understood (Dempsey

& Wagner, 1999). Distinct patterns between lung mechanics and gas exchange have been suggested to help provide insight into potential mechanisms of EIAH (Dominelli et al., 2013). The minimal hyperventilatory response could be due to a blunted peripheral chemosensitivity response (Craig & Stager, 1995; Granger et al., 2020; Johnson et al., 1992). A suppressed sensitivity to hypercapnia during moderate exercise has been shown to be greater in those who develop EIAH compared to those who do not and thus may contribute to the development (Granger et al., 2020). However, others have found no relationship between the resting hypoxic ventilatory response (HVR), exercise ventilation, and EIAH, implying that a widened A-aDO_2 has a dominant role (Hopkins et al., 1985). Another possible reason for a an absent or minimal hyperventilatory response is mechanical constraint (Dominelli et al., 2013; Johnson et al., 1992). At near maximal exercise intensities, a mechanical constraint such as expiratory flow limitation (EFL) has been shown to prevent an adequate alveolar hyperventilation response to maintain PaO_2 at near resting values (Dominelli et al., 2013). There is evidence to show that the widened A-aDO_2 is caused by a ventilation to perfusion ($\dot{V}A/\dot{Q}$; multiple inert gas elimination technique) mismatch, diffusion limitation and/or, an anatomical shunt (Gale et al., 1985; Torre-Bueno et al., 1985; Wagner et al., 1986; Hopkins et al., 1994). In highly trained endurance athletes, the observed A-aDO_2 has been shown to be higher than predicted during high intensity exercise which suggests that a diffusion limitation is present and could account for >50% of the A-aDO_2 widening (Hopkins et al., 1994). However, $\dot{V}A/\dot{Q}$ mismatch had the greatest effect on pulmonary gas exchange accounting for > 60% of A-aDO_2 widening (Hopkins et al., 1994).

1.3 Maximum flow volume curve, it's components and expiratory flow limitation

The respiratory system's capacity to generate flow and volume is relatively fixed. A maximal flow volume curve (MFVC) is used to measure the primary variables (expired and inspired capacities and flow rates) that define maximal ventilatory capacity. An MFVC is comprised of three loops – a resting flow-volume (FV) loop, a maximal exercise FV loop and a MFVC. All combination of flow and volume will be within the MFVC emphasizing the capacity to be relatively fixed. The inspiratory and expiratory volumes can increase through a change in end-inspiratory lung volume (EILV) and end-expiratory lung volume (EELV). However, at maximal exercise, the FV loop can intersect with the MFVC and result in EFL. Thus, ventilation becomes mechanically constrained and may adversely affect physiological function such as a decrease in stroke volume (Stark-Leyba et al., 2004), an increase in WOB and respiratory muscle fatigue due to relative hyperinflation (Johnson et al., 1992). During exercise EELV decreases which is advantageous as it places the diaphragm in a better mechanical position to perform work and lower the inspiratory WOB. However, when airflow limitation is present, EELV appears to increase with a normal healthy population (O'Kroy et al., 2000) and with older active men (Johnson et al., 1991) implying airflow limitation influences the increase in EELV. It has been suggested that those who have a lower ventilatory reserve and loss of elastic recoil, such as older active individuals, increase EELV to reach $\dot{V}E$ for exercise and avoid EFL while maintaining blood gas homeostasis (Johnson et al., 1991).

The ventilatory response to exercise is influenced by the integration of neural and humoral stimuli, and lung and chest wall mechanics (Dempsey, 1986). However, there is uncertainty as to what initiates and controls the level of $\dot{V}E$ during exercise. When strong humoral stimuli are

present in arterial blood, there is an accompanying hyperpnea during exercise. It is also well known that the carotid chemoreceptors are excited by those stimuli and may contribute to hyperpnoea. However, there is evidence that the ventilatory response to exercise is appropriate even when the input from the carotid bodies is surgically removed (Pan et al., 1998). Alternatively, chemoreceptors are not the primary drive for exercise hypernea but rather the 'fine-tuning' of ventilation during exercise (Dempsey et al., 1995). Intermittent hypoxia enhances the human HVR at rest (Foster et al., 2005) however the increase in HVR does not translate to an increase in ventilation during exercise (Foster et al., 2006). A diminished HVR and a lower $\dot{V}E$ during exercise in endurance athletes has been reported (Byrne-Quinn et al., 1971) where it may be beneficial due to lower a $\dot{V}E$ and less dyspnea (Scoggin et al., 1978). However, there is no physiological mechanism identified to explain why physical training would lower chemosensitivity. Levine et al., 1992 conducted an intense exercise training study where untrained participants increased their $\dot{V}O_2max$ by ~15% and HVR was unaltered suggesting that aerobic fitness and resting HVR are unrelated. This is consistent with cross-sectional work where ventilatory responsiveness in highly-, moderately-, and un-trained participants show no relationship between $\dot{V}O_2max$ and HVR (Sheel et al., 2006). A spectrum of HVR was seen in all training groups which points towards other factors being more important in the determination of hypoxic ventilatory control (Sheel et al., 2006). When considering the effect of HVR on performance, athletes who have a reduced hyperventilatory response had a greater decline in $\dot{V}O_2max$ and SaO_2 levels than those that had a greater hyperventilatory response (Gavin et al., 1998). These results are consistent with those who have a high rest HVR (Benoit et al., 1995). Hypoxic ventilatory responsiveness to maintain SaO_2 levels has a significant role in non-flow

limited highly-trained athletes however this relationship is not seen with those that are flow limited (Derchak et al., 2000).

Breathing a helium inspirate gas (21% O_2:79% He) is a method to increase the MFVC and thus partially alleviate mechanical constraint (i.e., EFL). The helium replaces nitrogen, allowing the airflow to remain more laminar and thus there is less resistance occurring (Babb, 1997). When breathing heliox gas compared to room air, participants can increase $\dot{V}E$ by alleviating EFL and thus improving the P_AO_2 and P_aO_2 (Dominelli et al., 2013). Participants who experience EIAH and EFL are able to partially offset EIAH with heliox and thus mechanical constraint plays a role in the development of EIAH (Dempsey et al., 1984; Dominelli et al., 2013).

1.4 Sex differences

The study of EIAH has largely been undertaken using male research participants and there are few studies that have sought to characterize EIAH in young female athletes. It has been estimated that 50% of young endurance athletes experience EIAH based upon pulse oximetry estimates of arterial oxygenation (Powers et al., 1988). However, there is some evidence to suggest a higher prevalence in young female athletes (Harms et al., 1998; Dominelli et al., 2013). Harms et al., 1998 questioned whether healthy young women of varying fitness levels (n=29) would be more vulnerable to EIAH. There was variability in response to exercise between the participants as some were able to maintain PaO_2 while others exhibited significant reductions in PaO_2 during both submaximal and maximal exercise. EIAH was inversely related to $\dot{V}O_2$max where the less fit subjects did not experience EIAH and had a minimal widening of the A-aDO_2. When considering sex effects, women had a substantially widened A-aDO_2 at a lower $\dot{V}O_2$max compared to similarly aged men and thus EIAH occurred at substantially lower work rates.

Female participants who demonstrated EIAH at maximal exercise also demonstrated it at submaximal exercise. These findings support a greater susceptibility to EIAH in women. Richards et al., 2004 suggested that EIAH is more prevalent in young female athletes (67%) than it is in men (50%) (Powers et al., 1998) when using pulse oximetry. However, other studies have shown women to demonstrate EIAH at the same severity and occurrence as men (Hopkins et al., 2000). Hopkins et al., 2000 studied young, trained females (n=17) during running and cycling with slow and fast increases in external work. At 90% $\dot{V}O_2$max a lower PaO_2 was observed during running versus cycling exercise and during the fast relative to the slow workload increments. 24% of their participants developed severe EIAH during the running fast incremental which is a lower prevalence than previously reported.

Sex differences with respect to the structure and function of the respiratory system at rest and during exercise have been reported. For example, women have smaller lungs and smaller larger conducting airways than men even when matched for height and lung size, respectively (Martin et al., 1987; Sheel et al., 2009; Ripoll et al., 2020). However, when controlling for height, the sex differences in airway area are attenuated but still persistent (Ripoll et al., 2020). The difference in absolute airway size is seen after >14 years of age which is near the time of puberty (Ripoll et al., 2020). Thus, the differences are associated with hormonal changes and are not innate. Having smaller airways cause women to have a lower maximum expiratory flow and reduced MFVC when compared to height matched men (Knudson et al., 1983). Thus, women are more prone to developing a mechanical constraint such as EFL, and leading to a higher WOB, specifically the resistive component (Guenette et al., 2007; Dominelli et al., 2015). A greater WOB results in an increase O_2 cost of breathing (Dominelli et al., 2015). Boys have larger lungs and lung volume

than girls starting at the age of 2 (Thurlbeck, 1982). Consequently, alveolar surface area is directly related to lung volume and thus larger in boys compared to girls (Thurlbeck, 1982). The total number of alveoli is greater in boys than in girls prior to puberty and thus these sex differences are innate (Thurlbeck, 1982). Women have a lower diffusion capacity for CO due to a lower pulmonary capillary blood volume and alveolar-capillary membrane diffusion capacity than men (Olfert et al., 2004; Bouwsema et al., 2017). These factors would cause a higher occurrence and severity of EIAH in women as they put the pulmonary system at a disadvantage and may not be able to meet the metabolic demands of a trained athlete.

1.5 Healthy aging

There are several structural and physiological changes to the pulmonary system that occur with healthy aging including; loss of lung elastic recoil (Anthonisen et al., 1970; D'Errico et al., 1989), a stiffening of the chest wall (Rizzato et al., 1970) and a loss of respiratory muscle strength (Black et al., 1969; Gosselin et al.,1993). Structural changes that affect the transfer of oxygen across the lung into the pulmonary capillaries include; decreased surface area of the lung (Niewoehner et al., 1974; Thurlbeck et al., 1967), decrease distensibility of the pulmonary arterial vasculature (Reeves et al., 1989); and increased diameter of the large airways (Tenney et al., 1956; Raine et al., 1963). These changes negatively impact the efficiency of the pulmonary system. For example, $\dot{V}A$ relative to pulmonary capillary prefusion is slightly increased non-uniformity (Edelman et al., 1968; Hagberg et al., 1988), dead space ventilation is increased (Tenney et al., 1956, Raine et al., 1976), arterial oxygenation, diffusion capacity, and pulmonary capillary blood volume decreases (Bachofen et al., 1973; Kanber et al., 1968; Crapo et al., 1982). There is a greater O_2 cost of ventilation in the aged athlete compared to the young athlete

(Johnson et al., 1991). Therefore, it is theorized that a greater proportion of cardiac output is directed to the lungs and less to the working muscles (Johnson et al.,1994).

Despite the latter decreases in pulmonary function, older healthy participants are able to maintain their blood gas homeostasis (PaO_2 within 5 mmHg of rest) during exercise (Johnson et al., 1994). Indicating the healthy aging respiratory system has large ventilatory reserves and that the aerobic capacity and pulmonary function age at a similar rate. However, this is not always the case with older endurance trained male athletes. Dempsey et al., 1993 studied EIAH on older endurance trained male athletes and saw a decrease of $PaO_2 < 75$ mmHg and A-aDO_2 widening of 30-40 mmHg. The development of EIAH with a of $\dot{V}O_2max$ of 35-55ml/kg/min is unique to the male masters athlete as the younger counterpart has only shown EIAH at a $\dot{V}O_2max > 65$ ml/kg/min. Préfaut et al., 1994 sought to characterize EIAH in male masters athletes (65 ± 3 years) and compared them to aged match controls as well as, endurance trained athletes to determine if aging potentiates EIAH. A decrease in PaO_2 greater than 10 mmHg from resting was observed in all male masters athletes (10/10) and in young, trained athletes (8/10). In contrast, the aged matched controls all had stable PaO_2 during exercise. When evaluating the effect of aging, there was a significantly greater drop in PaO_2 at a given workload for the masters athlete compared to the young athlete. Male masters athletes developed EIAH at lower intensities compared to the young athlete. Thus, indicating that aging increases the occurrence of EIAH. If the capacity of the pulmonary system is reduced with aging, and metabolic demands are increasing, the ability for the pulmonary system to maintain arterial blood gas homeostasis is limited. To our knowledge no studies characterizing EIAH in female masters athletes have been conducted.

1.6 Summary

The prevalence of EIAH across different human populations (e.g., male/female, young/aging) has not been clearly defined and there are relatively few studies with direct measures of arterial blood corrected to *in vivo* temperature. It is estimated that EIAH occurs in 50% of young male athletes (Powers et al., 1988) but this is based upon pulse oximetry, an indirect measure of SaO_2. There is some evidence to suggest that young women may be more susceptible to EIAH even at lower $\dot{V}O_2max$ than similarly aged men (Harms et al., 1998; Richards et al., 2004). However, this conclusion is controversial (Hopkins et al., 2004) and is based on relatively few data points and is further confounded by indirect estimates of SaO_2. It has been reported that male masters athletes experience EIAH (Préfaut et al., 1994) but again this is based on few observations. No studies have sought to characterize EIAH in female masters athletes but there is reason to predict an even greater sex effect on the prevalence of EIAH owing to the effects of aging on the respiratory system.

1.7 Research questions

1. Does EIAH occur in female masters athletes (40-60 years) during near maximal and maximal running?
2. Does EIAH occur in female masters athletes during sub-maximal running?

1.8 Hypotheses

1. Female masters athletes will experience EIAH at submaximal, near maximal and maximal exercise intensities.
2. Participants with a higher $\dot{V}O_2max$ will have greater prevalence of EIAH compared to participants with a lower $\dot{V}O_2max$.

For the purpose of this thesis, prevalence will be defined as the number of participants who develop EIAH versus the total number of participants in the study. Submaximal was considered at 60-70% and 75% $\dot{V}O_2$max intensity, near maximal was considered at 90% and 95% $\dot{V}O_2$max intensity, and maximal intensity was considered 100% $\dot{V}O_2$max intensity.

Chapter 2: Methods

2.1 Subjects

Six female masters athletes aged 48-57 years were recruited for testing. The participants had at least five years of endurance training. All participants were non-smokers, free of any cardiorespiratory illnesses, asthma, not currently pregnant or, formerly had a tumor or ulcer in their esophagus. The presence or absence of the menstrual cycle was recorded, and testing occurred at random points during the cycle if present.

2.2 Experimental overview

All protocols were sent to the Clinical Research Ethics Board at the University of British Columbia and were approved (H20-00446). Testing occurred on two separate days with at least 48 hours in between. Participants were asked to refrain from alcohol 24 hours, food and caffeine 2 hours and exercise 12 hours before the study. On the first day of testing, consent forms, physical activity, medical, and menstrual cycle history questionnaire were completed. Basic anthropometric measures were made followed by spirometry, body plethysmography, and diffusion capacity measures. A graded exercise test was conducted on a treadmill until exhaustion to determine $\dot{V}O_2max$ and exercise intensities for the experimental day of testing. On the second day, an arterial catheter was placed in the radial artery and participants were instrumented with an oesophageal thermistor and balloon catheter. Three to four constant load exercise tests at ~ 60-70%, 75%, 90-95% and 100% $\dot{V}O_2max$ were completed while sampling arterial blood and correcting it to *in vivo* temperature. Submaximal and maximal work rates were chosen as previous studies observed EIAH at both rates (Dempsey et al., 1984, Harms et al., 1998; Dominelli et al., 2013). Arterial blood was corrected to *in vivo* temperature because a

change in temperature will shift the ODC and thus change the PaO_2 and $PaCO_2$ values (Severinghaus, 1966).

2.3 Measurements and procedures

2.3.1 Spirometry and pulmonary diffusion

Pulmonary function measures including forced vital capacity (FVC), forced expiratory volume in 1 second ($FEV_{1.0}$), $FEV_{1.0}$/FVC, peak expiratory flow (PEF), and forced expiratory flow between 25 and 75% of FVC (FEF_{25-75}) were measured using spirometry. Total lung capacity (TLC), vital capacity (VC), inspiratory capacity (IC), inspiratory vital capacity (IVC) and $\dot{V}A$ were measured using body plethysmography (Vmax Autobox V62, CareFusion, USA). Single breath pulmonary diffusion capacity for carbon monoxide were measured and adjusted for hemoglobin concentration ($Hb201^+$, HemoCue, Sweden). All protocols followed the American Thoracic Society standards and values obtained were compared to reference values (Graham et al., 2019, Graham et al., 2017, Needham et al., 1954, Crapo & Morris, 1981, Cotes, 1975).

2.3.2 Arterial catherization and blood sampling

A 20- or 22-gauge arterial catheter was inserted into the radial artery by percutaneous cannulation by a physician. Local anesthesia (1% Xylocaine) was administered to the site prior to cannulation. The arterial catheter was connected to an arterial blood sampling kit (VP1, Edwards Lifescience, Irvine, CA, USA) to allow for repeated blood sampling and to flush the sample line with 0.9% saline. Dead space between the catheter and sampling port is 3 mL. Before sampling, an excess of dead space volume (10 mL) was withdrawn and then, an arterial blood sample for analysis (3 mL) were collected into pre-heparinized syringes (Pro-Vent, Smiths Medical, Keene, NH, USA) where

air was immediately evacuated. Samples were immediately analyzed (within 30 seconds) by a blood gas analyzer (ABL Flex80 CO-OX, Radiometer, Copenhagen, Denmark). Analyzed variables were: pH, P_aO_2, P_aCO_2, SaO_2, Na^+, K^+, Cl^-, $Ca^{2+,}$ [Hb], Hct, FO_2Hb, FCOHb, FMetHb, FHHb, and $cHCO_3^-$. Average total blood loss is estimated to be ~ 24-30 mL. Resting samples with a PaO_2 < 85 mmHg were analyzed in duplicate and all other repeated resting samples were in accord with the initial value.

2.3.3 Oesophageal pressure

A balloon tipped latex catheter (no. 47-9005; Ackard Laboratory, Cranford, NJ) was used to measure esophageal pressure and estimate pleural pressure. After administration of 2% Lidocaine (Xylocaine, 2% Lidocaine Hydrochloride) through the nasal passage, the balloon catheter passed through the nasal passage and down the esophagus to be positioned at the lower third of the esophagus. To ensure the balloon was empty, participants performed a Valsalva manoeuvre while the catheter was open to the atmosphere. Then 1 mL of air was injected into the balloon using a syringe (Milic-Emili et al., 1964). The oesophageal balloon pressure was measured using Validyne Pressure Transducer (model DP15-34, Validyne Enginerring, Northridge, CA, USA) The pressure transducer was calibrated before each test using a digital manometer (2021P, Digitron, Torquay UK).

2.3.4 Oesophageal temperature

The oesophageal temperature thermistor (Ret-1, Physitemp Instruments, Clinton, NJ, USA), was calibrated using water baths set at a range of physiological temperatures (35-42°C). A topical anesthesia (2% Lidocaine) was applied via a syringe starting at the nasal passage. The

oesophageal temperature thermistor was placed in the esophagus near the left ventricle and aorta based on a formula using the participant's height (Mekjavic et al., 1990). The oesophageal temperature thermistor was connected to a temperature sensor (Thermalert TH-5, Physitemp Instruments) and was recorded at blood draw.

2.3.5 Ventilatory and metabolic parameters

Participants breathed through a low resistance two-way non-rebreathing valve (model 2700B, Hans Rudolph, Kansas City, MO). Inspiratory and expiratory flow were measured with separate calibrated pneumotachometers (model 3813,Hans Rudolph, Kansas City, MO). Inspiratory and expiratory volumes were calculated by using the integration of their respective flow channels. Mixed expired gas was collected into a 5 L mixing chamber and sampled at the rear to be analyzed by calibrated O_2 and CO_2 analyzers (Model S-3-A/I and Model CD-3A, respectively, Applied Electrochemistry, Pittsburgh, PA). All volumes were corrected using the *Gay-Lussac* ideal gas laws and expressed in STPD.

2.3.6 Graded exercise test

On the first day of testing, a graded exercise test was performed on a treadmill (model 9-9001-MUSAP0, Star Trac, Los Angeles, CA). Participants were secured in a harness attached to a ceiling beam during all exercise testing. The participant sat on a chair placed on the treadmill for ~10 minutes to obtain resting values and then a self-selected warm up was performed for 5 minutes. The test began at 4 mph with 0% grade for 2 minutes. After, the speed increased 1 mph every 2 minutes until 9 mph. At 9 mph, the grade started to increase 2% every 2 minutes. The test continued until the participant reached volitional exhaustion and could no longer continue.

2.3.7 Constant load exercise test

On day 2, three to four constant load exercise tests were performed at ~ 60-70%, 75% ,90-95% and 100% $\dot{V}O_2$max intensity. The 100% $\dot{V}O_2$max trial was not always performed for all participants. Each constant load test was 4 minutes in duration (except the 100% $\dot{V}O_2$max which lasted 2 minutes). The 90-95% $\dot{V}O_2$max constant load test started at 90% $\dot{V}O_2$max for the first 3 minutes and went to 95% $\dot{V}O_2$max for the 4th minute. A blood sample of 3 mL was drawn at the 3rd and 4th minute of each effort (the 1st and 2nd minute for 100% $\dot{V}O_2$max). Temperature was recorded at the time of blood draw. Participants rested quietly for ~15-20 minutes where resting blood samples were taken before performing a 5-minute self-selected warm-up. Between each constant load exercise test, sufficient rest (~ 5 minutes) was given for the PaO_2 to return to resting value.

2.3.8 Heart rate

Heart rate was monitored continuously with a commercial heart rate monitor (T34, Polar, Electro, Kempele, Finland) and stored for subsequent analysis (LabChart v8.1.17, ADInstruments).

2.3.9 Data collection and processing

Raw data including flow, volume, ventilatory and mixed expired metabolic parameters were recorded continuously throughout a test at 200 Hz using a 16-channel analog-to-digital data acquisition system (PowerLab/16SP model ML 795, ADI, Colorado Springs, CO) and stored onto a computer for analysis (LabChart v8.1.17, ADInstrument, Colorado Springs, CO). Measurements recorded from the blood gas analyzer were stored on a computer for analysis and temperature correction.

Chapter 3: Data Analysis

3.1 Work of breathing

The WOB was calculated by creating pressure-volume (PV) loops. The last 30 seconds of each stage was taken, and 8-12 most consistent breaths (e.g. no swallows) were chosen to construct PV loops (Otis et al., 1950; Otis., 1954; Dominelli & Sheel, 2012). The area within the PV loop was separated into three components: inspiratory elastic work, inspiratory resistive work, and total expiratory work. The components were first created by connecting the EELV and EILV with a straight line to reflect total compliance. A right-angle triangle was then created by a vertical line from EELV to a horizontal line from EILV to represent inspiratory elastic work. The area created from the total compliance line and lower part of the PV loop (from EELV to EILV) represents the inspiratory resistive work. The area created from the horizontal line from EELV, and the upper part of the PV loop represents the total expiratory work. Each component was multiplied by Fb and reported as J/min.

3.2 Expiratory flow limitation

The presence of EFL was determined by using FV loops and MFVC. The MFVC was created by having the participant perform multiple FVC maneuvers at graded efforts and then using the highest flow rates at any given volume (Guenette et al., 2010). EELV was estimated by subtracting the IC volume from the participant's FVC. The FV loops were created by the 6 breaths prior to the IC maneuver of each constant load exercise test. The FV loops were then placed within the MFVC and aligned based on EELV. Visually, if the FV loop intersected with the MFVC, EFL was considered present.

3.3 Calculations and corrections for environmental conditions

Water vapor pressure was calculated using the formula below:

$$P_{H2O} = 5.56 \cdot 2.718^{(0.058t)}$$

Where P_{H2O} is the water vapor pressure and t is oesophageal temperature. Water vapor pressure was calculated to correct gas concentrations at different ambient environmental conditions (Stickland et al., 2013).

Physiological deadspace was calculated using the standard equation below:

$$V_D = V_T \cdot \frac{P_aCO_2 - P_{ET}CO_2}{P_aCO_2} - V_{DV}$$

Where V_D is physiological deadspace, V_T is tidal volume, P_aCO_2 is temperature corrected arterial carbon dioxide tension, $P_{ET}CO_2$ is mixed end-tidal carbon dioxide tension and V_{DV} is the breathing valve deadspace (130 mL). Arterial blood gases were corrected for esophageal temperature changes (Severinghaus, 1966). Esophageal temperature was chosen as it closely matches pulmonary artery temperature (Lefrant et al., 2003).

Alveolar PO_2 was calculated using the modified alveolar gas equation below:

$$P_AO_2 = F_iO_2 \cdot (P_B - P_{H_2O}) - \frac{P_aCO_2}{RER} \cdot (1 - F_iO_2(1 - RER))$$

Where P_AO_2 is ideal alveolar O_2, F_iO_2 is the fraction of inspired oxygen at room air, P_B the barometric pressure, P_{H2O} is the saturated water vapor pressure at esophageal temperature, P_aCO_2 is temperature corrected arterial carbon dioxide tension and RER is respiratory exchange ratio. The A-aDO_2 was calculated by subtracting P_aO_2 from P_AO_2. The oxyhemoglobin saturation was directly measured via the blood gas analyzer. S_aO_2 was calculated as if the pH, temperature and P_aCO_2 remained at standard resting conditions (7.4, 37ºC, 40 mmHg; respectively). Using ideal

resting conditions creates a scenario of indicating what percent of desaturation was solely due from changes in PaO_2. S_aO_2 was also calculated as if P_aO_2 remained at resting levels while pH, temperature and P_aCO_2 were at their respective levels.

Arterial oxygen content was calculated using the equation below:

$$C_aO_2 = \left(1.39 \cdot Hb \cdot \frac{S_aO_2}{100}\right) + 0.003 \cdot P_aO_2$$

Where C_aO_2 is the arterial oxygen content, Hb is hemoglobin concentration (g/dL), S_aO_2 is oxyhemoglobin saturation and P_aO_2 is arterial oxygen tension. Arterial oxygen content was directly measured by blood gas analysis when (i) S_aO_2 and P_aO_2 are at a resting level, (ii) S_aO_2 due to only P_aO_2 decrease, and (iii) S_aO_2 due to temperature, pH and P_aCO_2 changes. Using (ii) and (iii) method indicates which aspect influenced C_aO_2 the most (Kelman, 1966; Severinghaus, 1979).

Alveolar ventilation was calculated using the alveolar ventilation equation below:

$$\dot{V}_A = \left(\frac{VCO_2}{P_aCO_2}\right) \cdot K$$

Where $\dot{V}_A$ is alveolar ventilation, $\dot{V}CO_2$ is carbon dioxide production, $PaCO_2$ is arterial tension of carbon dioxide and K is a constant (0.863). The theoretical $\dot{V}_A$ and $\dot{V}_E$ needed to maintain P_aO_2 at resting levels were calculated. This was calculated by determining the P_AO_2 required to return P_aO_2 to resting levels by using the concurrent A-aDO_2 for every stage. The alveolar gas equation was rearranged to solve for P_aCO_2 with the calculated P_AO_2. The estimated P_aCO_2 with its concurrent $\dot{V}CO_2$ was then included in the alveolar ventilation equation to predict the needed $\dot{V}_A$. To predict $\dot{V}_E$, measured dead-space ventilation for each workload was used.

Bicarbonate content was calculated using the equation below:

$$HCO_3^- = 0.23 \cdot P_aCO_2 \cdot 10^{(pH-pKp)}$$

Where HCO_3^- is bicarbonate (mmol/L), P_aCO_2 is arterial tension of carbon dioxide (temperature corrected), pH is the negative base of hydrogen ions in solution (temperature corrected) and pKp is negative log base of the acid dissociation constant calculated with the equation below:

$$pKp = 6.125 - \log\left(1 + 10^{(pH-8.7)}\right)$$

3.4 Statistical analysis

Participants as a group were compared at different percentages of $\dot{V}O_2max$ using a repeated measured analysis of variance (repeated measures ANOVA) with a Tukey's post hoc test. Pearson product moment correlation was used to determine relationship between selected variables. A $p < 0.05$ was considered significant.

Chapter 4: Results

Note: Due to the COVID-19 pandemic and curtailment of research activities at the University of British Columbia the number of participants tested (n=6) is less than what was originally proposed (n=10). Statistical comparison between the EIAH and NEIAH group could not be completed as there is only n=1 in the NEIAH group. As such, data was analyzed as a group (n=6), and the grouping of EIAH (n=5) and NEIAH (n=1) is presented for descriptive purposes only.

4.1 Descriptive data

Anthropometric and pulmonary function measures are shown in Table 1, 2, and 3. Pulmonary function was similar to predicted values however there was large variability.

Table 1 – Anthropometric Measures

Variables	All (n=6)		EIAH (n=5)		NEIAH (n=1)
	Value	Range	Value	Range	Value
Age (years)	51.2±1.4	48-57	51.8±1.5	48-57	48
Height (m)	1.7±0.0	1.6-1.8	1.7±0.0	1.6-1.8	1.6
Weight (kg)	60.9±2	55-70	62±2.7	55-70	55.5
BMI (kg/m^2)	21.2±0.4	20.2-22.7	21.4±0.5	20.2-22.7	20.6
BSA (m^2)	1.7±0.0	1.6-1.9	1.7±0.0	1.6-1.9	1.6
Hb (g/dL)	13.3±0.6	11.1-14.5	12.8±0.7	11.1-13.8	14.5

Values are mean ± SD, and range (min-max). Body mass index (BMI), body surface area (BSA), hemoglobin (Hb).

Table 2 – Pulmonary Function Measures

Variables	All (n=6)		EIAH (n=5)		NEIAH (n=1)
	Value	Range	Value	Range	Value
FVC (L)	4.3±0.2	3.8-4.6	4.2±0.2	3.8-4.6	4.4
% Predicted	113±3	104-122	112±2.8	104-119	122
$FEV_{1.0}$ (L)	3.2±0.2	2.7-3.8	3.2±0.2	2.7-3.8	3.0
% Predicted	107±5	95-121	107±5.8	95-121	104
$FEV_{1.0}$/FVC	74.3±2.4	67-82	75.4±2.7	67-82	69
PEF (L/sec)	7.0±0.4	5.9-8.1	6.8±0	5.9-8.1	7.5
% Predicted	98±4	87-116	96±5	87-116	108
$FEF_{25\%-75\%}$	2.7±0	1.6-4.3	2.9±0.5	1.6-4.3	2.0
% Predicted	98±16	57-159	103±19	57-159	70

Values are mean ± SD, and range (min-max). Forced vital capacity (FVC), forced expiratory volume in 1 second ($FEV_{1.0}$), peak expiratory flow (PEF), forced mid expired flow ($FEF_{25\%-75\%}$).

Table 3 – Body plethysmography and diffusion capacity measures

Variables	All (n=6)		EIAH (n=5)		NEIAH (n=1)
	Value	Range	Value	Range	Value
TLC (L) (n=5)	6.4±0.2	5.7-6.9	6.5±0.3	5.7-6.9	6.0
% Predicted	107±3	102-117	110±3.9	102-117	112
VC (L) (n=5)	4.5±0.2	3.8-4.9	4.5±0.2	3.8-4.9	4.38
% Predicted	118±3.3	104-124	117±4.5	104-124	122
IC (L) (n=5)	2.8±0.2	2.4-3.4	2.9±0.2	2.5-3.4	2.4
% Predicted	117±5.8	105-140	121±7.1	108-140	105
IVC (L) (n=5)	4.0±0.2	3.6-4.5	4.0±0.2	3.6-4.5	3.9
% Predicted	92±2.7	86-101	93±3.1	86-101	90
$\dot{V}A$ (L) (n=5)	5.7±0.2	5.1-6.1	5.8±0.2	5.1-6.1	5.3
% Predicted	99±2.5	91-108	99.0±3.5	91-108	99
DLCO (ml/mmHg/min) (n=5)	32.8±2.9	24.0-37.5	37.2±3.1	27.8-37.5	24.0
% Predicted	113±9	86-127	119±7.2	98-127	86

Values are mean ± SD, and range (min-max). Total lung capacity (TLC), vital capacity (VC), inspiratory capacity (IC), inspiratory vital capacity (IVC), alveolar ventilation ($\dot{V}A$), lung diffusion capacity for carbon monoxide (DLCO).

4.2 Day 1 ventilatory and metabolic parameters

Table 4 represents $\dot{V}O_2$max test results from Day 1. All participants showed an expected response to exercise. All participants had a higher $\dot{V}O_2$max than % predicted based on age, weight, and height.

Table 4.0 – Day 1 $\dot{V}O_2$max test results

Variables	All (n=6)		EIAH (n=5)		NEIAH (n=1)
	Value	Range	Value	Range	Value
$\dot{V}O_2$ (L/min)	2.8±0.1	2.7-3.2	2.9±0.1	2.7-3.2	2.9
$\dot{V}O_2$ (ml/kg/min)	47.0±2.4	40.2-54.5	45.9±2.7	40.2-54.5	52.3
% Predicted	164±7	135-186	163±8	135-186	168
$\dot{V}CO_2$ (L/min)	2.9±0.1	2.7-3.2	2.9±0.1	2.7-3.2	2.8
RER	1.0±0.0	1.0-1.1	1.0±0.0	1.0-1.1	1.0
VT (L)	1.8±0.1	1.6-2.2	1.8±0.1	1.6-2.2	1.8
Fb (bpm)	50.7±2.6	39.1-56.8	50.7±3.1	39.1-56.8	50.7
$\dot{V}E$ (L/min)	97.0±2.2	91.8-105.9	97±2.6	91.8-105.9	101.2
HR (bpm)	163.2±5.6	148.7-183.5	163.2±6.2	148.7-183.5	148.7

Values are mean ± SD, and range (min-max). Oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$), respiratory exchange ratio (RER), tidal volume (VT), breathing frequency (Fb), minute ventilation ($\dot{V}E$), heart rate (HR).

4.3 Blood gases

Table 5 represents mean blood gas values at rest and exercise. PaO_2, $PaCO_2$, and pH all decreased while Hct % and ctHb increased. The % SaO_2 remained near resting values. PaO_2 significantly decreased from rest to 60% and 75% $\dot{V}O_2$max ($p<0.05$). The $PaCO_2$ did not

significantly change from rest to any exercise intensity ($p>0.05$). The % SaO_2 had a significant change from rest to 75% and 95% ($p<0.05$). The CaO_2 values were not significantly different from rest to any exercise intensity.

Table 5 – Mean data for blood gas values
(n=6 except for 100% n=4)

	Variables (n=6 except for 100% n=4)						
% $\dot{V}O_2max$ Stages	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	pH	SaO_2 (%)	Hct (%)	Hb (g/L)	CaO_2 (ml O_2/100ml blood)
Rest	99.7±2.5	38.3±1.1	7.41±0.01	97.8±0.1	37.3±1.7	12.1±0.6	16.8±0.8
60% - 1	91.1±3.6	36.5±1.7	7.41±0.01	97.2±0.3	38.4±1.5	12.5±0.5	17.1±0.7
60% - 2	90.0±2.3	36.7±1.8	7.41±0.01	97.2±0.3	38.6±1.5	12.5±0.5	17.2±0.7
75% - 1	89.2±3.7	38.00±1.8	7.40±0.01	96.8±0.4	38.3±1.5	12.4±0.5	17.0±0.7
75% - 2	86.3±3.0	37.0±1.5	7.39±0.01	96.7±0.3	38.82±1.5	12.6±0.5	17.2±0.7
90% - 1	87.8±4.2	34.8±0.9	7.37±0.01	96.1±1.0	39.0±1.8	12.7±0.6	17.2±0.8
95% - 1	86.7±3.7	35.3±1.0	7.35±0.01	95.8±0.5	39.4±1.6	12.8±0.5	17.3±0.8
100% - 1	92.5±6.1	32.6±1.3	7.39±0.01	96.4±0.5	41.5±1.3	13.5±0.4	18.4±0.6
100% - 2	92.4±4.8	33.4±1.6	7.34±0.01	96.2±0.4	42.1±1.0	13.7±0.3	18.6±0.5

Values are mean ± SD. Maximal oxygen uptake ($\dot{V}O_2max$), partial pressure of oxygen in arterial blood (PaO_2), partial pressure of carbon dioxide in arterial blood ($PaCO_2$), potential hydrogen (pH), oxygen saturation (SaO_2), hematocrit (Hct), hemoglobin (Hb), oxygen content of arterial blood (CaO_2).

Table 6 represents mean Na^+, K^+, Cl^-, and $CHCO_3^-$ values during Day 2. Na^+, K^+, and Cl^- all increased with increasing exercise intensity while, $CHCO_3^-$ decreased. Thus, all followed an expected response to exercise.

Table 6 – Electrolyte and metabolite mean data for blood gas values

	Variables (all n=6, except for 100% n=4)			
% $\dot{V}O_2$max Stages	Na^+	K^+	Cl^-	$cHCO_3^-$
Rest	141.9±0.8	3.9±0.0	104.8±0.6	23.4±0.7
60% - 1	143.2±0.8	4.9±0.2	107.0±0.7	22.6±0.6
60% - 2	141.7±0.8	4.7±0.1	107.3±0.7	22.6±0.6
75% - 1	143.7±0.6	5.0±0.1	107.7±0.7	23.1±1.0
75% - 2	141.5±0.7	4.9±0.1	107.3±0.7	22.1±0.5
90% - 1	144.7±0.8	5.4±0.1	109.0±0.6	19.9±0.4
95% - 1	143.7±0.8	5.4±0.1	109.2±0.8	19.3±0.6
100% - 1	144.5±0.9	5.6±0.0	109.0±0.7	19.4±0.9
100% - 2	144.0±0.7	5.8±0.1	110.3±0.6	17.8±0.8

Values are mean ± SD. Maximal oxygen uptake ($\dot{V}O_2$max), sodium (Na^+), potassium (K^+), chloride (Cl^-), concentration of bicarbonate ($cHCO_3^-$).

4.4 Day 2 ventilatory and metabolic data

Table 7 represents mean ventilatory and metabolic data during constant load exercise tests. All variables in Table 7 increased except for $P_{ET}CO_2$ which decreased.

Table 7 – Mean values for metabolic parameters during Day 2

	Variables (n=6 except for 100% n=4)							
% $\dot{V}O_2$max Stages	$\dot{V}E$ (L/min)	VT (L)	Fb (bpm)	$\dot{V}O_2$ (L/min)	$\dot{V}CO_2$ (L/min)	RER	$P_{ET}CO_2$	HR (bpm)
Rest	6.9±0.4	0.6±0.1	12.2±1.9	0.2±0.0	0.2±0.0	0.82±0.03	39.0±1.8	63.3±4.7
60% - 1	43.5±3.2	1.6±0.1	28.1±2.1	1.7±0.1	1.5±0.1	0.85±0.01	38.0±2.1	112.7±6.9
60% - 2	44.7±2.4	1.7±0.1	26.7±2.5	1.8±0.1	1.5±0.1	0.85±0.01	38.3±1.8	113.4±8.2
75% - 1	52.6±2.1	1.7±0.1	29.5±2.0	2.0±0.1	1.8±0.1	0.86±0.02	36.4±1.5	138.9±7.1
75% - 2	52.3±2.5	1.7±0.1	31.3±2.8	2.0±0.1	1.7±0.1	0.87±0.02	36.8±1.6	139.3±8.1
90% - 1	76.1±1.9	1.9±0.1	39.3±1.5	2.5±0.1	2.4±0.1	0.97±0.03	32.8±1.0	148.7±7.8
95% - 1	82.5±2.4	1.9±0.1	42.3±1.3	2.6±0.1	2.6±0.1	0.99±0.04	30.9±1.2	159.2±5.1
100% - 1	81.3±3.9	1.9±0.2	42.5±3.5	2.7±0.1	2.5±0.1	0.91±0.03	28.8±1.8	159.9±7.4
100% - 2	91.0±3.3	2.0±0.2	44.9±2.6	2.8±0.1	2.7±0.1	0.99±0.03	29.0±2.2	166.4±4.2

Values are mean ± SD. Minute ventilation ($\dot{V}E$), tidal volume (VT), breathing frequency (Fb), oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$), respiratory exchange ratio (RER), heart rate (HR).

Table 8 represents V_D, V_D/VT, $\dot{V}O_2$ and $\dot{V}A$ values during Day 2. V_D increased with higher exercise intensities. V_D/VT ratio decreased from rest but remained high compared to a younger counterpart. The $\dot{V}O_2$ attained during the constant load exercise tests were in close agreement with the % $\dot{V}O_2$max from Day 1.

Table 8 – Calculated metabolic parameters during Day 2

	Variables (n=6 except 100% n=4)			
% $\dot{V}O_2$max Stages	V_D (mL)	V_D/VT	$\dot{V}O_2$ (ml/kg/min)	$\dot{V}A$ (L/min)
Rest	22.2±2.9	0.58±0.05	3.5±0.2	3.9±0.2
60%-1	57.7±4.9	0.23±0.02	28.4±1.4	36.0±2.1
60%-2	60.0±5.2	0.22±0.02	29.7±1.4	37.0±1.2
75%-1	64.9±5.6	0.26±0.02	34.0±2.0	40.0±1.6
75%-2	61.3±5.5	0.25±0.03	33.5±2.1	40.4±2.2
90%-1	63.8±3.7	0.23±0.02	42.3±2.5	58.3±1.9
95%-1	64.7±3.6	0.26±0.01	43.9±3.1	60.8±1.9
100%-1	62.6±5.2	0.27±0.02	47.3±2.6	62.4±2.6
100%-2	64.8±3.4	0.25±0.02	48.2±3.7	69.0±2.3

Values are mean ± SD. Dead space (V_D), tidal volume (VT), oxygen uptake ($\dot{V}O_2$), alveolar ventilation ($\dot{V}A$).

Figure 1 represents mean ventilatory and metabolic data during day 2 constant load exercise tests. $\dot{V}E$ increased through an increase in VT, and Fb during higher intensity exercise. The $\dot{V}O_2$ compared to $\dot{V}CO_2$, but $\dot{V}CO_2$ had a sharp increase at 90% $\dot{V}O_2$max.

Figure 1 - Mean values during Day 2 constant load exercise tests
n=6 for all exercise intensities except n=4 at 100% $\dot{V}O_2$max.

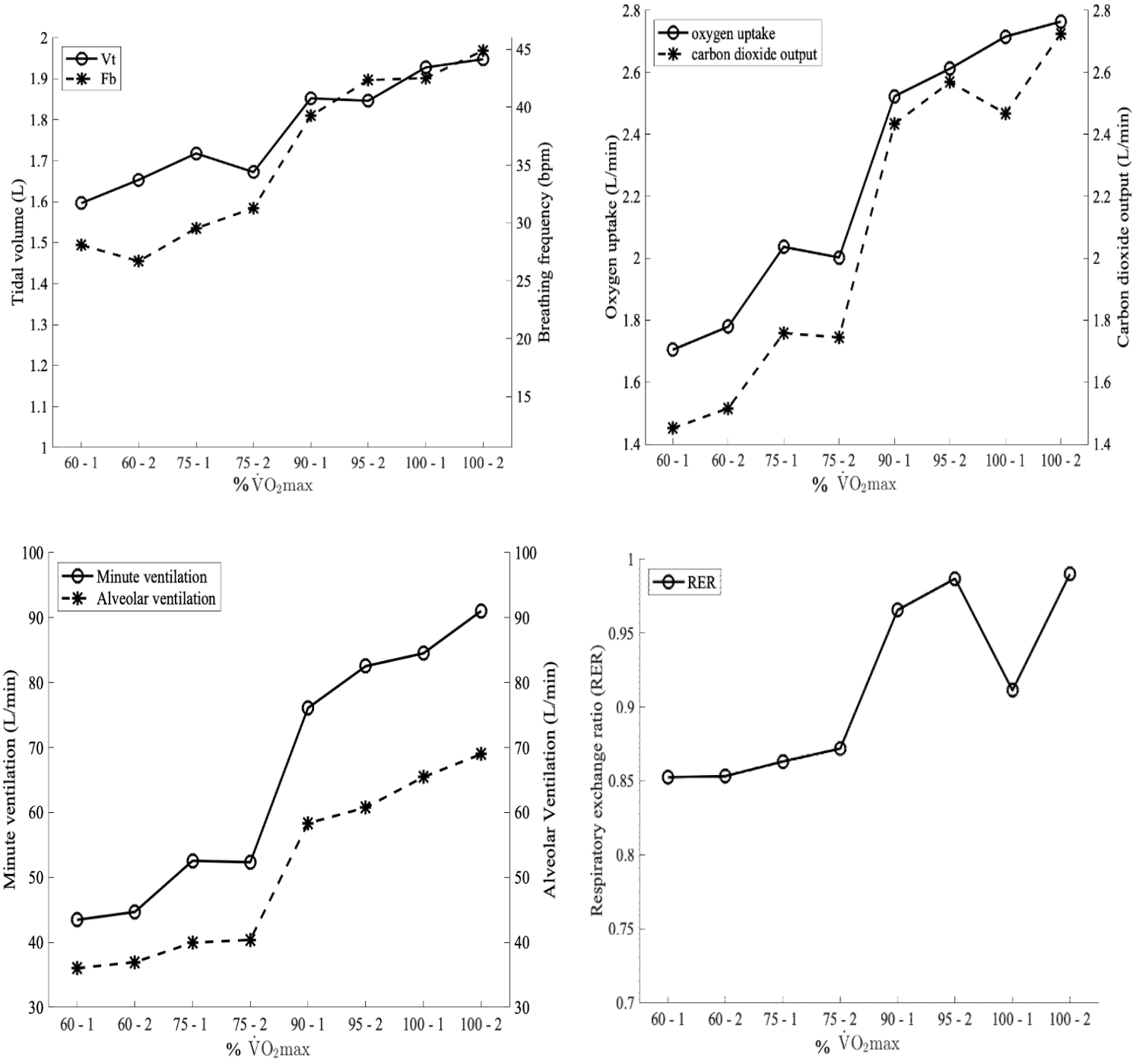
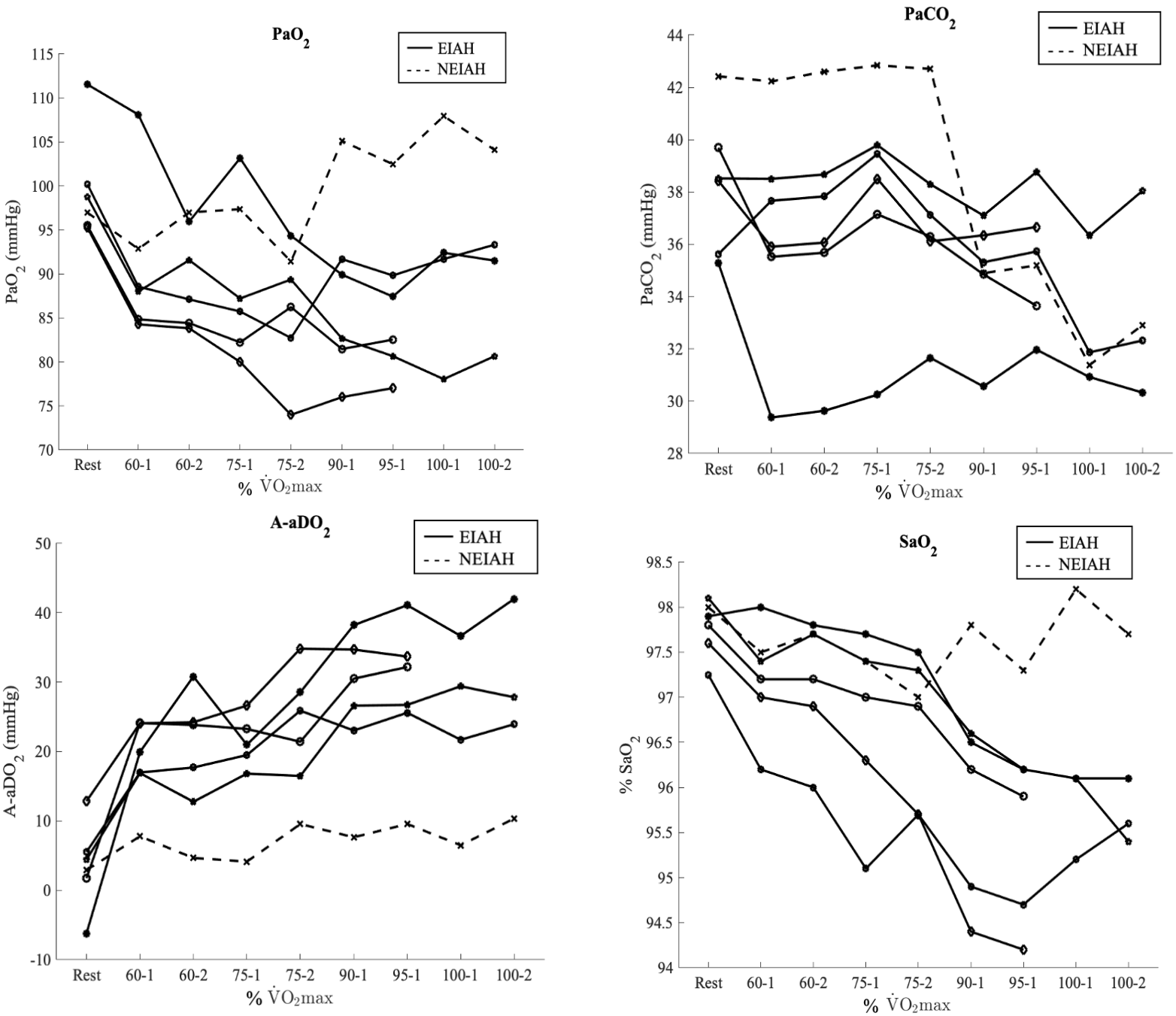


Figure 2 represents individual data points for blood gas values. All participants had a normal resting PaO_2 value (mean = 99.7±2.5 mmHg) except for one participant who had a resting PaO_2 of 111 mmHg. The participant who did not experience EIAH, represented with the broken line, maintained their PaO_2 levels and even increased it at higher exercise intensity. The NEIAH participant's $PaCO_2$ remained near resting until 90% $\dot{V}O_2$max where it began to decrease by 11 mmHg. The NEIAH participant's % SaO_2 was maintained near resting. The participants who experienced EIAH, decreased their PaO_2 > 10 mmHg from resting, decreased their $PaCO_2$ and % SaO_2 from rest. They widened their A-aDO_2 gradient upwards of 30 mmHg whereas the NEIAH maintained the A-aDO_2 gradient near resting. Figure 3 represents the mean blood gas values grouped into EIAH (n=5) and NEIAH (n=1).

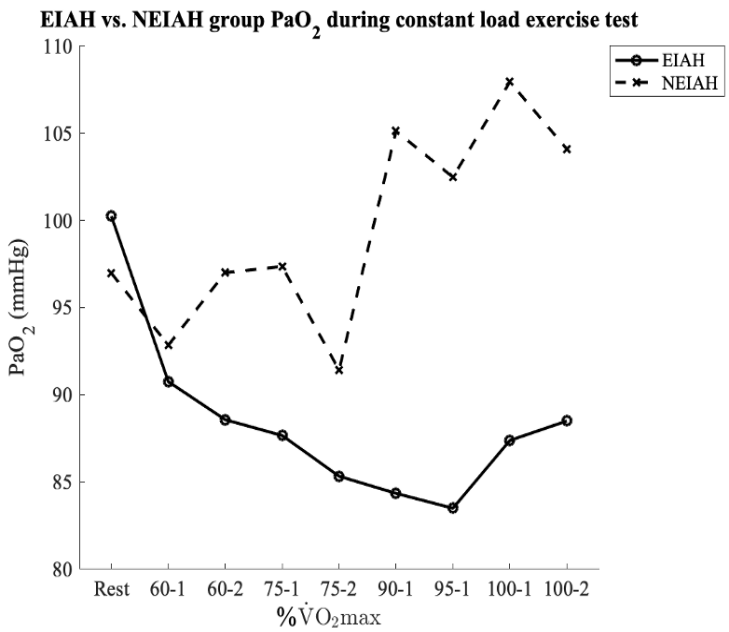
Figure 2 – Individual data points for PaO_2, $PaCO_2$, A-aDO_2 and %SaO_2
n=6 for all except n=4 at 100% $\dot{V}O_2$max. Solid lines (-) represent participants who developed EIAH. Line with spaces (- -) represent participant who did not develop EIAH.

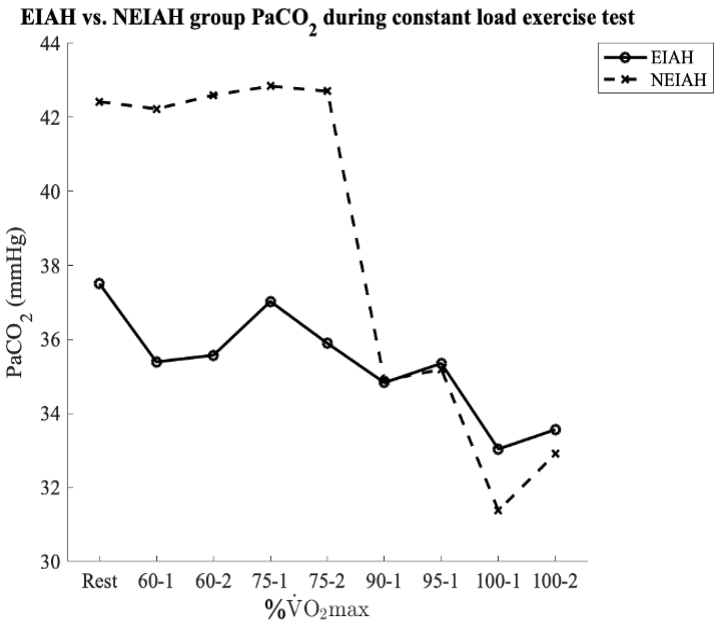


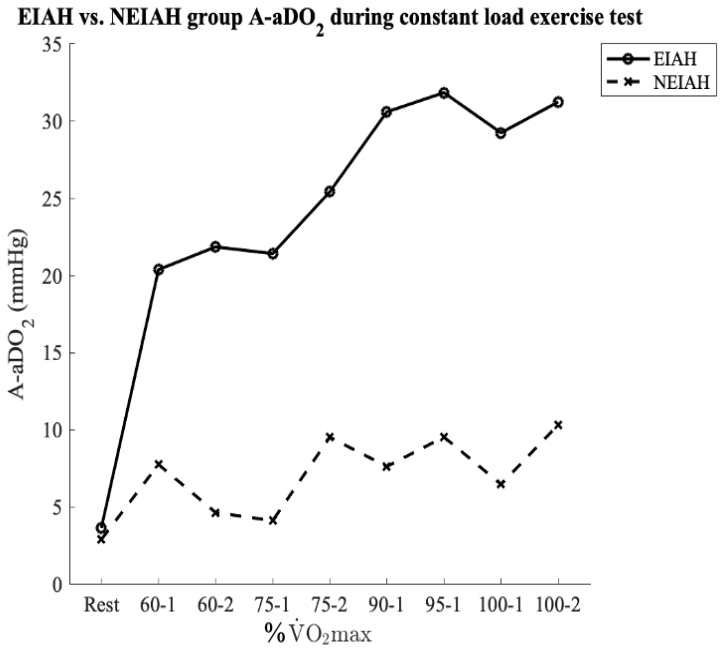
Maximal oxygen uptake ($\dot{V}O_2$max), partial pressure of oxygen in arterial blood (PaO_2), partial pressure of carbon dioxide in blood ($PaCO_2$), alveolar to arterial oxygen difference (A-aDO_2), saturation of oxygen (SaO_2).

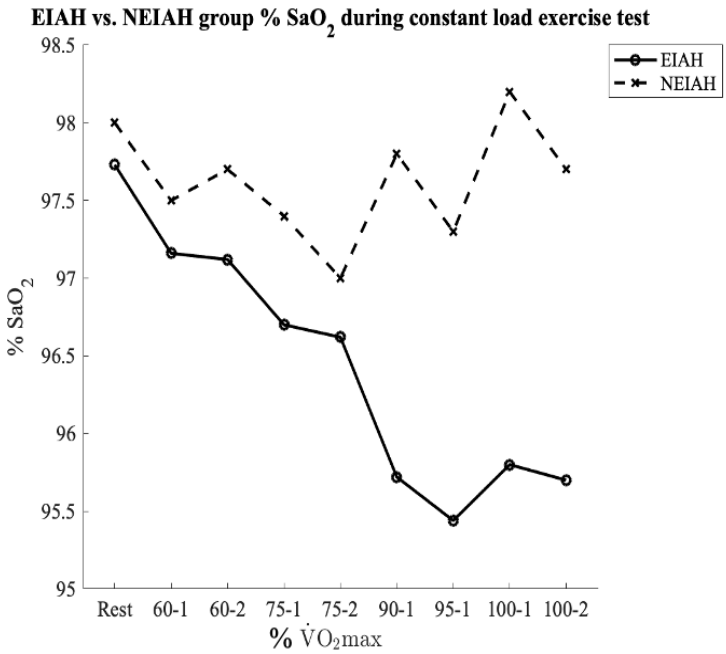
Figure 3 – Mean values for PaO_2, $PaCO_2$, A-aDO_2 and % SaO_2 for the EIAH group and NEIAH group

n=6 for all except n=4 at 100% $\dot{V}O_2max$. Solid lines (-) represent EIAH group. Line with spaces (- -) represent NEIAH group.



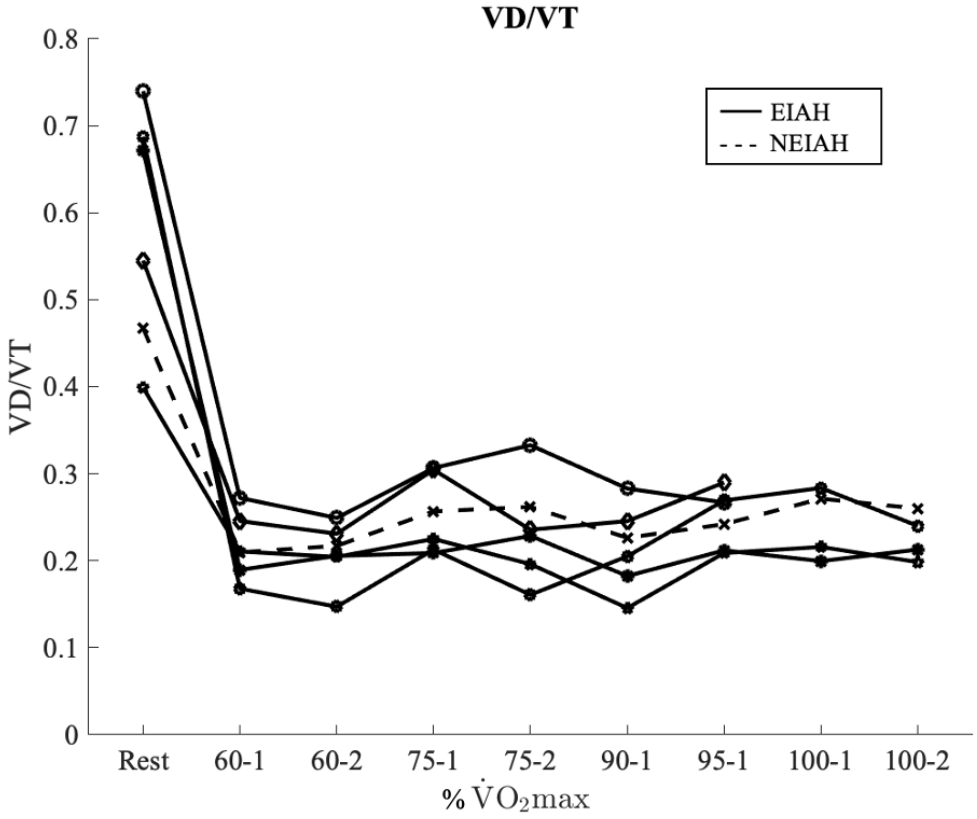






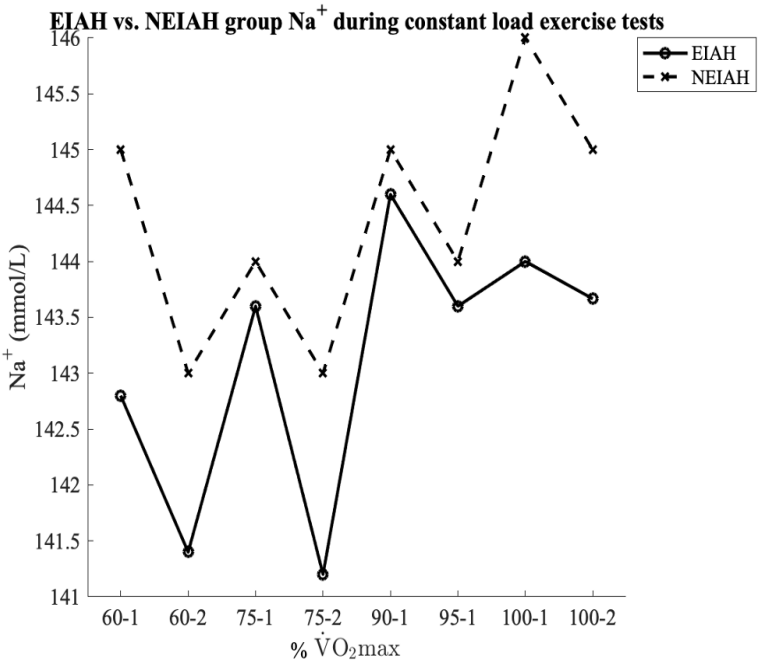
Maximal oxygen uptake ($\dot{V}O_2max$), partial pressure of oxygen in arterial blood (PaO_2), partial pressure of carbon dioxide in blood ($PaCO_2$), alveolar to arterial oxygen difference (A-aDO_2), saturation of oxygen (SaO_2).

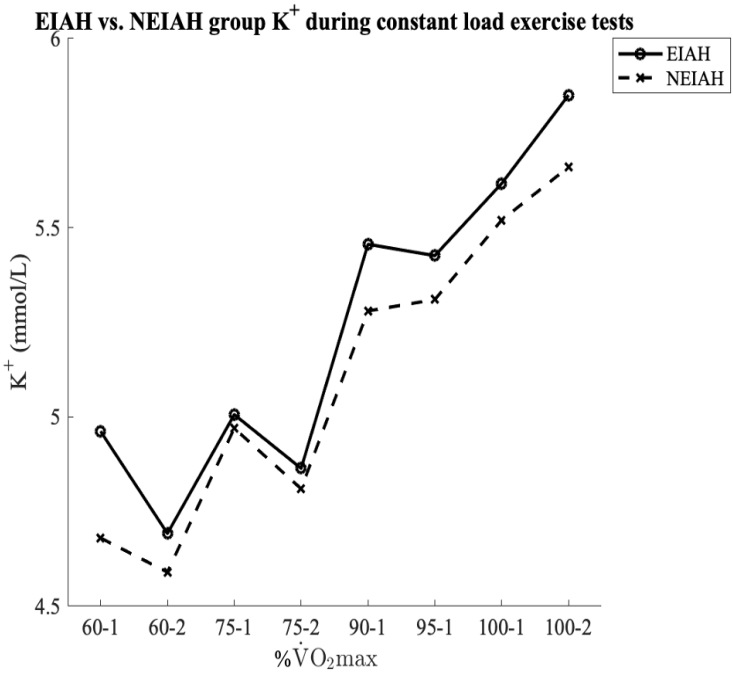
Figure 4 – Individual VD/VT vs, %$\dot{V}O_2$max
n=6 for all except n=4 at 100%. Solid lines (-) represent EIAH group. Line with spaces (- -) represent NEIAH group.

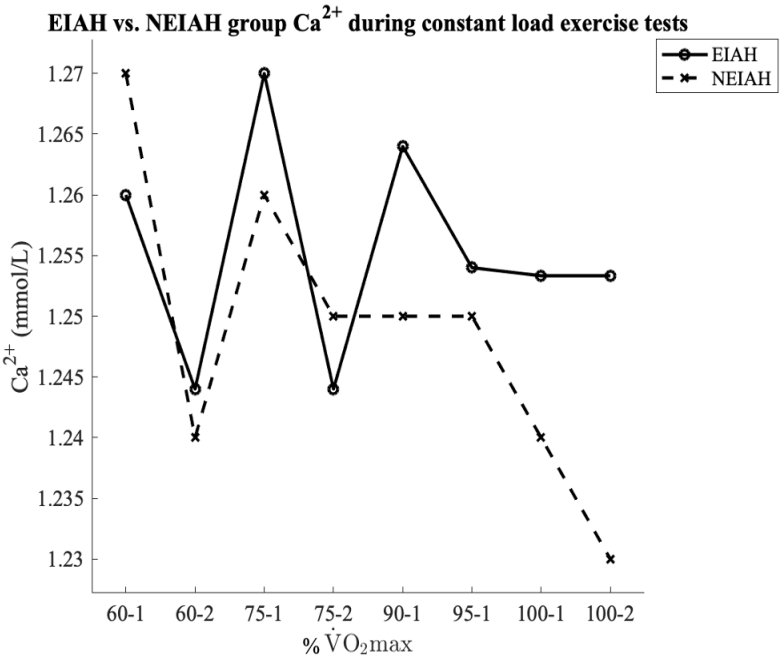


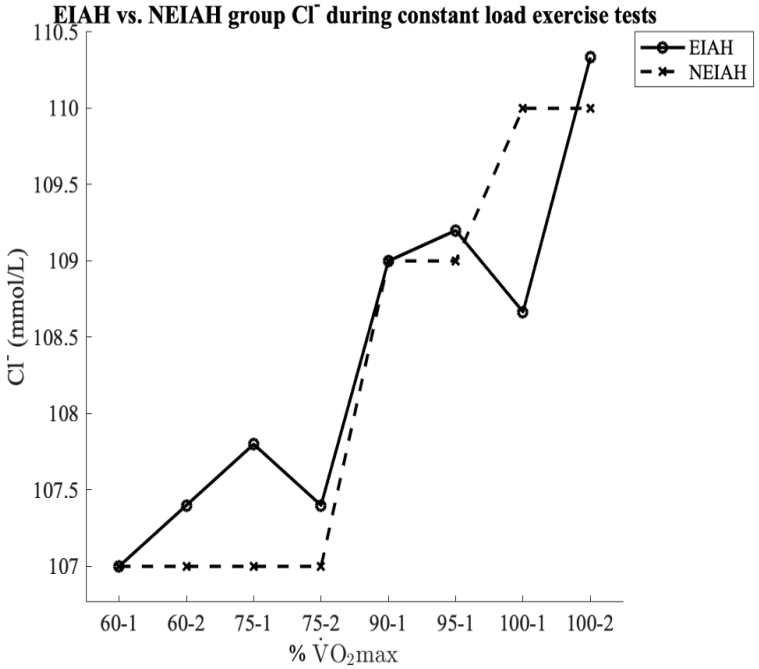
Maximal oxygen uptake ($\dot{V}O_2$max), dead space (VD), tidal volume (VT).

Figure 5– Electrolyte and metabolite data grouped into EIAH vs. NEIAH
n=6 for all except n=4 at 100%. Solid lines (-) represent EIAH group. Line with spaces (- -) represent NEIAH group.



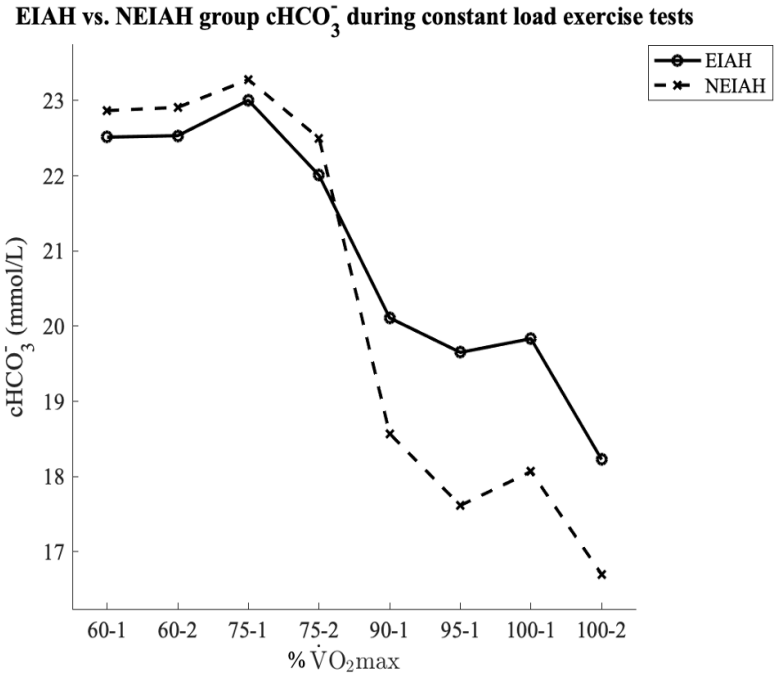


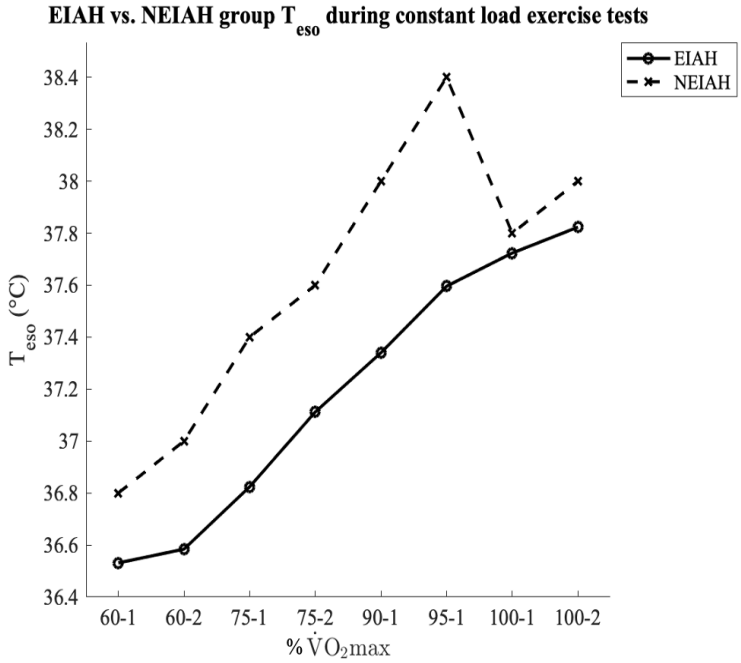


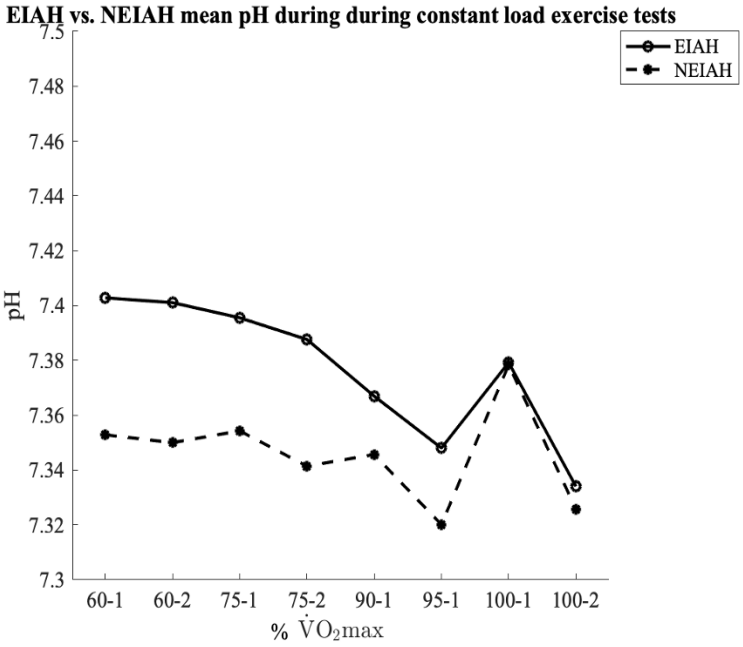


Maximal oxygen uptake ($\dot{V}O_2max$), sodium (Na^+), potassium (K^+), chloride (Cl^-), concentration of bicarbonate ($cHCO_3^-$).

Figure 6– Acid – base, esophageal temperature during constant load exercise test
n=6 for all except n=4 at 100% $\dot{V}O_2max$. Solid lines (-) represent EIAH group. Line with spaces (- -) represent NEIAH group.

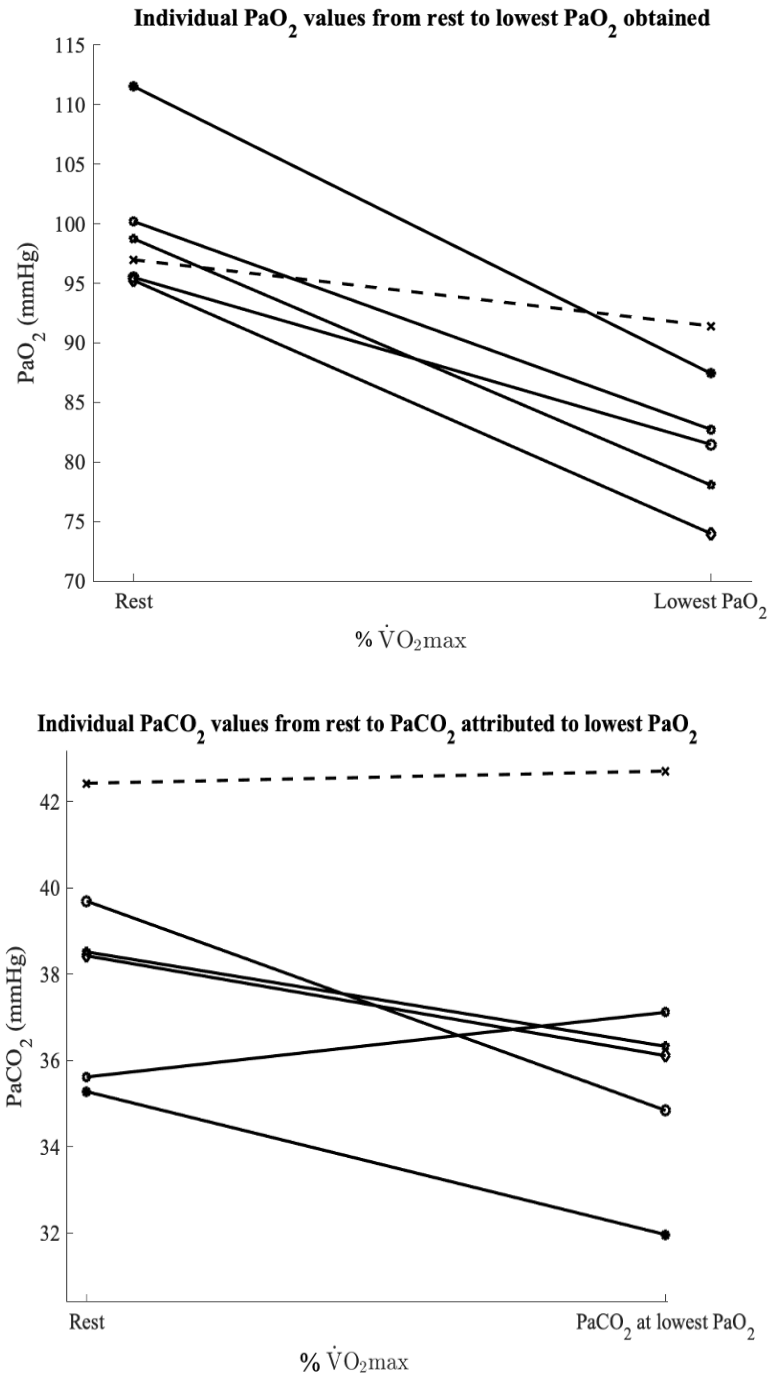






Maximal oxygen uptake ($\dot{V}O_2max$), concentration of bicarbonate ($cHCO_3^-$), esophageal temperature (T_{eso}), potential hydogren (pH).

Figure 7 – Individual PaO_2 and $PaCO_2$ values from rest to greatest decrease in PaO_2 with attributed $PaCO_2$

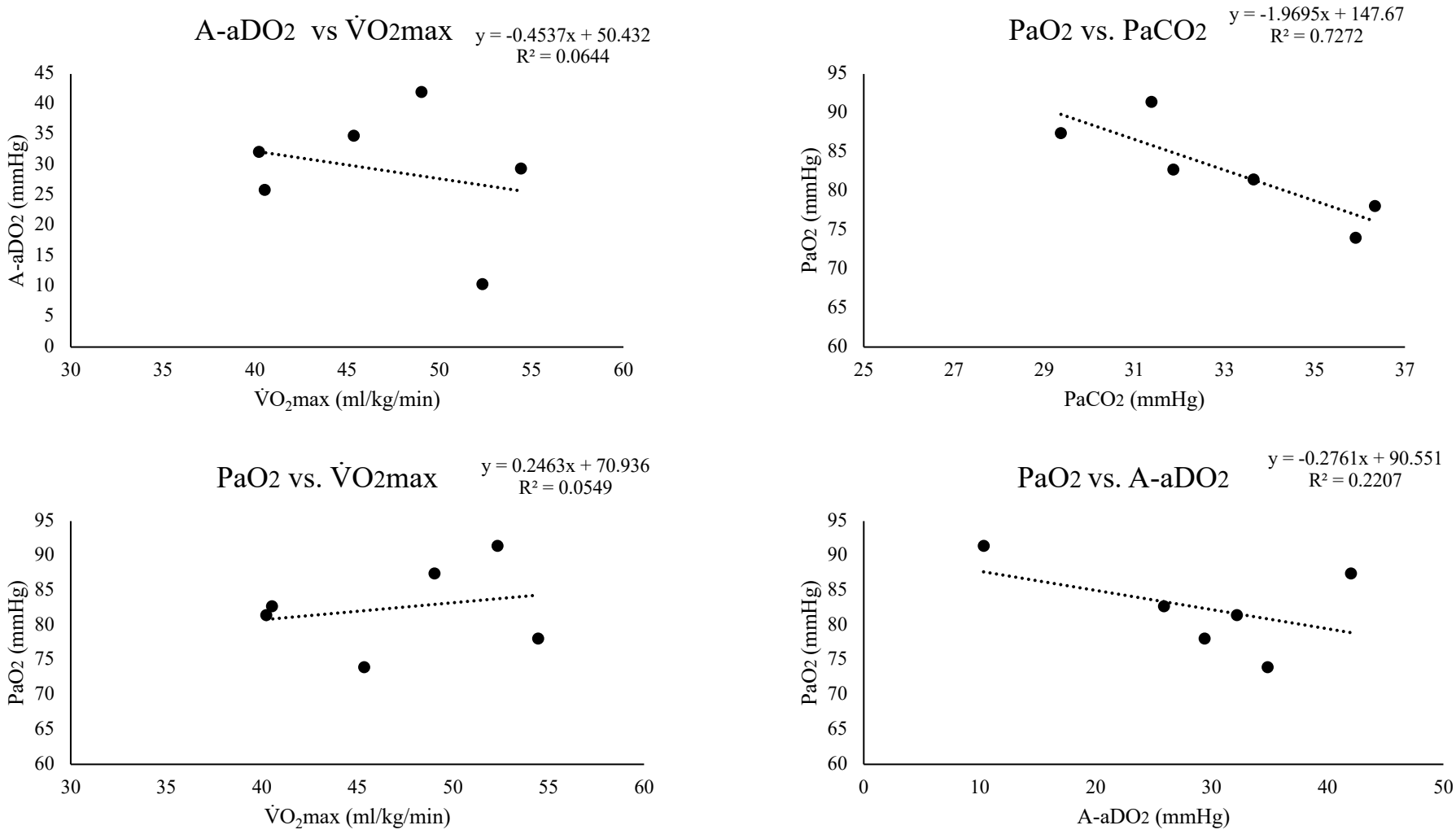


Maximal oxygen uptake ($\dot{V}O_2max$), partial pressure of oxygen in arterial blood (PaO_2), partial pressure of carbon dioxide in arterial blood ($PaCO_2$).

4.5 Relationships between blood gas variables

Figure 8 represents the relationships between blood gas variables. PaO_2 and $PaCO_2$ represent the lowest values achieved. A-aDO_2 represent the largest gradient achieved and $\dot{V}O_2$max was based on the results of Day 1. There was no relationship found between $\dot{V}O_2$max and PaO_2, A-aDO_2 and PaO_2, or $\dot{V}O_2$max and A-aDO_2. There was a relationship found with PaO_2 and $PaCO_2$ where higher a PaO_2 coincided with a lower $PaCO_2$.

Figure 8– Relationships between blood gas variables

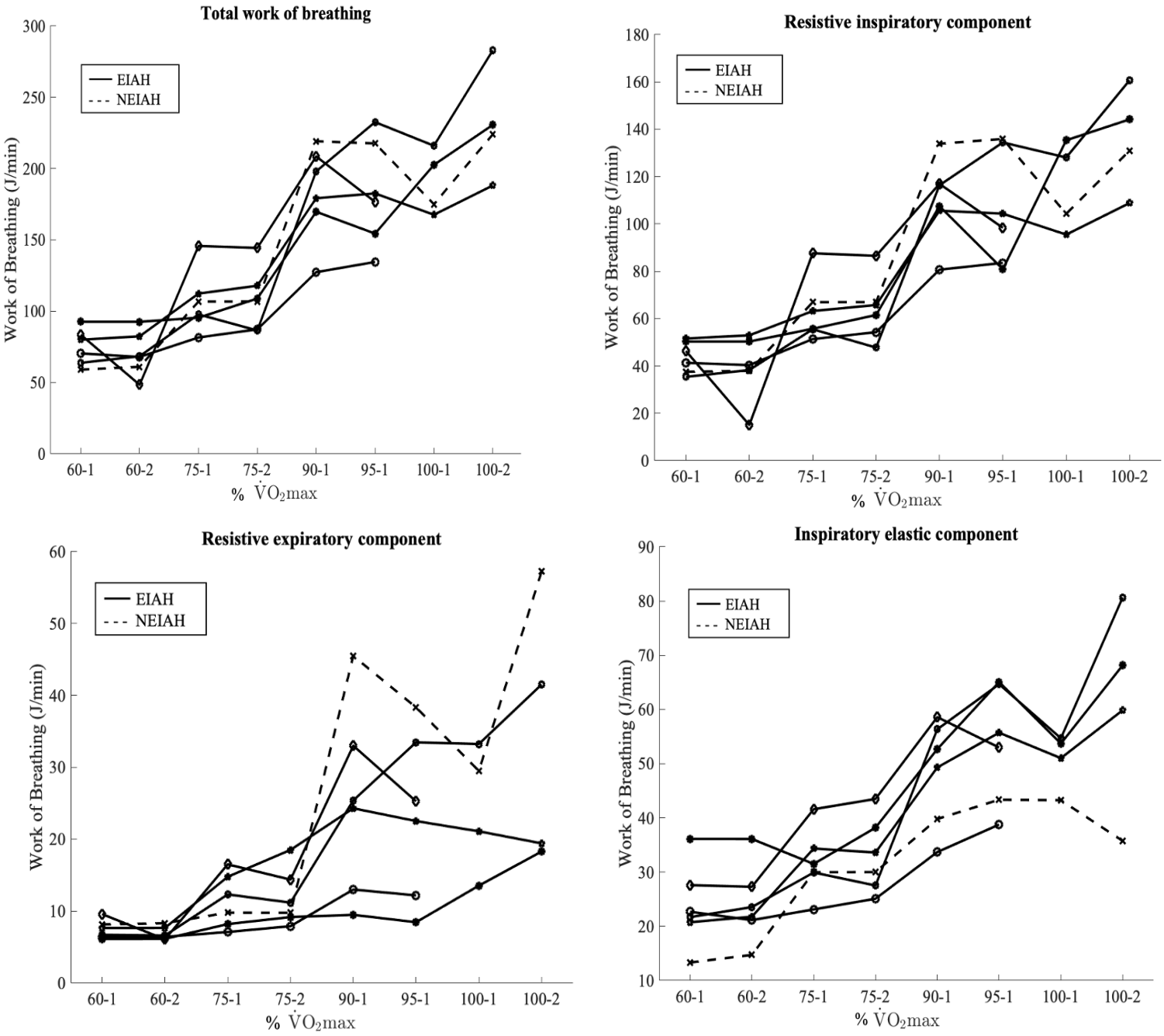


Maximal oxygen uptake ($\dot{V}O_2max$), partial pressure of oxygen in arterial blood (PaO_2), partial pressure of carbon dioxide in arterial blood ($PaCO_2$), Alveolar to arterial oxygen difference ($A\text{-}aDO_2$).

4.6 Work of breathing

Figure 9 represents the total WOB and its components: resistive inspiratory, resistive expiratory, and inspiratory elastic at all exercise intensities. The total WOB ranged from 48 to 144 J/min, 127 to 232 J/min, and 130 to 283 J/min at submaximal, near-maximal and maximal exercise levels, respectively. All components of total WOB increased with resistive inspiratory increasing the greatest.

Figure 9 – Work of breathing and its components
n=6 for all except n=4 at 100%. Solid lines (-) represent EIAH group. Line with spaces (- -) represent NEIAH group.



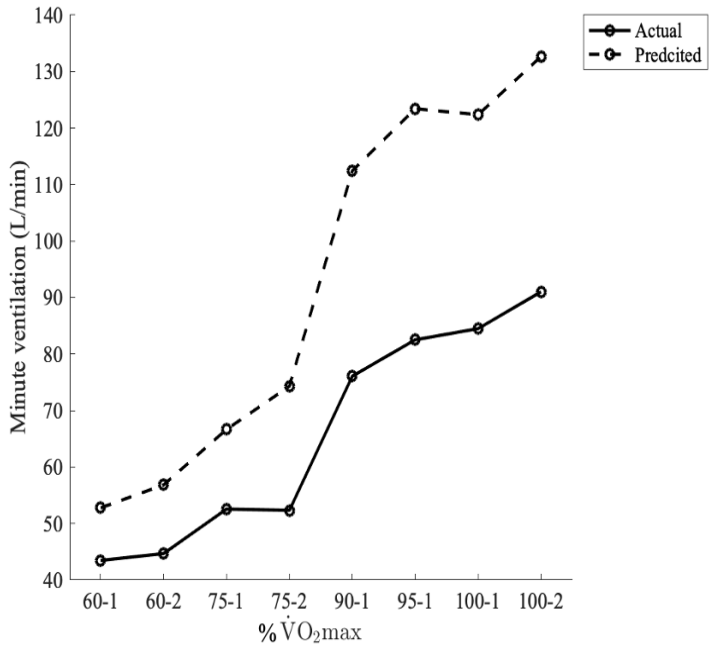
Maximal oxygen uptake ($\dot{V}O_2max$).

4.7 Predicted values to maintain resting PaO_2

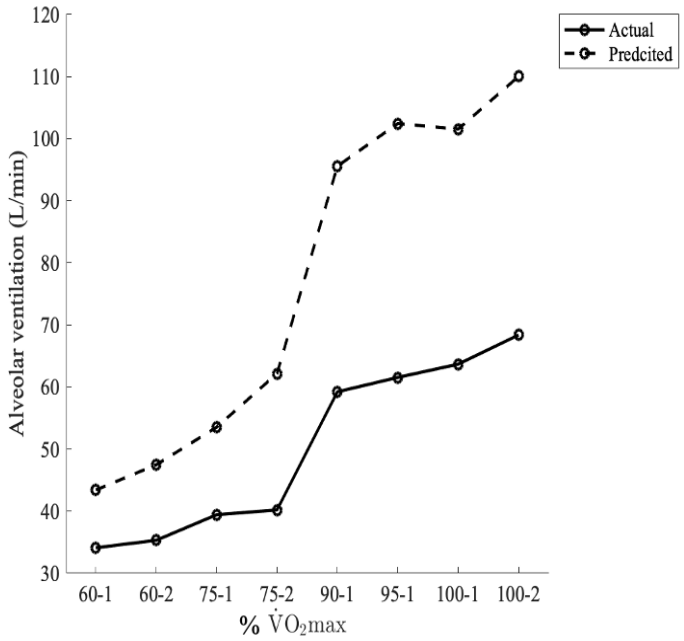
Figure 10 shows actual and predicted $\dot{V}E$, $\dot{V}A$, and $PaCO_2$ needed to maintain PaO_2 at rest. The mean $\dot{V}E$ (and thus $\dot{V}A$) predicted was Δ 14 L/min, Δ 39 L/min and Δ 40 L/min from actual $\dot{V}E$ (and $\dot{V}A$) at submaximal., near-maximal and maximal exercise levels, respectively. The mean $PaCO_2$ predicted was Δ 9 mmHg, Δ 12 mmHg, and Δ 9 mmHg at submaximal., near-maximal, and maximal exercise levels, respectively. Figure 11 shows the same data as Figure 10 however grouped into EIAH and NEIAH. Figure 13 shows actual and ideal (only for CaO_2) CaO_2 and SaO_2 and their change due to PaO_2, and temperature and pH.

Figure 10 – $\dot{V}E$, $\dot{V}A$ and $PaCO_2$ achieved and predicted to maintain PaO_2 at rest
Solid lines (-) represent actual values obtained. Line with spaces (- -) represent predicted values to maintain PaO_2 at rest.

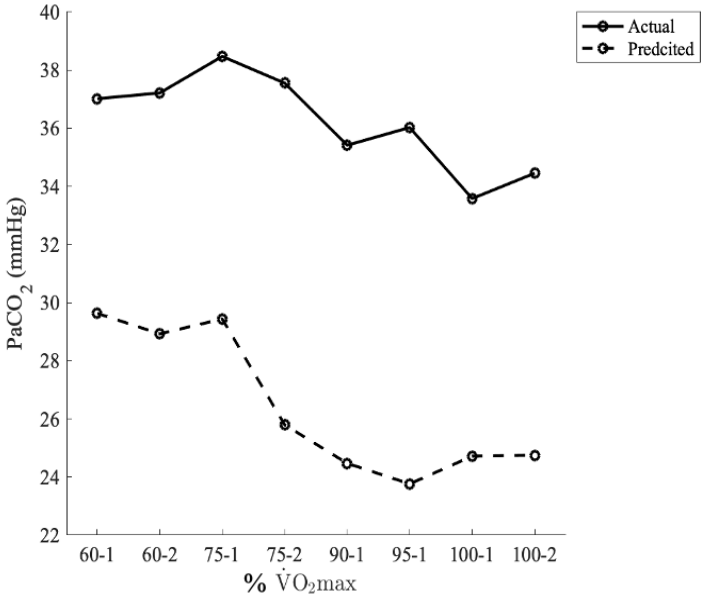
Mean $\dot{V}E$ and predicted $\dot{V}A$ to maintain resting PaO_2



Mean $\dot{V}A$ and predicted $\dot{V}A$ to maintain resting PaO_2

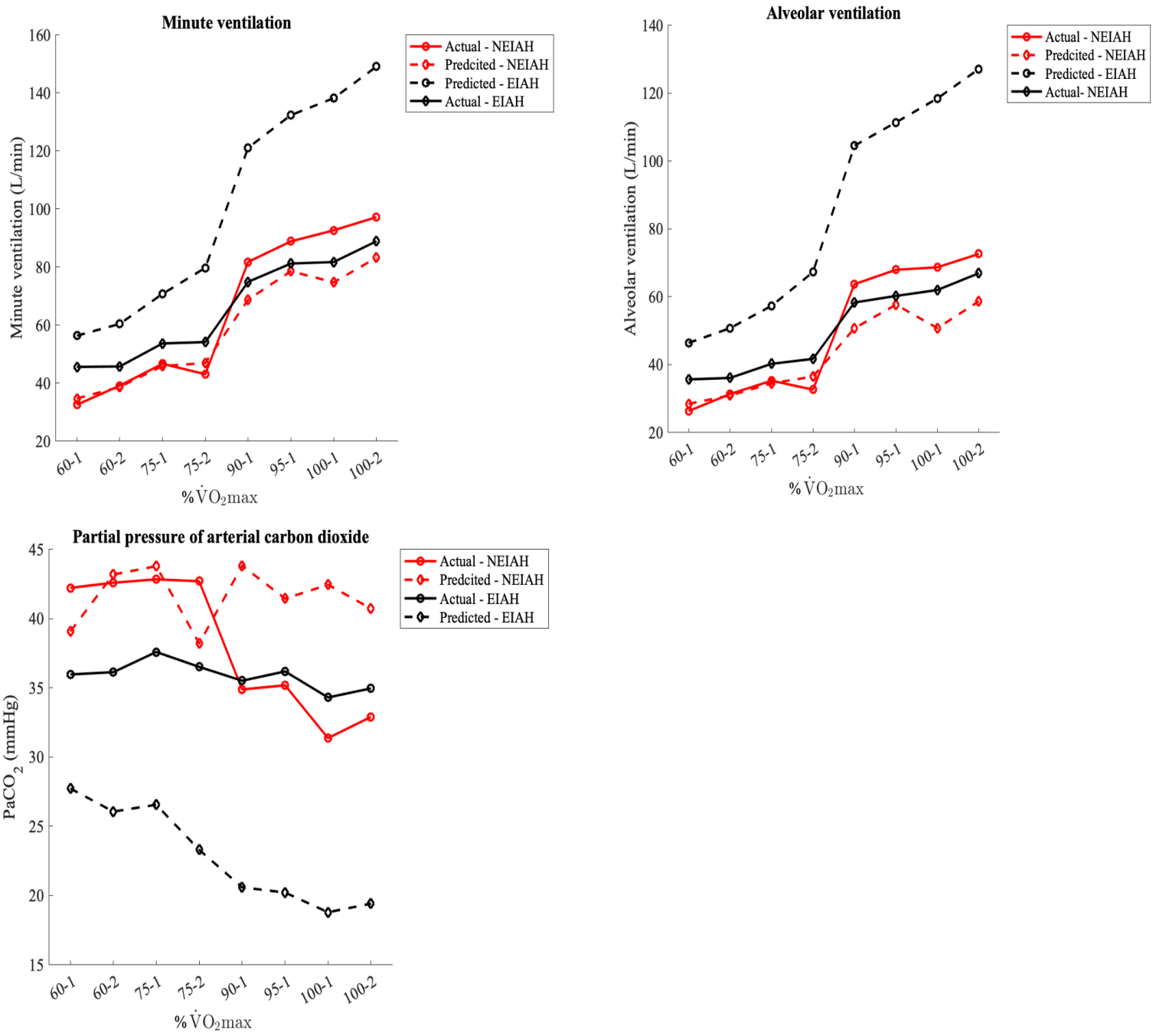


Mean $PaCO_2$ and predicted $PaCO_2$ to maintained resting $PaCO_2$



Maximal oxygen uptake ($\dot{V}O_2max$), partial pressure of carbon dioxide in arterial blood ($PaCO_2$).

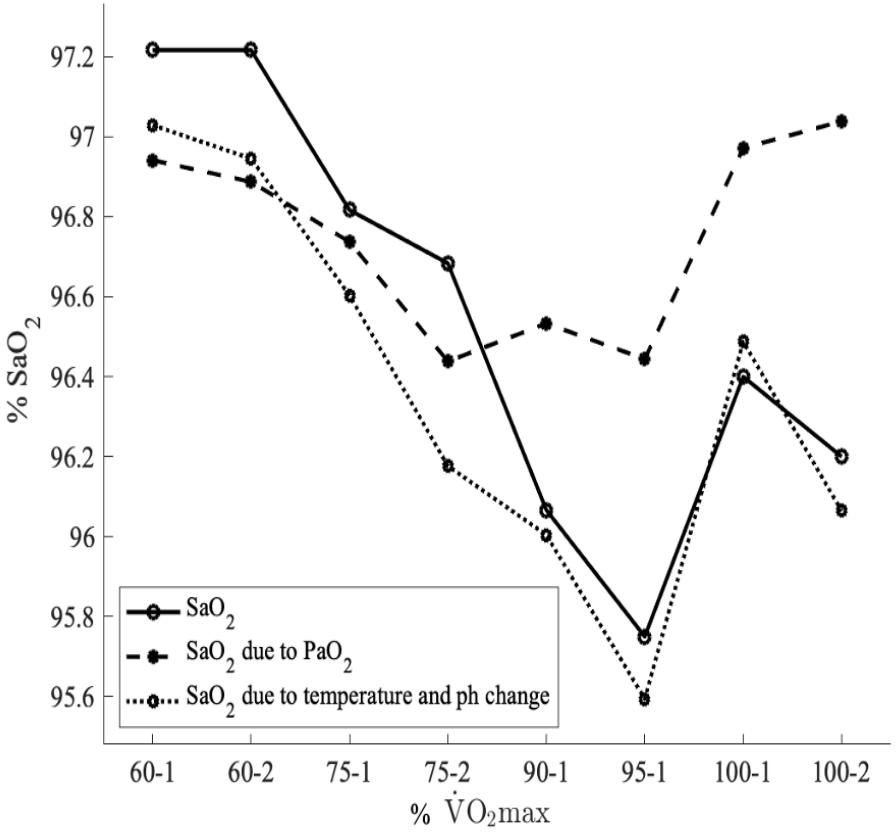
Figure 11 – $\dot{V}E$, $\dot{V}A$, and $PaCO_2$ achieved and predicted grouped into EIAH and NEIAH



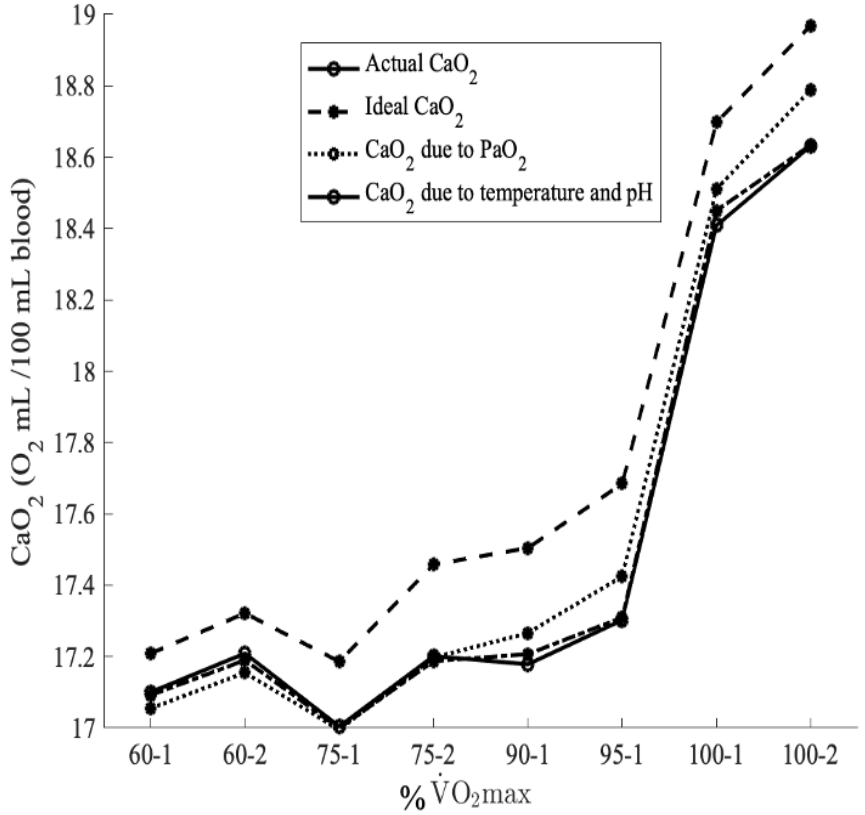
Solid red line (-) with open circle points represent actual values obtained for NEIAH. Red line with spaces (- -) and open circle points represent predicted values obtained for NEIAH group. Solid black line (-) with open circle points represent actual values obtained for EIAH group. Black line with spaces (--) and diamond points present predicted values to maintain PaO_2 at rest for EIAH group. Maximal oxygen uptake ($\dot{V}O_2max$), partial pressure of carbon dioxide in arterial blood ($PaCO_2$).

Figure 12 – SaO_2 and CaO_2 obtained, actual, due to a drop in PaO_2 and temperature, pH during constant load exercise tests

SaO_2, SaO_2 due to PaO_2, and SaO_2 due to temperature and pH change



Mean CaO_2, ideal CaO_2, CaO_2 due to PaO_2, and CaO_2 due to temperature and pH change

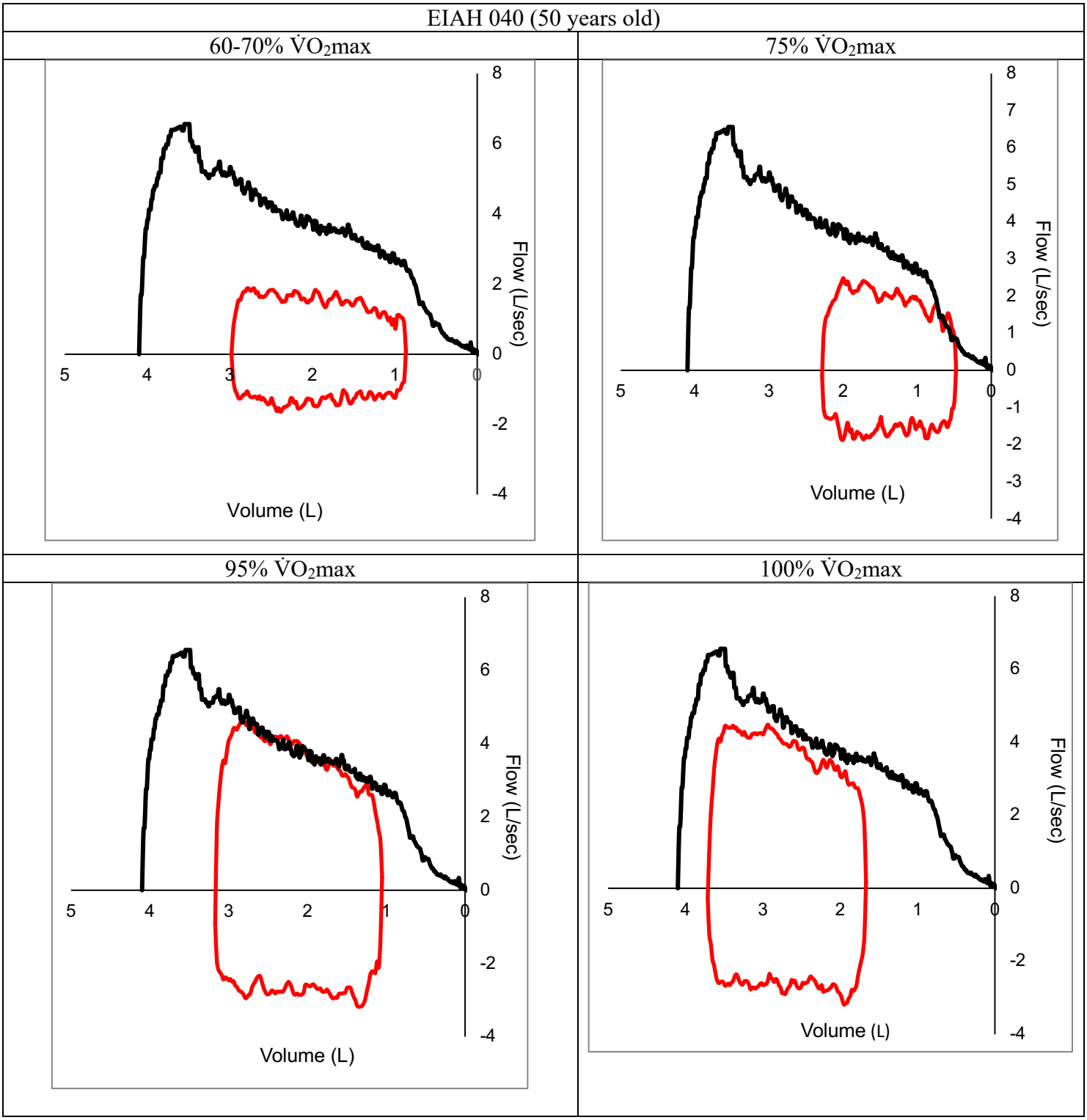


The line with spaces (--) and open circles represent actual CaO_2 obtained. The line with spaces (--) and closed circles represent ideal CaO_2 to maintain PaO_2 at rest. The dotted line (…) with open circles represent CaO_2 due to a change in PaO_2. The solid line (-) with open circles represent CaO_2 due to a change in temperature and pH. maximal oxygen uptake ($\dot{V}O_2max$), oxygen saturation (SaO_2), oxygen content of arterial blood (CaO_2).

4.8 Expiratory flow limitation

Figures 13,14, and 15 represent MFVC and FV loop at different exercise intensities for each participant. Figures 13 and 14 represent participants who experienced EIAH at all exercise intensities and encounter EFL at all exercise intensities. Figure 15 represents the participant who did not experience EIAH but develops EFL at 75% $\dot{V}O_2$max and onwards. All participants tended to breathe at higher lung volumes as exercise intensity increased.

Figure 13 – MFVC and FV loops at different exercise intensities

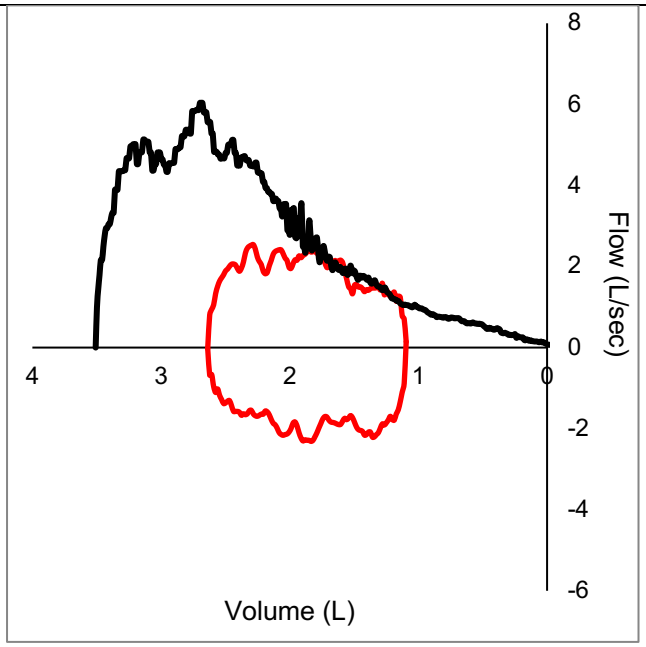


Black line represents maximal expiratory flow volume curve (MEFVC), red line represents tidal volume (TV)

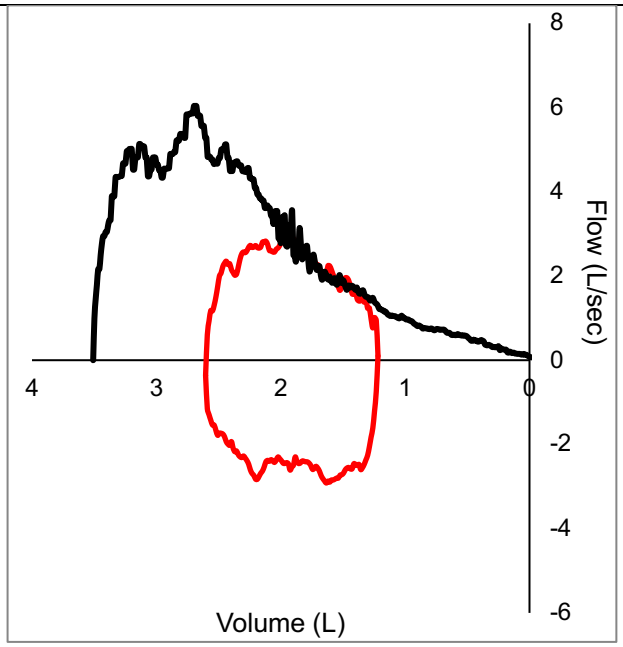
Figure 14 - MFVC and F-V loops at different exercise intensities

EIAH050 (53 years old)

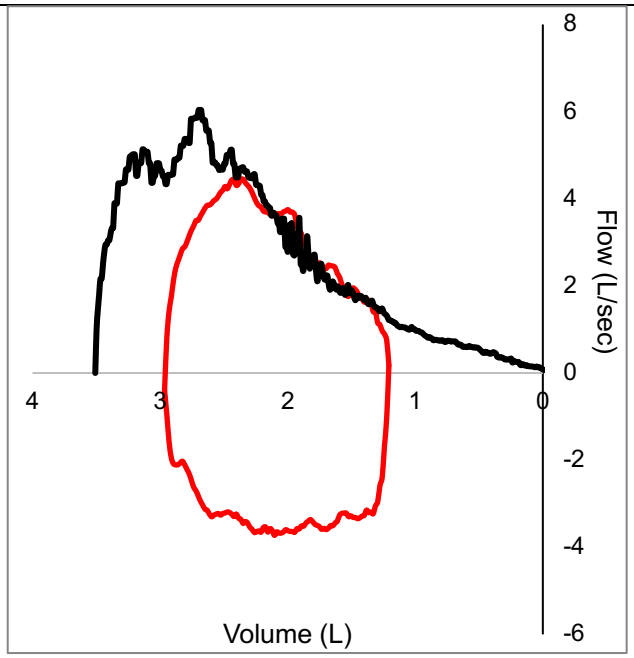
60-70% $\dot{V}O_2max$



75% $\dot{V}O_2max$

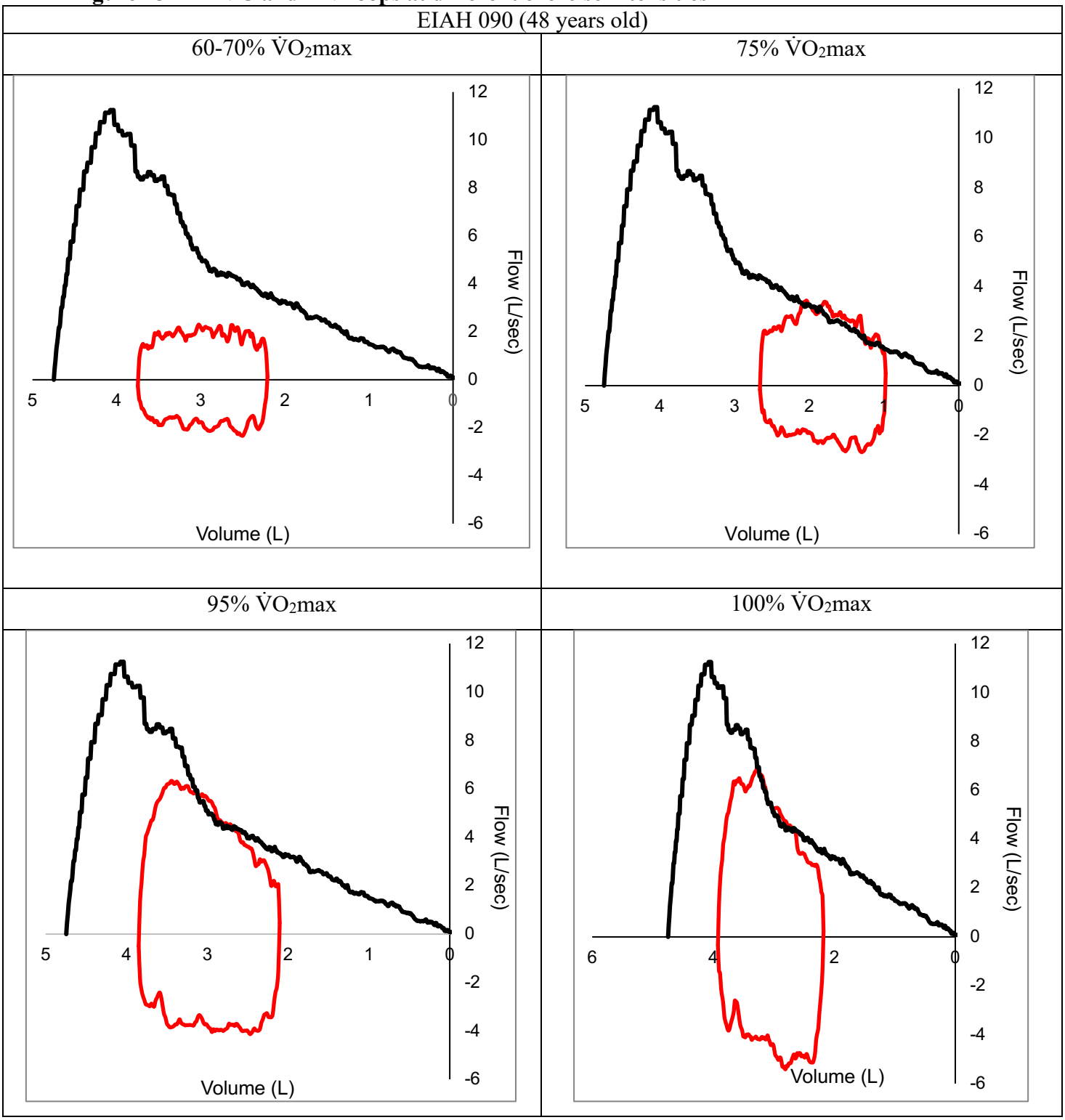


95% $\dot{V}O_2max$



Black line represents maximal expiratory flow volume curve (MEFVC), red line represents tidal volume (TV)

Figure 15 - MFVC and F-V loops at different exercise intensities



Black line represents maximal expiratory flow volume curve (MEFVC), red line represents tidal volume (TV)

Chapter 5: Discussion

The purpose of this thesis was to characterize EIAH in female masters athletes during submaximal, near-maximal, and maximal treadmill running exercise. It was hypothesized that female masters athletes would experience EIAH across all exercise intensities. The main findings are twofold.

First, female masters athletes experience EIAH during submaximal, near-maximal, and maximal exercise although there was between-subject variability with respect to the severity. A range of PaO_2 values along with a range of A-aDO_2 gradients were observed at each exercise intensity. There was a significant change in PaO_2 from rest to 60% and 75% $\dot{V}O_2$max ($p<0.05$). There was a small but significant change in % SaO_2 from rest to 75% and 95% $\dot{V}O_2$max ($p<0.05$), and minimal change in CaO_2 from rest. The participants who developed EIAH (n=5) appeared to have a minimal hyperventilatory response as indicated by the minimal reduction in $PaCO_2$ (- 2-6 mmHg from rest) ($p>0.05$) compared to the participant who did not develop EIAH (- 11.0 mmHg from rest).

Second, $\dot{V}O_2$max was not associated with the nadir PaO_2 ($r = 0.23$ $R^2 = 0.05$) suggesting that aerobic fitness is unrelated to the prevalence or severity of EIAH in female masters athletes. Healthy aging seems to play a role in the development of EIAH as there are lower ventilatory reserves and DLCO accompanied with an increase V_D to meet the demands of the metabolic system. Healthy older individuals show EFL at lower intensities and a higher O_2 cost of breathing relative to younger individuals (Johnson et al., 1991; Johnson et al.,1994). Thus, lower

alveolar hyperventilation, diffusion limitation and a higher O_2 cost of breathing may play a larger role in the mechanisms of EIAH in the aged athlete. The variability of age-related effects on the pulmonary system are an important consideration when characterizing EIAH as it will impact the susceptibility and mechanisms of EIAH.

5.1 Major findings

5.1.1 Inter-subject variability

During exercise, the PaO_2 is generally maintained close to resting levels and is accomplished with an appropriate ventilatory response. For the purpose of this study, EIAH was defined as a decrease in PaO_2 < 10 mmHg from rest (Dempsey & Wagner, 1999). Figure 2 shows individual data points for gas exchange variables during rest and exercise. At rest, most participants had a PaO_2 that was within the expected range (96-100 mmHg). One participant's resting PaO_2 (111 mmHg) can be considered high as there was evidence of hyperventilation ($\dot{V}E$ = 7.3 L/min; $PaCO_2$ = 35.3 mmHg). All participants completed the 60-70%, 75%, 90% and 95% $\dot{V}O_2max$ constant load exercise tests. During submaximal exercise stages (60-70% and 75% $\dot{V}O_2max$) a range of PaO_2 values were observed (74-108 mmHg). During heavy and near-maximal exercise (90% and 95% $\dot{V}O_2max$) a similar degree of inter-subject variability was observed (76-105 mmHg). A sub-sample of participants (n=4) ran at a velocity corresponding to 100% $\dot{V}O_2max$ and PaO_2 ranged from 78-107 mmHg. Between-subject variation in PaO_2 during submaximal and maximal exercise intensities have been reported previously (Dempsey et al., 1984; Rice et al., 1999; Harms et al., 2000; Dominelli et al, 2013). Figure 2 shows the % SaO_2 during exercise

with changes from rest to submaximal (95-98%), near maximal (94-97%) and maximal (95-98%) exercise. The individual A-aDO_2 gradients are shown in Figure 2 with a range during submaximal (4-35 mmHg), near maximal (8-41 mmHg) and maximal (7-42 mmHg) exercise intensities.

All but one participant (n=5/6) developed EIAH at moderate intensities which is consistent with previous reports in young trained female and male athletes (Dempsey et al., 1984; Harms et al., 1998; Rice et al., 1999) and male masters athletes (Préfaut el al., 1994). However, this is the first investigation to document EIAH in female masters athletes.

In a young healthy adult, the pulmonary system is ideally designed and regulated to maintain blood gas homeostasis even during heavy intensity exercise. The limiting factors in the O_2 transport and utilization chain lie in the cardiovascular and musculoskeletal systems. However, as one increases aerobic fitness level there is a training adaptation to the cardiovascular and musculoskeletal system but not to the pulmonary system. Thus, the capacity for gas exchange, chest wall and ventilatory control become the limiting factor to maximal O_2 consumption. The idea of the pulmonary system limiting homeostasis during exercise is termed the "Demand vs. Capacity" theory and may explain EIAH at maximal exercise (Dempsey et al., 1986). However, it does not explain the reduction in arterial oxygenation during submaximal exercise where the lungs still have the capacity to increase $\dot{V}A$ to meet metabolic demand and maintain blood gas homeostasis.

5.1.2 EIAH at submaximal exercise level

During submaximal exercise there were significant reductions in PaO_2 and pH which should have presumable stimulated the chemoreceptors to increase $\dot{V}E$. However, an appropriate hyperventilatory response to maintain blood gas homeostasis was absent.

During treadmill running there appears to be a greater gas exchange impairment relative to cycle exercise (Hopkins et al., 2000). The lower SaO_2 observed may be explained by a diffusion limitation or $\dot{V}A/\dot{Q}$ mismatch but not the differences in $\dot{V}E$ (Gavin & Stager, 1999). Gas exchange impairment is indicated through a widening of the A-aDO_2 gradient. There is some speculation that when there is a motion disturbance such as a foot strike it changes the P_{eso} and may cause small peripheral blood vessels and airways to occlude temporarily leading to a $\dot{V}A/\dot{Q}$ mismatch. (Johnson et al., 1992; Dominelli et al., 2013). EIAH at submaximal exercise may have been caused by a $\dot{V}A/\dot{Q}$ mismatch as there was a widening of the A-aDO_2 gradient in the current study.

As exercise intensity increases, more blood is diverted to the respiratory muscles and the cost of breathing increases. Developing EIAH at submaximal exercise may be a strategy to minimize the cost of breathing and become more economical as there is no negative impact on performance. The PaO_2 decreased significantly from rest to submaximal exercise however the SaO_2 remained constant until the last blood draw at 75% $\dot{V}O_2$max where it significantly decreased from rest. The CaO_2 did not drop significantly and even trended upwards due to hemoconcentration and likely an increase in red cell release from the spleen (Stewart et al., 2013). As such, and based on the

Fick equation one would predict that exercise performance would not have been negatively impacted as CaO_2 was maintained.

At submaximal intensities, EFL was present in 2 of 3 participants at 60% $\dot{V}O_2$max and 3 of 3 participants at 75% $\dot{V}O_2$max. A mechanical constraint could have been a factor to the development of EIAH as it is preventing the $\dot{V}E$ from increasing sufficiently to maintain PaO_2. Despite encountering EFL, one participant was able to $\dot{V}E$ appropriately to maintain resting PaO_2 values. The other participants who encountered EFL at submaximal would have needed to ventilate an extra 10-40 L/min (depending on % $\dot{V}O_2$max) to maintain PaO_2 values near resting.

5.1.3 NEIAH participant

It is recognized that little conclusion can be drawn based on the lone participant who did not develop EIAH. As such, only brief comment is provided. The participant had similar lung function values as the rest of the group except for a larger FVC and VC. The participant's $\dot{V}O_2$max (52 ml/kg/min) was higher than the average of the group (47 ml/kg/min). The $PaCO_2$ was maintained near rest (42 mmHg) at submaximal (42 mmHg) and then decreased at near-maximal (35mmHg) and maximal exercise (31 mmHg). The participant encountered EFL at all exercise intensities (except for 60% $\dot{V}O_2$max) and ventilated appropriately to maintain resting PaO_2 during submaximal exercise. However, at near maximal and maximal exercise the participant ventilated more than necessary by 10-13 L/min and 14-18L/min, respectively as evidence by PaO_2 surpassing that were greater than rest (+10 mmHg). There are inter-individual differences in the ventilatory response to hypercapnia (Schaefer, 1958). Previously, a significant

relationship between the ventilatory response to hypercapnia and SaO_2 was found; where those who had a lower ventilatory response to hypercapnia had a lower SaO_2 and thus a higher susceptibility to EIAH (Granger et al., 2020). The participant may have had a higher 'sensitivity' to hypercapnia and thus a greater ventilatory response to prevent EIAH. It is unclear as to why the participant did not experience EIAH as they experienced EFL and had a similar $\dot{V}O_2max$ as the other participants. The observations from this participant points towards the between-subject variability in the occurrence of EIAH and that other factors such as, the hyperventilatory response to hypercapnia may play a role in the development.

5.1.4 Aerobic fitness level and EIAH

It was hypothesized that aerobic fitness level would be related to the severity of EIAH which is consistent with previous observations (Dempsey et al., 1984) and that highly trained female athletes develop EIAH at a higher severity than untrained females (Dominelli et al., 2013). However, no significant correlation between aerobic fitness level ($\dot{V}O_2max$) and nadir PaO_2 achieved was observed ($r= 0.23$, $R^2= 0.05$, $p>0.05$). When interpreting these findings, it is important to note the range of $\dot{V}O_2max$ (40-55 ml/kg/min) in the athletic population studied was relatively small compared to the general population.

No relationship between $\dot{V}O_2max$ and $A\text{-}aDO_2$ was found ($r = -0.25$ $R^2 = 0.06$ $p>0.05$) and thus other factors other than aerobic fitness may point towards gas exchange impairment in female masters athletes. A relationship found was that those with a higher PaO_2 had a lower $PaCO_2$ (r =

-0.85, $R^2 = 0.73$, $p<0.05$). A lower $PaCO_2$ corresponds to higher levels of $\dot{V}E$ occurring to achieve blood gas homeostasis.

5.1.5 Comparison to men

The current study did not measure EIAH in male masters athletes, thus comparisons will be made based upon previous studies with male masters athletes. Préfaut et al., (1994) measured arterial blood gasses during exercise in male masters athletes who were older (65.3±2.6 years) and less aerobically fit ($\dot{V}O_2max$; 37.8±2.1 mL/kg/min) compared to the current study (age: 51 years, $\dot{V}O_2max$: 47 ml/kg/min). Despite the differences, the reduction in PaO_2 (10-24 mmHg) was comparable to that seen in the present study (see Figure 2 & 3). The $\dot{V}E$ was lower in male masters athletes compared to the female masters athletes in the present study. The $PaCO_2$ significantly increased from rest in the male masters athletes but did not change significantly in the current study. The absence of a decrease in $PaCO_2$ in both Préfaut et al., (1994) and the current study suggest no hyperventilation occurred in male and female masters athletes.

Although the pulmonary function values of the current study were greater than the participants of Préfaut et al. (1994), the PaO_2 still decreased to the same degree. The lungs and larger conducting airways are smaller in women than in men (Martin et al., 1987;Ripoll et al., 2020; Sheel et al., 2009), lower maximum expiratory flow and a reduced MVFC (Knudson et al., 1983) may have caused the PaO_2 to decrease similarly despite the age difference in the current study and Prefaut et al. (1994). We could speculate that diffusion limitation plays a larger role in the development of EIAH in female masters athletes compared to their male counterpart as there is a reduction in DLCO. There is an increase in oxygen cost of breathing that is theorized to divert blood from working muscles to the respiratory muscles which may have increased susceptibility

of EIAH for female masters athletes. A limitation of Préfaut et al. (1994) work is that they did not correct blood gases to *in vivo* temperature which likely resulted in overestimation of PaO_2 values. Thus, if they were corrected to *in vivo* temperature, female masters athletes may have had a greater reduction in PaO_2. Préfaut et al. (1994) described EIAH occurring in two distinct patterns. The first pattern was an isolated decrease in PaO_2 during light intensity exercise. The second pattern was a decrease in PaO_2 associated with a widening of the A-aDO_2 at heavy intensity exercise. The patterns are similar to the current study where the isolated decrease in PaO_2 may be related to alveolar hypoventilation during submaximal exercise. The A-aDO_2 widening may have been related to a diffusion limitation, $\dot{V}A/\dot{Q}$ mismatch, and/or shunt during near-maximal, and maximal exercise (Gale et a., 1985; Torre-Bueno et al., 1985; Wagner et al., 1986; Hopkins et al., 1994).

There are adaptations to the cardiovascular and musculoskeletal systems with aerobic exercise training, however there are little to none in the respiratory system (Saltin et al., 1973). Thus, with intensive aerobic training, the respiratory system can become the limiting factor to blood gas homeostasis. (Dempsey et al., 1984, Johnson et al., 1992). In young endurance-trained males, this occurs at high levels of $\dot{V}O_2max$ (65 ml/kg/min) and has not been reported in untrained males. Trained and untrained females have been shown to develop EIAH, relating to the substantially lower capacities of the lung and thus becoming the limiting factor at a lower fitness level. When healthy aging is combined with the increased capacities of the cardiovascular and musculoskeletal system from exercise training, the pulmonary system may be limited at even lower fitness levels in female masters athletes. Based on the participants of the current study 86% of female masters athletes experienced EIAH at light and heavy exercise intensities. The

occurrence is higher than previously reported in young trained and untrained females (60-75%) (Dominelli, 2012).

5.1.6 Comparison to young women

The effects of healthy aging on the lung and chest wall are variable (Johnson & Dempsey, 1991) but it is generally accepted that the pulmonary system ages at a similar rate as the cardiovascular system and metabolic demand. Thus, even with lower ventilatory reserves than their younger counterparts they are able to maintain blood gas homeostasis. However, when the older adult trains there are adaptations to the cardiovascular and skeletal systems, causing larger reserves to meet metabolic demand, however not in the pulmonary system. Thus, there is variability in the capacity of the different physiological systems as there is a greater stimulus on the cardiovascular-skeletal muscle component compared to the lungs (Johnson & Dempsey, 1991). The current study's average resting PaO_2 and $PaCO_2$ were 100 mmHg and 38 mmHg respectively. These values are similar to young females (Dominelli et al., 2013) although there have been reports of a decreased resting PaO_2 in older adults (Johnson & Dempsey, 1991). A larger decrease in PaO_2 from rest was seen in the current study's older female athletes compared to young females (Dominelli et al., 2013), relating to the effects of healthy aging. A similar observation was seen when comparing young and old male athletes (Johnson & Dempsey, 1991; Préfaut et al., 1994). The A-aDO_2 widening of the current study was similar compared to the young females but remained slightly wider. It is important to note the average $\dot{V}O_2$max (47 ml/kg/min) of the participants in the current study is similar to a previous study of young females (48 ml/kg/min) (Dominelli et al., 2013). An important discrepancy between the young and old female athletes were the $\dot{V}E$ and $\dot{V}A$. During exercise the average $\dot{V}E$ and $\dot{V}A$ for the current study ranged from 43-91 L/min and 36-69 L/min, respectively. Whereas in young female athletes

the $\dot{V}E$ and $\dot{V}A$ were 58-115 L/min and 54-93 L/min (Dominelli et al., 2013). The large difference between the $\dot{V}E$ and $\dot{V}A$ are due to the increase in dead space ventilation that occurs with aging (Johnson & Dempsey, 1991). V_D increases due to the increased diameter of large airways and over ventilated area (Tenney & Miller, 1956; Raine & Bishop, 1963). With aging, dead space ventilation increases and approaches ~30% of $\dot{V}E$ whereas in young athletes it is ~13% of $\dot{V}E$ (Johnson et al., 1994). The V_D/VT ratio is a good indicator of the how much dead space is affecting $\dot{V}E$. At rest the average V_D/VT ratio was 0.58 and decreased to 0.23 at submaximal exercise with a slight increase during higher intensities. The V_D/VT ratios measured are similar to previous work done on healthy fit older males (Johnson et al, 1994). With an increase in dead space ventilation, there is a decrease in alveolar ventilation for a given $\dot{V}E$. Thus, the increase in V_D may play an important factor towards the development of EIAH in the aged athlete compared to the young athlete.

Like the young adult, the majority of blood flow is directed to the base of the lung however, blood flow to the apex of the lung is higher in older adults leading to a larger $\dot{V}A/\dot{Q}$ mismatch (Johnson & Dempsey, 1991). Thus, $\dot{V}A/\dot{Q}$ mismatch could be playing a larger role in the development of EIAH with older athletes.

The WOB during exercise varied on average from 48-146 J/min at submaximal, 127-233 J/min at near maximal, and 130-283 J/min at maximal exercise levels. Similar WOB values were seen in young females at submaximal exercise, however at maximal exercise, the young females were reaching approximately ~300 J/min. (Dominelli et al., 2013). The lowered WOB could be due be due to a lower $\dot{V}E$ in female masters athletes as they reached an average $\dot{V}E$ of 91 L/min and the

young females reached 115 L/min (Dominelli et al., 2013). When looking at $\dot{V}A$ at maximal exercise, the young athletes had an average of 76 L/min (Dominelli et al., 2013) whereas the older athletes were at 69 L/min relating to the amount of dead space ventilation occurring from aging.

Despite a decrease in ventilatory reserves, the older adult can usually reach appropriate $\dot{V}E$ for metabolic demand. They do so by increasing EELV during exercise to avoid EFL thereby sacrificing inspiratory muscle length and increasing the WOB (Johnson et al., 1991). As well as greater bronchodilation during exercise (Johnson & Dempsey, 1991). The older athlete experiences the same degree of EFL but at a lower $\dot{V}O_2max$ and $\dot{V}E$ where most young athletes only encounter EFL at 150-160 L/min (Johnson et al.,1994). The participants in the current study experienced EIAH and EFL at submaximal levels where $\dot{V}E$ was as low as 40 L/min. This is comparable with older male masters athletes who encountered EFL and EIAH at lower $\dot{V}O_2max$ than their younger counterpart (Johnson & Dempsey, 1991; Préfaut et al., 1994).

5.2 Methodological considerations

5.2.1 Menstrual cycle

Menopause occurs at ~51 years old (McKinlay et al., 1972) which is near the age of the current study's participants (48 to 57 years). However, it is important to note the time frame of menopause occurrence is variable and many factors influence it (Gold, 2011). We recorded if the participants were regularly menstruating (including current phase), or if menopause occurred. Four participants were still menstruating regularly and two were post-menopausal. No analysis was conducted on whether there was a relationship between the presence or absence of the

menstrual cycle, or phase, and EIAH. MacNutt et al. (2012) studied resting and exercise ventilatory response and chemosensitivity across the different phases of the menstrual cycle. Submaximal exercise ventilation and sensitivity to CO_2 was not affected by the menstrual cycle phase (MacNutt et al., 2012). Thus, if the menstrual cycle was present, testing occurred at random points of the menstrual cycle. When comparing pre- and post-menopausal women there is a significant difference between pulmonary function (FEV1.0 and FVC) when compared at % of predicted values (Memoalia et al., 2018). Central and peripheral chemoreflex drives to breathe were evaluated in similar aged pre- and post- menopausal women (Preston et al., 2008). Postmenopausal women had a reduced central chemoreflex drive to breathe and was associated with decreased concentration of female sex steroid hormone resulting in an increased resting $PaCO_2$ (Preston et al., 2008). This led to alveolar hypoventilation in post-menopausal women which may have played a role in the development of EIAH. Others have shown the HVR during exercise to be similar between pre- and post- menopausal women and the differences were more related to aging (Richalet et al., 2020).

5.2.2 Expiratory flow limitation

The original proposal for the current study did not include measuring EFL. However, during testing we decided to measure EFL as it would give better insight on possible mechanisms of EIAH. 3 of 6 participants were measured for EFL during exercise. When measuring EFL, MFVCs are usually recorded at the mouth which do not account for thoracic gas compression. When comparing a MFVC created from the mouth recording to body plethysmography the volumes were larger and thus the related flows were lower (Ingram & Schilder, 1966b). During exercise, bronchodilation occurs which will increase maximal expiratory flows at 50% of VC

and thus underestimate the flow during exercise (Johnson et al., 1992). If using pre-exercise MFVC, there is an underestimation of flow which will have implications of overestimating EFL. Performing multiple IC maneuvers at different efforts from TLC to residual volume (RV) postexercise has been recommended to account for thoracic gas compression and bronchodilation (Guenette et al., 2010). In the current study pre-exercise MFVC was not measured and thus post-exercise MFVC were used, accounting for thoracic gas compression and bronchodilation. Without pre-exercise MFVC it is not possible to distinguish the effect of thoracic gas compression and bronchodilation on EFL. We followed the recommendation of performing IC and FVC maneuvers in the same position as a change in position can alter flow (Haas et al., 1982; Banzett et al., 1988).

5.2.3 Work of breathing

The WOB was calculated using PV loops and separating the area into its components: elastic inspiratory, resistive inspiratory and total expiratory work. To minimize error, 8-12 consistent breaths were chosen to create the PV loops. The total compliance was derived however, not separated into its components: lung and chest wall. It is difficult to separate total compliance because of the invasiveness required to measure chest wall compliance. Another method to calculate WOB is by creating Campbell diagrams. However, this method relies on an accurate determination of operation lung volumes such as functional residual volume (FRC) and a regression equation to predict chest wall compliance (Estenne et al., 1985). By using either method (PV loops or Campbell diagrams) it is assumed that all appreciable work is reflected in the oesophageal pressure changes and that the chest wall and abdomen don't move abnormally. It is also assumed that the change in total volume occurs in a consistent manner between the

abdomen and thorax. However, with increasing intensity, the abdomen can account for a great proportion of volume change (Grimby et al., 1968). These assumptions are generally accepted at rest but during exercise it underestimates the WOB (Goldman et al., 1976). When abdominal wall stabilization and chest wall distortion work are considered, the total WOB can be up to 25% greater compared to the WOB calculated using Campbell diagrams (Goldman et al., 1976). It is important to note the difficulty in determining the contribution of abdominal wall stabilization and chest wall distortion. Chest wall distortion is greater in the older adult and thus the WOB calculations may be underestimated (Johnson & Dempsey, 1991).

5.2.4 $\dot{V}O_2$max and $\dot{V}O_2$peak

The current study did not perform a $\dot{V}O_2$max verification phase post incremental exercise test on a treadmill. However, the recorded values of RER (range 1.0-1.1), $\dot{V}E$ (range 92-106 L/min) and $P_{ET}CO_2$ (25-35 mmHg) reflect maximal work. The data collected on Day 1 were used to determine velocities at different % $\dot{V}O_2$max for Day 2. The $\dot{V}O_2$ recorded during the maximal constant load exercise test were within 5% of the predicted value with only 1 participant going over their calculated $\dot{V}O_2$max by 2%. Therefore, the $\dot{V}O_2$max test from Day 1 can be considered the participant's maximal oxygen consumption. Dalleck et al. (2012) used a verification phase of 105% peak work rate to determine if a 'true' $\dot{V}O_2$max was reached during incremental exercise testing in older fit adults. The $\dot{V}O_2$max did not differ between the incremental and verification phase. Well trained endurance athletes performed an incremental treadmill test and a verification phase 30% higher than the incremental phase (Hawkins et al., 2007). There was no difference found between the incremental and verification phase $\dot{V}O_2$max (Hawkins et al., 2007). Thus, the

verification phase may not be necessary in well trained athletes as they are comfortable performing higher intensity exercise and working near their exercise limits.

5.2.5 Temperature

The change in blood temperature will have an effect on gas tension as per the shift in the ODC. The blood gas analyzer assumed a blood temperature of 37°C. The blood gas values were temperature corrected to *in vivo* temperature (Severinghaus, 1966). The placement of the oesophageal temperature probe was based on the participant's height and aimed to be between the aorta and right ventricle (equivalent to the 8^{th} and 9^{th} thoracic vertebrae) (Mekjavic et al., 1990) as this was considered the optimal site for oesophageal temperature measurement (Kistin et al., 1950; Snell, 1973). Pulmonary artery temperature is a good reflection of core temperature however, it is an invasive procedure and associated with a high risk. Alternative temperature measurement sites that are less invasive include: oesophageal, rectal, peripheral arterial, and intramuscular. Peripheral arterial and intramuscular temperature are not ideal as they do not represent the temperature of the lungs and thus serve little purpose for the current study. We chose oesophageal temperature as it best reflects pulmonary artery temperature compared to other measures (Robinson et al., 1998; Lefrant et al., 2003).

5.3 Methodological improvements

5.3.1 Constant load exercise test time

The constant load exercise tests were 4 minutes in duration at submaximal and near-maximal exercise intensities, and 2 minutes at maximal exercise intensity. When no lactic acidosis is present the $\dot{V}O_2$ and $\dot{V}CO_2$ will reach steady state by 3 and 4 minutes, respectively (Wasserman

et al., 2011). Thus, at submaximal exercise intensity it is estimated that the participants were at steady state. However, with near-maximal and maximal exercise intensity it is not clear. There was variability between the 3rd and 4th minute blood gas values and thus difficult to determine if they were at steady state. The aging athlete takes longer to achieve steady state compared to the young athlete; increasing the uncertainty of 4 minutes being enough to achieve steady state. The participants completed a health questionnaire and PAR-Q + form to ensure general good health. Thus, the participants can be considered healthy and the variation in PaO_2 observed during constant load exercise test is unlikely to be related to disease. A methodological improvement would be to increase the length of stages and have both blood samples comparable to each other. At maximal, a minimal warm up (1-2 minutes) prior to increasing the velocity to 100% $\dot{V}O_2max$ may have helped better estimate the metabolic and blood gas values at maximal.

Chapter 6: Unresolved questions and future direction

6.1 EIAH in healthy untrained humans

It was previously thought that only highly trained endurance male trained athletes with a high $\dot{V}O_2$max (65ml/kg/min) could experience EIAH (Dempsey et al., 1984), however untrained females have also been shown to develop it (Harms et al., 1998; Dominelli et al., 2013). Future studies of EIAH on a wider range of $\dot{V}O_2$max values would be beneficial to establish reference standards of EIAH occurrence. These reference standards will help understand to what degree aerobic exercise training influences the development of EIAH. Is EIAH occurring due to exercise training, differences in physiology, or a combination of both?

6.2 Menstrual cycle

The menstrual cycle has been shown to affect the ventilatory response (Lebrun, 1993), hemoglobin, and Hct concentrations (Vellar, 1974). The changes to the ventilatory response and concentration of hemoglobin may have an impact on the severity of EIAH. It has been shown that DLCO significantly varies during the menstrual cycle where the highest value occurs prior to menses, and lowest during the third day of menses (Sansores et al., 1995). DLCO varies even with no significant changes in hemoglobin or pulmonary capillary blood volume (Sansores et al., 1995). The variation in DLCO could have an impact on diffusion, and thus respiratory gas exchange. The $\dot{V}O_2$ kinetic response, maximal lactate at steady state, and time to exhaustion during a $\dot{V}O_2$max test was not affected by the menstrual or oral contraceptive cycle (Mattu et al., 2020). Thus, there may not be a difference in prevalence of EIAH during the different stages of the menstrual cycle.

6.3 Cycle ergometer versus treadmill exercise

Reductions in PaO_2 have been reported to vary depending on the modality of exercise. During maximal exercise, the PaO_2 was consistently higher during cycling compared to treadmill exercise even under the same conditions of O_2 uptake (Hopkins et al., 2000). The $\dot{V}E$ and thus $\dot{V}A$ were higher during cycling compared to running, resulting in a lower $PaCO_2$ and higher PaO_2 (Hopkins et al., 2000). The reduction in PaO_2 may be due to hypoventilation during treadmill running. The A-aDO_2 was wider during treadmill running pointing towards possible gas exchange inefficiency. It has been speculated that a diffusion limitation could account for the differences in PaO_2 from a lower capillary blood volume as the cardiac output was slightly lower in running (Hopkins et al., 2000). A $\dot{V}A/\dot{Q}$ mismatch may have caused a wider A-aDO_2 as the EELV during running is elevated compared to cycling. The above study was conducted in female athletes and a similar conclusion in male athletes using pulse oximetry was found (Gavin & Stager, 1999).

A reduced PaO_2 and a wider A-aDO_2 during treadmill exercise may be due to the differences in EFL. EFL causes non-uniformity in $\dot{V}E$ distribution by increasing intra thoracic pressure and thus compressing small airways (Johnson et al, 1992). Running consistently causes transient pressure changes. Miller et al. (2007) have shown that these intra-thoracic pressure changes can affect central hemodynamics by reducing cardiac output and hindlimb blood flow. Tolerating EIAH may be a strategy to minimize potential negative consequences of increasing WOB and hyperpnea.

The mean V_D/VT ratio was 0.23 at submaximal, and slightly increased at heavier intensities. The V_D/VT ratios appear higher than in young female athletes. It has been shown that the V_D/VT

ratio is lower during cycling compared to treadmill running (Hopkins et al., 2000), relating to a more efficient $\dot{V}E$. The difference in the V_D/VT ratio during treadmill and cycle exercise might be emphasized in female masters athletes as it increases with aging. The increase V_D/VT ratio may be contributing to a reduced PaO_2 and wider $A\text{-}aDO_2$ during treadmill exercise.

6.4 Multiple inert gas elimination technique for $\dot{V}A/\dot{Q}$ mismatch

The multiple inert gas elimination technique is a method used to quantify interregional distribution of $\dot{V}A/\dot{Q}$. There is a greater $\dot{V}A/\dot{Q}$ mismatch in older compared to younger adults (Wagner et al., 1974) which may relate to the non-preferential $\dot{V}E$ at lower regions of the lung as there is airway narrowing or closures (Edelman et al., 1968). However, the majority of the blood is still going to the lower regions of the lung (Edelman et al., 1968) leading to a $\dot{V}A/\dot{Q}$ mismatch. The capillary surface area and DLCO decrease with aging (Horvath & Borgia, 1984; Crapo et al., 1982, Farney et al., 1977) thus leading to a greater vulnerability to $\dot{V}A/\dot{Q}$ mismatch. There is an increase in V_D attributed to an increase in larger airways and overventilated areas (Raine & Bishop, 1963; Tenney & Miller, 1956) which is causing a greater $\dot{V}A/\dot{Q}$ mismatch. Therefore, there is a higher vulnerability for $\dot{V}A/\dot{Q}$ mismatch in the aged and may contribute to EIAH.

6.5 PaO_2, $\dot{V}O_2$max, and performance

Highly trained male athletes who experience exercise-induced arterial O_2 desaturation of $\leq 92\%$ increase their $\dot{V}O_2$max when breathing hyperoxic gas (Powers et al.,1989). There is a relationship between the increase in $\dot{V}O_2$max when breathing hyperoxic gas and the normally occurring decrease in SaO_2. For example, participants who develop the greatest degree of desaturation under normoxic conditions had the greatest increase in $\dot{V}O_2$max when inspiring a hyperoxic gas and prevented a decrease in SaO_2. (Harms et al., 2000). The $\dot{V}O_2$max improved by

~2% for each 1% decrease in SaO_2 starting from >3% desaturation from rest (Harms et al., 2000). These participants were able to exercise for a longer duration and some were able to perform another stage of the incremental treadmill exercise test (Harms et al., 2000).

Although $\dot{V}O_2max$ is not a good predictor of performance (Snell & Mitchel, 1984), the extent to which a decrease in SaO_2 affects performance should be considered. Koskolou & McKenzie (1993) sought to determine at what point the reduction in SaO_2 affects performance in highly trained male cyclists. The participants performed a 5-minute cycling test to exhaustion under three conditions: (i) normoxic air, (ii) mild hypoxemia air to induce 90% SaO_2, (iii) moderate hypoxemia air to induce 87% SaO_2. Statistical significance was only reached during moderate levels of hypoxaemia where SaO_2 of 87% impairs maximal performance. However, there was a clear linear relationship between the reduction in SaO_2 and total work performed during both mild and moderate hypoxemia. The rate of peripheral fatigue development influences central motor drive and exercise performance (Amann et al., 2006). When breathing hyperoxic air, CaO_2 is increased and the O_2 delivery to the working muscles is improved. Thus, alleviating peripheral locomotor muscle fatigue and changing the central motor output. Therefore, there is an increase in central neural and power output, and improved time trial performance (Amann et al., 2006). $\dot{V}O_2max$ is not a good predictor of performance (Snell & Mitchel, 1984) but it has been shown to increase susceptibility to EIAH where PaO_2 decreases and thus consequently a reduction in SaO_2 and CaO_2 are observed (Dempsey et al., 1984). A question to consider is at what point does an increase in $\dot{V}O_2max$ cause EIAH, where blood gases are not maintained near resting, and performance can be affected? Is it advantageous to slightly increase $\dot{V}O_2max$ if you encounter EIAH?

6.6 EIAH and endurance exercise

Previous studies and the current study researched EIAH during short-duration constant load, and incremental exercise testing (Dempsey et al., 1984; Harms et al., 1998; Dominelli et al., 2013). It is not known what happens to blood gas values during long-duration exercise. Do they continue to drop, plateau, or increase back to resting values? Further research on long duration exercise and EIAH should be considered.

Chapter 7: Conclusion

Female masters athletes experience EIAH at submaximal, near maximal, and maximal exercise levels, however with considerable variability in terms of severity. One participant did not experience EIAH at any exercise intensity despite having similar lung function, $\dot{V}E$, encountered EFL and had a higher $\dot{V}O_2max$ than the group mean. The observations from this participant points towards the between-subject variability in the occurrence of EIAH. No relationship was found between the nadir PaO_2 value achieved and $\dot{V}O_2max$. Although, it is important to note the the range of $\dot{V}O_2max$ in the population studied was small compared to the general population. The occurrence of EIAH in female masters athletes appear to be higher than young females and similar to male masters athletes. The mechanisms of EIAH seem to be similar as young females however a $\dot{V}A/\dot{Q}$ mismatch may play a larger role due to healthy aging of the pulmonary system. Further research of EIAH and impact on performance should be considered. Another question to consider is, are the mechanisms of EIAH changing due to healthy aging?

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Appendices

Appendix A Forms and questionnaires
A.1 Consent form

THE UNIVERSITY OF BRITISH COLUMBIA

School of Kinesiology
210, War Memorial Gym
6081 University Boulevard
Vancouver, B.C., Canada V6T
1Z1

a place of mind

Participant Information and Consent Form
(Please read through carefully and sign the last page of the document if you would like to consent to the study)
Exercise-induced arterial hypoxaemia in female masters athletes

Principal Investigator: William Sheel, Ph.D.
School of Kinesiology
The University of British Columbia
Office: [redacted]

Co-Investigators: Viviana Shiffman, B.S.c
Michael Leahy, B.Sc., M.Sc.
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Michael Koehle MD, Ph.D.
Donald C. McKenzie, M.D., Ph.D.
James McKinney, M.D.
Bevan Hughes, M.D.
Peter Rose, M.D.

Contact Person: Viviana Shiffman, BSc
School of Kinesiology
The University of British Columbia
[redacted]

Study Contact Number: [redacted]
24 hours: [redacted]

1. INVITATION

You are being invited to take part in this research study because you are an endurance trained female athlete between the ages of 40 to 60, with no history of cardiopulmonary (i.e. heart and/or lung) ailments or tumours and/or ulcers in the esophagus.

2. YOUR PARTICIPATION IS VOLUNTARY

Your participation in this study is completely voluntary. You have the right to refuse participation in this study. Should you choose to participate, you may opt to withdraw from the study at any time without penalty. Before you decide, it is important for you to understand what the research involves. This consent form will tell you about the study, why the research is being done, what will happen to you during the study and the possible benefits, risks and discomforts.

3. WHO IS CONDUCTING THE STUDY?

The study is being conducted by Dr. William Sheel, Viviana Shiffman and the study team members, of the Health and Integrative Physiology Laboratory at the University of British Columbia. The study is funded by the Natural Science and Engineering Research Council (NSERC) of Canada. Details of source of funding can be provided upon request.

4. BACKGROUND

During exercise, the active muscles require more oxygen (O_2) in order to maintain an exercise intensity and homeostasis. Homeostasis is the ability to maintain a proper equilibrium within the body at which we can function in. This is done by the lungs bringing more O_2 into the body through larger and more frequent breaths. The heart also contributes by pumping larger blood volumes (known as stroke volume) and increasing the heart rate. Therefore, a healthy human is able to maintain homeostasis in the face of maximal exercise. However, in an endurance trained athlete, the demand for O_2 may be so high that they are unable to maintain homeostasis at maximal and even sometimes at submaximal exercise. When an endurance athlete trains, their muscles and heart adapt to have larger reserves, but their lungs do not, thus they are unable to maintain homeostasis. This phenomenon is termed exercise-induced arterial hypoxaemia (EIAH). EIAH reflects the inability of the healthy lungs to meet the muscle and heart demands of heavy exercise. To measure EIAH, the amount of O_2 in the blood must be measured with an arterial catheter (a needle attached to a tube in order to draw blood). Researchers draw blood samples while a participant is exercising to measure the amount of O_2 in the blood at that certain exercise level. Research has primarily utilized young male athletes and few studies have characterized EIAH in young female athletes. From the studies that have been conducted it seems that female athletes are more susceptible to EIAH and occurs at even lower exercise levels compared to male athletes. When healthy aging is considered, male masters athletes had a higher prevalence and severity of EIAH compared to their younger counterpart. However, no studies have sought to characterize EIAH in female masters athletes.

5. WHAT IS THE PURPOSE OF THE STUDY?

The primary purpose of the study is to characterize exercise-induced arterial hypoxaemia in female masters athletes at maximal and submaximal exercise levels.

6. WHO CAN PARTICIPATE IN THIS STUDY?

You may be able to participate in this study if:

- You are a female between the ages of 40-60 years

- You are endurance trained runner with a minimum of 5 years of experience and a VO_2 max of 45 ml/kg/min. VO_2 max (also known as maximal oxygen uptake) is defined as the maximum rate of oxygen consumption measured during a maximal exercise test. Thus, a VO_2 max of 45ml/kg/min means the body is able to consume 45 ml of oxygen per kilogram per minute.

- You have normal lung function
- You have no symptoms of cardiopulmonary disease (such as exercise-induced asthma)
- You are proficient in the English language

7. WHO SHOULD NOT PARTICIPATE IN THE STUDY?

You cannot participate in the study if:

- You have a history of asthma and/or cardiopulmonary disease
- You are a current smoker or previously smoked in the past 10 years
- You are pregnant
- You formerly or currently have a tumor or ulcer in your esophagus
- You have any restrictions to exercise testing based on the Physical Activity Readiness Questionnaire (PAR-Q+)

8. WHAT DOES THE STUDY INVOLVE?

Overview of the Study

You are being invited to participated in two data collection test days and your participation in the study is entirely voluntary. The sessions will take place at the Healthy and Integrative Physiology Laboratory at the Chan Gunn Pavilion, Rm 220 at the University of British Columbia, Vancouver Campus. This study will require a total of 2 hours on day 1 and 3 hours on day 2 of commitment. Day 1 and day 2 will be separated by at least 48 hours but no more than 7 days. Before any measurements are taken, a physical activity readiness questionnaire (PAR-Q+) will be administered along with a participant contact information and medical and physical activity history forms. You will not be required to answer any questions that you do not feel comfortable answering.

If You Decide to Join This Study: Specific Procedures

Day 1

Prior to testing, you will be asked to refrain from alcohol 24 hours, food and caffeine 2 hours and exercise 12 hours before the study. On day one of testing, anthropometric measures (height and weight) will be obtained and a pulmonary function test will be conducted. The pulmonary function test will measure forced vital capacity, forced expiratory volume in 1 second, peak expiratory flow and maximum voluntary ventilation. Pulmonary diffusion capacity for carbon monoxide (measures the transfer of gas from air in the lung to red blood cells) will also be measured. The tests will be conducted using body plethysmography (Vmax Autobox V62, CareFusion, USA) while following the American Thoracic Society protocol. Body plethysmography is lung function test used to measure lung volumes, capacities and resistances. Following, you will perform a graded treadmill exercise to exhaustion test so we can obtain your maximal rate of oxygen consumption (VO_2 max). You will also be briefed on signs and symptoms of when to stop the test as a precaution. The protocol includes 10 minutes of resting, 5 minutes of a self-selected warm up, then a baseline at 2.5 mph and 0% grade for 2 minutes with an increase of 0.5 mph and 2% grade every 2 minutes until exhaustion. Measurements of metabolic and ventilatory parameters will be

collected. Primary metabolic parameters include, amount of oxygen and carbon dioxide in each breath in and out. Primary ventilatory parameters include tidal volume (amount of air that is moving in and out of the lung with each breath) and breathing rate. As well as, heart rate via a heart rate monitor, rate of perceived exertion (RPE) via the Borg scale 6-20 and O_2 saturation via a finger oximeter. The Borg scale matches how hard you feel you are exerting yourself with a number from 6-20.

Day 2

On day two of testing, local anesthesia (1% Xylocaine) will be administered prior to insertion of an arterial catheter into the radial artery. The radial artery is located at the upper part of the forearm. A topical anesthesia (2% Lidocaine) will be applied from the nose down the esophagus prior to the placement of the temperature thermistor and an esophageal balloon catheter in the lower third of the esophagus. The temperature thermistor (which detects the surrounding temperature) is attached to a thin tube that will be inserted starting from your nose down to the lower third of the esophagus (the throat). The esophageal balloon catheter will be placed in similar fashion. The esophageal balloon catheter will be connected to a pressure transducer along with mouth pressure (from the mouth piece). After instrumentation, you will rest in a chair before completing a self-selected warm-up. Initial resting arterial blood samples (≈3 mL) will be taken 10 minutes after instrumentation. You will perform 3 constant load exercise tests at 50%, 75% and 90-95% VO_2 max on a treadmill. Each constant load exercise test will be 3 to 4 minutes in duration and blood samples of 3 mL will be drawn every minute and esophageal temperature will be recorded. Esophageal pressure will be measured throughout the constant load exercise tests. A trained physician (Dr. Michael Koehle, Dr. Bevan Hughes or, Dr. Peter Rose) will be in charge of the catheter insertion and blood sampling. The primary contact (Viviana Shiffman) will be in charge of analysis and disposal. The intended use of the blood samples is to analyze them immediately by a blood gas analyzer. They will be disposed via biohazard protocols immediately after analysis. There will be no commercial use. Sufficient rest will be given between constant load exercise test in order for blood oxygen levels (PaO_2) to return to resting values. After the exercise test, you will perform an active cool down followed by seated resting. Oxyhemoglobin saturation levels (how much oxygen is attached to hemoglobin in your blood) and heart rate will be continuously monitored to ensure your safety.

WHAT ARE MY RESPONSIBILITIES?

You will be expected to participate in two testing sessions (2 hours and 3 hours) and to avoid alcohol for 24 hours, food and caffeine for 2 hours, and exercise for at least 12 hours prior to testing.

9. WHAT ARE THE POSSIBLE HARMS AND DISCOMFORTS?

When completing a pulmonary function test, you could potentially experience mild light-headedness or breathlessness. You can also cough or wheeze at the end of some of the breathing tests. However, these sensations are short-lived and will subside when the test is terminated. When completing a diffusion capacity assessment, there are small traces of carbon monoxide (CO) which might make you feel dizzy or light-headed. Minimal trials will be conducted with a minimum of 3 minutes between each trial to ensure your safety.

Insertion of the arterial catheter may cause discomfort when inserting the arterial catheter into radial artery. Discomfort may persist during testing. Other potential minimal risks include: occlusion of the artery (1.5%), defined as a blockage or narrowing of an artery, local infection (0.72%), haematoma formation (14.40%) defined as clotting of the blood like a bruise, bleeding at the puncture site (0.53%), sepsis (0.13%) defined as a condition where harmful microorganisms are present in the blood or other tissues and the body's response to their presence which can lead to malfunction of various organs, shock and death, pseudoaneurysm (0.09%) defined as a blood vessel wall being injured and thus leaking blood collects in the surrounding tissue. Local anesthesia will be used to minimize discomfort.

When inserting the temperature thermistor into the esophagus and esophageal balloon catheter you may feel mild discomfort or soreness in the nostrils and upper airway during the placement . It is possible that you may experience a nosebleed as a result of the placement. You may also experience slight discomfort as a result of 'gagging' while swallowing the thermistor and during the removal of the tube (less than 5% of people). This may cause some people to vomit (less than 1% of people). Perforation of the esophagus (a small hole being poked through the esophageal wall) is very rare. A numbing gel called lidocaine will be used to minimize the discomfort. Adverse reactions to lidocaine are extremely rare but include light-headedness, blurred/double vision, euphoria, confusion, dizziness, convulsions, sensations of heat, cold or numbness (all of these happen in less than 1% of people). You will not be allowed to participate in the study if you are known to be sensitive to local anesthetics or if you have allergies to latex. We are unaware of any laboratory that has experienced any of the aforementioned adverse reactions to such a small amount of lidocaine. Tape will be used in order to minimize movement.

There is also a small risk that the thermistor in your esophagus may be placed in the wrong position. In some extremely rare cases, the catheter can enter your trachea (windpipe). This happens in less than 0.5% of placements. If this occurs, you may experience mild discomfort in the back of your throat, and you may gag or vomit. In this event, you will be provided with immediate medical assistance. The severity of the illness and willingness of the participant to continue will dictate if the experiment is carried out any further. There is mild discomfort in the throat that generally does not persist after 5-6 hours post trial. There is a small chance this persists in the following day, and if so the next day of the trial can be postponed. There must be a minimum of 48 hours between trial days, so this can be extended if you wish, as it is only a minimum.

To minimize risk, a trained physician will be inserting the catheter and will be taped down to minimize movement. During all exercise testing, you will be harnessed into a harness to minimize risk of falling.

In addition, you will not be allowed to participate in the study if you are pregnant. Reported risks associated with participating in strenuous exercise during pregnancy are: dizziness, chest pain, preterm labour and decreased fetus movement. If you expect you may be pregnant, you are encouraged to take a pregnancy test before participating in the study (the research team will not provide pregnancy tests).

11. WHAT ARE THE POTENTIAL BENEFITS OF PARTICIPATING?

As a result of your participation in this study, you will receive detailed pulmonary function assessment and your VO_2 max results. These can be used help create your own personal training regime. Beyond this, you may not directly benefit from participating in this study.

12. WHAT HAPPENS IF I DECIDE TO WITHDRAW MY CONSENT TO PARTICIPATE?

You may withdraw from this study at any time without giving reasons. If you choose to enter the study and then decide to withdraw at a later time, you have the right to request the withdrawal of your information and/or samples collected during the study. This request will be respected to the extent possible. Please note however that there may be exceptions where the data and/or samples will not be able to be withdrawn for example where the data and/or sample is no longer identifiable (meaning it cannot be linked in any way back to your identity) or where the data has been merged with other data. If you would like to request the withdrawal of your data and/or samples, please let your study doctor know.

13. WILL TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

Your confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the presence of the investigator or his or her designate by NSERC and the UBC Clinical Research Ethics Board for the purpose of monitoring the research. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law. You will be assigned a unique study number as a participant in this study. This number will not include any personal information that could identify you (e.g., it will not include your Personal Health Number, SIN, or your initials, etc.). Only this number will be used on any research-related information collected about you during the course of this study, so that your identity will be kept confidential. Information that contains your identity will remain only with the Principal Investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

Your de-identified research data may be published or deposited into a publicly accessible location at the time of publication. This data could include sex, age, height and weight. At no time will identifying information, such as your name, birth date or street address be included in such data. This means that other researchers may analyze the data for different reasons other than those described in this consent form. Once the data is made publicly available, you will not be able to withdraw your data. The extent of the risk of you being identified through public data is unknown, but currently appears to be low.

The biospecimens (blood samples) results will be linked to your unique study number. As stated above, this number will not include any personal information that could identify you (e.g., it will not include your Personal Health Number, SIN, or your initials, etc.). The blood samples will be immediately analyzed (within ~30 seconds of the sample being drawn) After analysis, the blood sample will be immediately disposed of by following the UBC biomedical disposal procedures. Biomedical waste will be collected in a red biohazard bag (double bagged) with a biohazard symbol. A biological waste disposal tag (red) will be attached to each bag explaining the waste content (Human blood & body fluids). The biomedical waste inside the bag will be stored in the freezer located in Chan Gunn for scheduled pick-up by UBC Environment Services Facility

(ESF). Catheters will be disposed of by following the disposal for sharps and syringe procedure. They will be collected in approved plastic "sharp containers". A biological waste disposal tag will be attached indicating the contents. The container will then be brought the building's designated area for pick-up and disposal. At the end of the study, data collected will be kept in a locked filing cabinet or in a password protected and encrypted computer for at least five years after the work is published or otherwise presented. After five years, data will be destroyed by shredding all paper forms and erasing all electronic forms. There are no plans for future use of the data after the study is complete. Co-investigator UBC Professor M. Koehle (MD, PhD, Sports Medicine Physician) will meet with you in the unlikely event that abnormal values are observed with respect to blood values. Please note that no blood is being stored for subsequent analysis. There is a possibility that you may have a low hemoglobin value and this will be discussed in this event.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected and also give you the right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

14. WHAT HAPPENS IF SOMETHING GOES WRONG?

By signing this form, you do not give up any of your legal rights and you do not release the study doctor, participating institutions, or anyone else from their legal and professional duties. If you become ill or physically injured as a result of participation in this study, medical treatment will be provided at no additional cost to you. The costs of your medical treatment will be paid by your provincial medical plan and/or by the study sponsor [Natural Sciences and Engineering Research Council of Canada (NSERC)].

In the unlikely event of a medical emergency during the study, immediate care will be provided by researchers with valid CPR and AED certification (Primary Contact: Viviana Shiffman and co-investigators: Mick Leahy, Shalaya Kipp, and Michael Koehle) who will be present in the study area at all times. There is an automated emergency defibrillator and first aid supplies (including airway management material) in the study area and the distance to the nearest hospital emergency room is less than 1 km.

15. WHAT WILL THIS STUDY COST ME?

This study does not impose a cost on the participant. If you choose to drive to the laboratory where the study will be conducted, you will be reimbursed for parking. A parking receipt will be required for reimbursement.

16. IF I HAVE QUESTIONS ABOUT THE STUDY PROCEDURES DURING MY PARTICIPATION, WHO SHOULD I SPEAK TO

If you have any questions or desire further information about this study before or during participation, or if you experience any adverse effects, you can contact Viviana Shiffman (phone: [redacted]; email: [redacted]) or Dr. William Sheel ([redacted]).

17. WHO DO I CONTACT IF I HAVE ANY QUESTIONS OR CONCERNS ABOUT MY RIGHTS AS A SUBJECT?

If you have any concerns or complaints about your rights as a research subject and/or your experiences while participating in this study, contact the *Research Participant Complaint Line* in the University of British Columbia Office of Research Ethics by e-mail at *RSIL@ors.ubc.ca* or by phone at *604-822-8598* (Toll Free: 1-877-822-8598). Please reference the study number [H20-00446] when calling so the Complaint Line staff can better assist you.

Exercise-induced arterial hypoxaemia in female master athletes

CONSENT FORM

My signature on this consent form means:

- I have read and understood the subject information and consent form.
- I have had sufficient time to consider the information provided and to ask for advice if necessary.
- I have had the opportunity to ask questions and have had satisfactory responses to my questions.
- I understand that all of the information collected will be kept confidential and that the results will only be used for scientific objectives.
- I understand that my participation in this study is voluntary and that I am completely free to refuse to participate or to withdraw from this study at any time.
- I understand that I am not waiving any of my legal rights as a result of signing this consent form.
- I understand that there is no guarantee that this study will provide any benefits to me

I will receive a signed and dated copy of this consent form for my own records.

I consent to participate in this study.

Subject's Signature	Printed Name	Date

Person Obtaining Consent	Printed Name and Study Role	Date

A.2 PAR-Q + form

2019 PAR-Q+

The Physical Activity Readiness Questionnaire for Everyone

The health benefits of regular physical activity are clear; more people should engage in physical activity every day of the week. Participating in physical activity is very safe for MOST people. This questionnaire will tell you whether it is necessary for you to seek further advice from your doctor OR a qualified exercise professional before becoming more physically active.

GENERAL HEALTH QUESTIONS

Please read the 7 questions below carefully and answer each one honestly: check YES or NO.	YES	NO
1) Has your doctor ever said that you have a heart condition ☐ OR high blood pressure ☐?	☐	☐
2) Do you feel pain in your chest at rest, during your daily activities of living, **OR** when you do physical activity?	☐	☐
3) Do you lose balance because of dizziness **OR** have you lost consciousness in the last 12 months? Please answer **NO** if your dizziness was associated with over-breathing (including during vigorous exercise).	☐	☐
4) Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)? **PLEASE LIST CONDITION(S) HERE:** _____	☐	☐
5) Are you currently taking prescribed medications for a chronic medical condition? **PLEASE LIST CONDITION(S) AND MEDICATIONS HERE:** _____	☐	☐
6) Do you currently have (or have had within the past 12 months) a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be made worse by becoming more physically active? Please answer **NO** if you had a problem in the past, but it **does not limit your current ability** to be physically active. **PLEASE LIST CONDITION(S) HERE:** _____	☐	☐
7) Has your doctor ever said that you should only do medically supervised physical activity?	☐	☐

If you answered NO to all of the questions above, you are cleared for physical activity.
Please sign the PARTICIPANT DECLARATION. You do not need to complete Pages 2 and 3.

- Start becoming much more physically active – start slowly and build up gradually.
- Follow International Physical Activity Guidelines for your age (www.who.int/dietphysicalactivity/en/).
- You may take part in a health and fitness appraisal.
- If you are over the age of 45 yr and NOT accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.
- If you have any further questions, contact a qualified exercise professional.

PARTICIPANT DECLARATION

If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that the community/fitness center may retain a copy of this form for its records. In these instances, it will maintain the confidentiality of the same, complying with applicable law.

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

If you answered YES to one or more of the questions above, COMPLETE PAGES 2 AND 3.

Delay becoming more active if:

- You have a temporary illness such as a cold or fever; it is best to wait until you feel better.
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ at **www.eparmedx.com** before becoming more physically active.
- Your health changes - answer the questions on Pages 2 and 3 of this document and/or talk to your doctor or a qualified exercise professional before continuing with any physical activity program.

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FOLLOW-UP QUESTIONS ABOUT YOUR MEDICAL CONDITION(S)

1. Do you have Arthritis, Osteoporosis, or Back Problems?

If the above condition(s) is/are present, answer questions 1a-1c — If **NO** ☐ go to question 2

1a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
1b.	Do you have joint problems causing pain, a recent fracture or fracture caused by osteoporosis or cancer, displaced vertebra (e.g., spondylolisthesis), and/or spondylolysis/pars defect (a crack in the bony ring on the back of the spinal column)?	YES ☐ NO ☐
1c.	Have you had steroid injections or taken steroid tablets regularly for more than 3 months?	YES ☐ NO ☐

2. Do you currently have Cancer of any kind?

If the above condition(s) is/are present, answer questions 2a-2b — If **NO** ☐ go to question 3

2a.	Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of plasma cells), head, and/or neck?	YES ☐ NO ☐
2b.	Are you currently receiving cancer therapy (such as chemotheraphy or radiotherapy)?	YES ☐ NO ☐

3. Do you have a Heart or Cardiovascular Condition? This includes Coronary Artery Disease, Heart Failure, Diagnosed Abnormality of Heart Rhythm

If the above condition(s) is/are present, answer questions 3a-3d — If **NO** ☐ go to question 4

3a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
3b.	Do you have an irregular heart beat that requires medical management? (e.g., atrial fibrillation, premature ventricular contraction)	YES ☐ NO ☐
3c.	Do you have chronic heart failure?	YES ☐ NO ☐
3d.	Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months?	YES ☐ NO ☐

4. Do you have High Blood Pressure?

If the above condition(s) is/are present, answer questions 4a-4b — If **NO** ☐ go to question 5

4a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
4b.	Do you have a resting blood pressure equal to or greater than 160/90 mmHg with or without medication? (Answer **YES** if you do not know your resting blood pressure)	YES ☐ NO ☐

5. Do you have any Metabolic Conditions? This includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes

If the above condition(s) is/are present, answer questions 5a-5e — If **NO** ☐ go to question 6

5a.	Do you often have difficulty controlling your blood sugar levels with foods, medications, or other physician-prescribed therapies?	YES ☐ NO ☐
5b.	Do you often suffer from signs and symptoms of low blood sugar (hypoglycemia) following exercise and/or during activities of daily living? Signs of hypoglycemia may include shakiness, nervousness, unusual irritability, abnormal sweating, dizziness or light-headedness, mental confusion, difficulty speaking, weakness, or sleepiness.	YES ☐ NO ☐
5c.	Do you have any signs or symptoms of diabetes complications such as heart or vascular disease and/or complications affecting your eyes, kidneys, **OR** the sensation in your toes and feet?	YES ☐ NO ☐
5d.	Do you have other metabolic conditions (such as current pregnancy-related diabetes, chronic kidney disease, or liver problems)?	YES ☐ NO ☐
5e.	Are you planning to engage in what for you is unusually high (or vigorous) intensity exercise in the near future?	YES ☐ NO ☐

2019 PAR-Q+

6. Do you have any Mental Health Problems or Learning Difficulties? This includes Alzheimer's, Dementia, Depression, Anxiety Disorder, Eating Disorder, Psychotic Disorder, Intellectual Disability, Down Syndrome

If the above condition(s) is/are present, answer questions 6a-6b If **NO** ☐ go to question 7

6a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
6b.	Do you have Down Syndrome **AND** back problems affecting nerves or muscles?	YES ☐ NO ☐

7. Do you have a Respiratory Disease? This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary High Blood Pressure

If the above condition(s) is/are present, answer questions 7a-7d If **NO** ☐ go to question 8

7a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
7b.	Has your doctor ever said your blood oxygen level is low at rest or during exercise and/or that you require supplemental oxygen therapy?	YES ☐ NO ☐
7c.	If asthmatic, do you currently have symptoms of chest tightness, wheezing, laboured breathing, consistent cough (more than 2 days/week), or have you used your rescue medication more than twice in the last week?	YES ☐ NO ☐
7d.	Has your doctor ever said you have high blood pressure in the blood vessels of your lungs?	YES ☐ NO ☐

8. Do you have a Spinal Cord Injury? This includes Tetraplegia and Paraplegia

If the above condition(s) is/are present, answer questions 8a-8c If **NO** ☐ go to question 9

8a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
8b.	Do you commonly exhibit low resting blood pressure significant enough to cause dizziness, light-headedness, and/or fainting?	YES ☐ NO ☐
8c.	Has your physician indicated that you exhibit sudden bouts of high blood pressure (known as Autonomic Dysreflexia)?	YES ☐ NO ☐

9. Have you had a Stroke? This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event

If the above condition(s) is/are present, answer questions 9a-9c If **NO** ☐ go to question 10

9a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	YES ☐ NO ☐
9b.	Do you have any impairment in walking or mobility?	YES ☐ NO ☐
9c.	Have you experienced a stroke or impairment in nerves or muscles in the past 6 months?	YES ☐ NO ☐

10. Do you have any other medical condition not listed above or do you have two or more medical conditions?

If you have other medical conditions, answer questions 10a-10c If **NO** ☐ read the Page 4 recommendations

10a.	Have you experienced a blackout, fainted, or lost consciousness as a result of a head injury within the last 12 months **OR** have you had a diagnosed concussion within the last 12 months?	YES ☐ NO ☐
10b.	Do you have a medical condition that is not listed (such as epilepsy, neurological conditions, kidney problems)?	YES ☐ NO ☐
10c.	Do you currently live with two or more medical conditions?	YES ☐ NO ☐

PLEASE LIST YOUR MEDICAL CONDITION(S) AND ANY RELATED MEDICATIONS HERE: _____

_____

GO to Page 4 for recommendations about your current medical condition(s) and sign the PARTICIPANT DECLARATION.

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If you answered NO to all of the FOLLOW-UP questions (pgs. 2-3) about your medical condition, you are ready to become more physically active - sign the PARTICIPANT DECLARATION below:

- It is advised that you consult a qualified exercise professional to help you develop a safe and effective physical activity plan to meet your health needs.
- You are encouraged to start slowly and build up gradually - 20 to 60 minutes of low to moderate intensity exercise, 3-5 days per week including aerobic and muscle strengthening exercises.
- As you progress, you should aim to accumulate 150 minutes or more of moderate intensity physical activity per week.
- If you are over the age of 45 yr and **NOT** accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.

If you answered **YES** to **one or more of the follow-up questions** about your medical condition:

You should seek further information before becoming more physically active or engaging in a fitness appraisal. You should complete the specially designed online screening and exercise recommendations program - the **ePARmed-X+ at www.eparmedx.com** and/or visit a qualified exercise professional to work through the ePARmed-X+ and for further information.

Delay becoming more active if:

- You have a temporary illness such as a cold or fever; it is best to wait until you feel better.
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ **at www.eparmedx.com** before becoming more physically active.
- Your health changes - talk to your doctor or qualified exercise professional before continuing with any physical activity program.

- You are encouraged to photocopy the PAR-Q+. You must use the entire questionnaire and NO changes are permitted.
- The authors, the PAR-Q+ Collaboration, partner organizations, and their agents assume no liability for persons who undertake physical activity and/or make use of the PAR-Q+ or ePARmed-X+. If in doubt after completing the questionnaire, consult your doctor prior to physical activity.

PARTICIPANT DECLARATION

- All persons who have completed the PAR-Q+ please read and sign the declaration below.
- If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that the community/fitness center may retain a copy of this form for records. In these instances, it will maintain the confidentiality of the same, complying with applicable law.

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

For more information, please contact
www.eparmedx.com
Email: eparmedx@gmail.com

Citation for PAR-Q+
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The PAR-Q+ was created using the evidence-based AGREE process (1) by the PAR-Q+ Collaboration chaired by Dr. Darren E. R. Warburton with Dr. Norman Gledhill, Dr. Veronica Jamnik, and Dr. Donald C. McKenzie (2). Production of this document has been made possible through financial contributions from the Public Health Agency of Canada and the BC Ministry of Health Services. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada or the BC Ministry of Health Services.

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3. Chisholm DM, Collis ML, Kulak LL, Davenport W, and Gruber N. Physical activity readiness. British Columbia Medical Journal. 1975;17:375-378.
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11-01-2018

A.3 Health questionnaire

Medical questionnaire form
Exercise-induced arterial hypoxaemia in female master athletes

Subject ID#: _____

Age: _____ (years)

To the best of your knowledge:

1. Are you in good general health?
   Please circle one: yes OR no

   If no, please specify any known problems:
   _____
   _____

2. Has a doctor told you that you have high blood pressure?
   Please circle: yes OR no

   If yes, please specify: _____

3. Have you ever had a heart attack?
   Please circle: yes OR no

4. Has a doctor told you that your cholesterol is at a high risk-level?
   Please circle: yes OR no

   If yes, please specify:_____

5. Do you have diabetes of has a doctor told you that you have pre-diabetes?
   Please circle: yes OR no

   If yes, please specify: _____

6. Has a doctor told you that you have intrapulmonary arteriovenous anastomoses (a vessel that shunts blood from an artery to a vein and thus bypassing a capillary)?
   Please circle: yes OR no

   If yes, please specify: _____

7. Has a doctor told you that you have a patent foramen ovale (a hole in the heart)?
   Please circle: yes OR no

   If yes, please specify: _____

Version 1.0 (July 27, 2020) [H20-00446]

A.4 Menstrual cycle questionnaire

Menstrual History Questionnaire
Exercise-induced arterial hypoxaemia in female master athletes

Study ID # : _____

Age: _____

Height _____ Weight _____

1. Have your menstrual periods stopped permanently?
Please circle one.

a. NO – I am still menstruating.

b. YES - No menstrual periods, I have had menopause.

c. YES – I had menopause, but now I have periods
because I am taking medication (hormones).

d. NOT SURE

IF YES to either b or c:

2a. At what age did your menstrual periods stop?
Age = _____(years)

2b. Have you ever used estrogen replacement therapy (such as Premarin, Estraderm, Ogen, Estrace, etc.)? Please circle: yes or no

IF YES to a:

2b. At present which statement best describes your menstrual cycle?
___I'm still having regular periods: The date of my last period was: ___/___/_____
___My periods are irregular: The date of my last period was: ___/___/_____

3. Are you currently using any oral contraceptive (birth control pills) for any reason (birth control, acne, menstrual irregularity, etc.)?
Please circle: yes or no

If yes, please specify: _____

_____

A.5 Exercise training form

Exercise training

Please specify the type of exercise training, days per week and approximately how many km/week.

Example:
Exercise: Running
Days per week:5/week
Approximate km/week (if applicable): 25km/week

1. Exercise: _____

   Days per week: _____

   Approximate km/week (if applicable): _____

2. Exercise: _____

   Days per week: _____

   Approximate km/week (if applicable): _____

3. Exercise: _____

   Days per week: _____

   Approximate km/week (if applicable): _____

4. Exercise: _____

   Days per week: _____

   Approximate km/week (if applicable): _____