THE EFFECT OF PROPORTIONAL ASSIST VENTILATION ON DIAPHRAGM ELECTRICAL ACTIVITY

by

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B.Sc., The University of British Columbia, 2017

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Kinesiology)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

October 2021

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The effect of proportional assist ventilation on diaphragm electrical activity

submitted by Emily A.M. Gerson in partial fulfillment of the requirements for

the degree of Master of Science

in Kinesiology

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Abstract

The diaphragm is the largest contributing muscle in a spontaneous breath. Classically, when failure in this muscle occurs, mechanical ventilation is implemented to reduce acute respiratory failure. The proportional assist ventilator (PAV) is a type of mechanical ventilator that can maintain gas homeostasis in dynamic exercise. However, PAV's effect on the diaphragm, accessory respiratory muscles, and effectiveness during lower intensity exercise is still unclear. **PURPOSE:** To investigate the diaphragm electrical activity during low exercise intensity (10% below gas exchange threshold (GET)) while reducing the work of breathing via a proportional assist ventilator (PAV). **METHODS:** 8 participants (n = 4 male, n = 4 female; 26.8 ± 1 years) completed two days of testing. On day one, subjects performed a maximal VO_2 exercise test on a cycle ergometer. On day 2, subjects cycled at 10% below gas exchange threshold (GET) while alternating breathing on the PAV and spontaneously. Electromyography of the diaphragm (EMG_{di}), scalenes (EMG_{SCA}), and sternocleidomastoids (EMG_{SCM}), work of breathing (WOB), Pressure time product of the esophagus (PTP_{es}), diaphragm (PTP_{di}) and gastric (PTP_{ga}) were measured throughout the experimental protocol. **RESULTS:** WOB was lower while breathing on the PAV during medium ($p \leq 0.05$) and high ($p \leq 0.01$) unloading conditions. PTP_{es} was significantly lower while breathing on the PAV for low, medium, and high unloading assistance ($p \leq 0.05$; $p \leq 0.01$; $p \leq 0.01$) compared to spontaneous breathing. PTP_{di} was significantly lower while breathing on the PAV for low ($p < 0.05$), medium and high comparisons ($p \leq 0.01$; $p \leq 0.01$) compared to spontaneous breathing. While PTP_{gas} was significantly lower when breathing on the PAV during high levels of unloading ($p \leq 0.01$) compared to spontaneous breathing.EMG_{di} was lowered while breathing during all PAV unloading levels (low, medium, and high) compared to spontaneous breathing ($p \leq 0.05$; $p \leq 0.05$; $p \leq 0.05$). EMG_{SCA} was reduced when breathing on the PAV during high unloading versus spontaneous breathing ($p \leq 0.05$). EMG_{SCM} showed no reductions between PAV unloading levels and spontaneous breathing. **CONCLUSION:** PAV reduces WOB during exercise below 50% of VO_{2MAX} and simultaneously reduces the diaphragm electrical activity.

Lay Summary

Use of respiratory muscles during exercise comes at an energetic cost. The proportional assist ventilator (PAV) is a mechanical ventilator used to reduce the work of breathing (WOB), offsetting metabolic demands, and shifting blood flow to active working muscles. The current literature suggests that PAV can reduce WOB during exercise and may be suitable for rehabilitation purposes. The purpose of this thesis was to determine the effects of PAV during a low exercise intensity for both WOB, and the electrical activity of the respiratory muscles. It was found that PAV reduced both WOB and electrical activity of the diaphragm. This thesis suggests that the PAV can reduce WOB and the output of the diaphragm while exercising at a low to moderate intensity.

Preface

This research study was designed by myself, Emily A.M. Gerson, with the help of my committee (Dr. Bill Sheel, Dr. Paolo Dominelli, Dr. Jordan Guenette, and Dr. Tania Lam), and members of the Health and Integrative Physiology Lab at the University of British Columbia. The scheduling, testing, analysis and writing was performed by myself, Shalaya Kipp, Mick Leahy, Andrew Ramsook, Dr. Bruno Archiza, Dr. Carli Peters, Dr. Paolo Dominelli, Dr. Yannick Molgat-Seon, and other members of the lab. Interpretation was completed by myself with assistance from the Health and Integrative Physiology Lab students. All methods executed in this thesis was approved by the University of British Columbia's Research Ethics Board (H18-03414).

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List of Abbreviations

ANOVA	Analysis of Variance
CPV	Constant Pressure Ventilator
CVP	Constant Volume Ventilator
EELV	End Expiratory Lung Volume
EMG	Electromyography
EMG_{di}	Electromyography of the Diaphragm
EMG_{SCA}	Electromyography of the Scalene muscles
EMG_{SCM}	Electromyography of the Sternocleidomastoid muscles
EMG_{Sur}	Electromyography recorded on the surface of a muscle
f_B	Frequency of Breathing
HR	Heart Rate
IC	Inspiratory Capacity (Maneuver)
MIP	Maximal Inspiratory Pressure
PAV	Proportional Assist Ventilator
PTP	Pressure Time Product
PTP_{es}	Pressure Time Product of the Esophagus
PTP_{di}	Pressure Time Product of the Diaphragm
PTP_{gas}	Pressure Time Product of the Gastric
$\dot{Q}$	Cardiac Output
RER	Respiratory Exchange Ratio
RMS	Root Mean Squared
SNIFF	Sniff (Maneuver)

$\dot{V}_E$	Minute Ventilation
$\dot{V}_T$	Tidal Volume
$\dot{V}CO_2$	Carbon Dioxide Output
$\dot{V}O_2$	Oxygen Uptake
$\dot{V}O_{2MAX}$	Maximal Oxygen Uptake
WOB	Work of Breathing

Acknowledgements

I would like to express my deepest gratitude to Dr. Sheel for his patience and support throughout this chapter of my life. Navigating a thesis is challenging, albeit attempting to finish one while losing a parent and enduring a pandemic. I will forever be grateful for my time with Dr. Sheel and my experience in the Health and Integrative Physiology Laboratory.

I would like to acknowledge members of the Health and Integrative Physiology Laboratory and the Cardiopulmonary Exercise Physiology Laboratory for their continued support throughout this process. Thank you to Bruno Archiza for helping conduct the study and ensuring that everything ran smoothly. Mick Leahy, Shalaya Kipp and Paige Reinhard thank you for all your hard work in helping during piloting, testing, analysis, and writing. Dr. Paolo Dominelli, for taking the time to fly to Vancouver to help run the PAV for this study. This was an integral part of the experiment, and this thesis would not be possible without your contribution. I would also like to thank Andrew Ramsook and Dr. Yannick Molgat-Seon for their help in recording, analyzing, and understanding EMG. I would like to thank my family for their support throughout this entire process. Lastly, I would like to thank NSERC for providing funding for this thesis and to my committee for the ongoing support and guidance regarding this research topic.

In loving memory Bonny Gerson.

Chapter 1: Introduction

The diaphragm is the largest contributor of the respiratory muscles, accounting for 70% of the total activity within a spontaneous breath (Mead & Loring, 1982). Like other skeletal muscles, the ability of the diaphragm to generate force is dependent upon the mechanical and contractile properties of the muscle including the length (length tension relationship), velocity of shortening (force-velocity relationship), and the rate at which the muscle is stimulated (force-frequency relationship) (Rochester, 1985). Respiratory muscle shortening is measured as the change in volume of a structure that the muscle displaces (e.g. ribcage, abdomen, or lungs), while the velocity of shortening can be measured as flow and force as pressure. Using the variables of change in volume and change in pressure, the work of breathing (WOB) can be estimated. The efficiency of the respiratory muscles to generate force and/or velocity of contraction has implications regarding the metabolic cost of breathing.

As exercise intensity increases, so does the WOB and sympathetic vasomotor outflow. Evidence shown in both humans and experimental animals to convey the increase in sympathetic activity can be attributed to a reflex originating within the contracting diaphragm (Sheel *et al*., 2018; Hill 2000). Regulation of blood flow to contracting skeletal muscle (i.e. the diaphragm) is modulated by the competing effects of local metabolic-induced vasodilation, and sympathetically induced vasoconstriction. During low intensity exercise, O_2 delivery via local vasodilation is prioritized, while during higher intensity whole body exercise blood pressure regulation and therefore vasoconstriction increases in priority. The working hypothesis is that the global increase in sympathetic activity originating from the diaphragm during heavy exercise serves to elicit vasoconstriction in locomotor muscles during exercise and presumably redistribute blood to the muscles of respiration (Aaker & Laughlin, 2002).

To investigate the relationship between WOB and the respiratory muscles, researchers have manipulated the WOB via mechanical ventilators including include inspiratory pressure support systems, continuous positive airway pressure, and proportional assist ventilation (PAV). Other non-mechanical manipulations of WOB include the use of bronchodilators and Heliox (He-O_2) gas. Bronchodilators are beta-2 agonists, which target the beta-2 receptors of the lung airways. When beta-2 receptors are activated, the smooth muscles of the bronchioles relax. Relaxation of the smooth muscle in the bronchioles enables increased airflow in the lung. Similarly, inhalation of Heliox also increases airflow to the lung by reducing airflow resistance. Heliox is a mixture of 79% helium and 21% oxygen. Compared to room air (78% nitrogen, 21% oxygen), helium has a comparable viscosity, but has a density six times lower than nitrogen. Due to Heliox's sizably smaller density improves airflow by transforming turbulent flow to laminar flow (Hashemian & Fallahian, 2014). Clinically, the PAV has been proposed as a tool for rehabilitation applications (Ambrosino & Rossi, 2002). However, most studies have reduced the WOB via a PAV at relatively high exercise intensities of 75-100% of maximum (Dominelli *et al.,* 2016; Wetter *et al.*, 1999). While many rehabilitation programs prescribe exercise at intensities at less than 75% of maximum.

It is currently unclear what effect the PAV has on the WOB when exercise is performed at low intensities of exercise or what the effect is on the electrical and contractile properties of the diaphragm. The purpose of this thesis is to evaluate how PAV influences reductions in WOB and electrical activity of the diaphragm during exercise. To further evaluate this topic, the purpose of the following literature review provides a summary regarding functional anatomy and pulmonary physiology, current concepts regarding the use and application of the PAV, and techniques regarding electromyography of the diaphragm (EMG_{di}). This thesis seeks to examine EMG_{di} during a low intensity exercise and the effects of PAV. Using EMG_{di} will permit quantification of the 'normal' activity of the diaphragm during dynamic exercise performed at low intensities.

1.1 REVIEW OF LITERATURE

Dynamic whole-body exercise requires a highly coordinated, regulated, and integrated physiological response. Increases in metabolic demands require increases tidal volume ($\dot{V}_T$), frequency of breathing (fb) and minute ventilation ($\dot{V}_E$) occur and are constantly assess via chemosensitivity to mitigating excess energy expenditure to reduce WOB (Otis, 1954). From the onset of dynamic exercise to approximately 60% of maximum, increases in $\dot{V}_E$ are brought about by increases in $\dot{V}_T$, after which increases in fb contribute to the rise in $\dot{V}_E$. The plateau of V_T is necessary, as it ensures optimal lung compliance. During exercise, cardiac output ($\dot{Q}$) increases upwards of six-fold to meet the metabolic demands of working muscles for oxygen delivery and carbon dioxide elimination. It is well known that endurance training causes adaptations to cardiovascular and metabolic systems with limited change to the pulmonary system (Reuschlein, *et al.*, 1948) although the pulmonary system does not appear to limit exercise in healthy individuals (Dempsey, 1986).

1.1.1 Functional Anatomy and Physiology of the Diaphragm and respiratory musculature

The diaphragm is often considered the principal muscle of respiration during a spontaneous breath (Macklem, *et al.*,1978; Mognoni, Saibene, & Sant'ambrogio, 1969), since it accounts for 70% of the total muscular activity in respiration (Luo, Moxham, & Polkey, 2008). It is an easily distensible musculotendinous structure which assumes a domed position at rest and flattens when activated (Vetrugno et al., 2019). The diaphragm is composed of three segments, one central tendon (non- contractile), and two muscular portions (costal and crural diaphragm). The diaphragm is attached to the ribs via the zone of apposition. During contraction, the change in muscle fiber length causes a thickening of the diaphragm wall, which leads to the diaphragm moving caudally during inspiration (McCool, Manzoor, & Minami, 2018). The diaphragm's unique 3-dimensional structure serves as an anatomical division of the abdomen from the thorax (Vetrugno *et al.*, 2019), and its innervation is supplied by the right and left phrenic nerves (C3-C5), which provide both sensory and motor function (McCool et al., 2018; Nason et al., 2012).Weakness in the diaphragm muscle is characterized with breathlessness and respiratory failure (Luo, Moxham, & Polkey, 2008).

During resting breathing, inspiration requires active intentional contraction of the respiratory muscles, while expiration is passive. As $\dot{V}_{\mathrm{E}}$ increases, expiration becomes active and additionally requires abdominal contraction to increase tidal volume and regulated end-expiratory lung volume (EELV). At rest, the flattening of the diaphragm increases the thoracic space due the change in orientation of the abdominal cavity in a downwards and forwards direction. While the diaphragm contracts, the rib cage is subsequently forced upwards via contraction of the scalene and external intercostal muscles. Coordination of inspiratory muscle movement enables an increase in the volume of the thoracic cavity and creates a negative pressure system within the interpleural space. At rest, the intrapleural pressures typically range from -6 and -2 cm H20 for inspiration and expiration, respectively. Due to the elastic properties of the chest wall and the lung recoil tendencies, a slight negative pressure is maintained intrathoracically to balance these two opposing structures. Further, this small range of pleural pressures magnify a larger change in volume of the lung, which gives the lung compliance at low-to-moderate lung volumes. At high lung volumes, compliance is low due to the stretched predisposition of the lung, thereby inhibiting any change in pressure to change volume. Large pressure changes, and subsequent volume changes, seen in conditions of exercise can compromise the muscular length-tension relationship of the diaphragm. Subsequently, the diaphragms length-tension relationship alters the maximal force production, and consequently puts the diaphragm in a compromised position to increase fatigue.

1.1.2 **Work of Breathing**

To act of sustaining appropriate alveolar ventilation requires a sustained energy by the respiratory musculature (Dominelli, Henderson, & Sheel, 2016). WOB provides an energetic cost of breathing at varying ventilations (Milic-Emili, Mead, Turner, & Glauser, 1964).WOB can further be divided into three areas of work: inspiratory elastic, inspiratory resistive, and total expiratory. At rest, expiration is passive and expiratory WOB is low whereas when the abdominals are activated under forceful exhalation there is an increase in the expiratory WOB (Aaron, Seow, Johnson, & Dempsey, 1992; Dominelli *et al.*, 2015). Resistive work comes from efforts the respiratory system must expend to overcome the resistance from the resistance from airway diameter, demonstrated by Poiseuille's Law:

$$\dot{V} = \frac{P\pi r^4}{8nl}$$

According to Poiseuille's law, radius is the largest contributing factor to resistance, such that the air around the walls has a lower flow rate than the air closer to the middle of the airway (Otis, 1954). Elastic work of breathing is the work required to overcome the elastic forces of the lung with a tendency to collapse inwards, to inflate it fully (Otis, 1954). Without mechanical constraint, the respiratory muscle's oxygen cost during maximal exercise has shown to be approximately 10 to 15% of total body VO_2 (Aaron, Seow, Johnson, & Dempsey, 1992; Dominelli *et al.,* 2015).

1.1.2.1 Experimentally Reducing WOB

To provide a better understanding of the complex relationship between ventilation, WOB, and the bioenergetics of the respiratory muscles, researchers experimentally manipulate the WOB. Manipulation of WOB is accomplished by increasing the resistive or elastic load (De Troyer & Boriek, 2011) or decreasing the WOB (Dominelli et al., 2016).A common method in reducing the WOB during experimental trials with exercise is done by chemical manipulation of the inspirate. By replacing Nitrogen (N_2) with Helium (He), the change of density (N_2 = 1.25 kg m^{-3}, He = 0.18 kg m^{-3}), will enable a greater propensity to laminar flow, such that the resistive WOB will decrease for the subject. Using He to manipulate WOB has been used in experimental settings with both healthy and clinical populations (Babb, 1997; Dominelli et al., 2012; Eves, Petersen, Haykowsky, Wong, & Jones, 2006). However, there are some disadvantages using He to manipulate the work of breathing. Firstly, the effects of He are dependent upon the level of ventilation. He reduces WOB minimally when ventilation is low and amplifies the reduction in WOB as ventilation increases (Dominelli *et al.,* 2016). Other solutions to consistently reduce WOB involves mechanical ventilation where a portion of the respiratory work is done via mechanical ventilation.

1.1.2.2 Pressure Support Systems

Clinically, mechanical ventilation is initiated to restore pulmonary gas exchange in patients with acute respiratory failure. Using a pressure support system is a preventative measure to reverse life threatening hypoxemia and progressive respiratory acidosis (Ambrosino & Rossi, 2002; Tobin, 2001). Severe dyspnea, rapid, and shallow breathing patterns are reliable signs of respiratory distress and impeding ventilatory pump failure (Ambrosino & Rossi, 2002). To keep pulmonary gas concentrations viable, four types of ventilators have been used. These include constant volume ventilators (CVV), constant pressure ventilators (CPV), tank ventilators, and patient-cycled ventilators. CVV deliver a pre-set volume of gas to the patient via a motor driven piston or cylinder and are ventilators suitable for longer term ventilation scenarios. CVP's also deliver a pre-set pressure to the patient; however, they differ from CVV because they do not require an electrical source, and instead use compressed gas. Tank ventilators (i.e., "the iron lung") work by delivering negative pressure to the outside of the patient's chest and body (excluding the head) thereby expand the patient's chest to allow for air to flow into the lungs during inspiration. Finally, patient cycled ventilators, such as PAV, use the patient's inspiratory effort to trigger the inspiratory phase of the breath cycle. While there is a vast amount of knowledge regarding ventilation mode, pattern, patient interaction, and applications, for the purposes of this review only details pertaining to proportional assist ventilation will be further discussed.

1.1.2.3 **Proportional Assist Ventilator**

PAV is a type of patient/subject cycled ventilator which was proposed to improve patient-ventilator interaction by bringing one of the two oscillatory pumps (mechanical ventilators) under the control of the other (i.e. the patient's central control of breathing) (Younes *et al.,* 1992, Younes *et al.,* 1994). The PAV works by amplifying the patient's effort without a preselected target volume or pressure thus allowing a spontaneous breathing pattern. Ultimately, this allows the subject to attain ventilation and breathing pattern that matches the participant's instantaneous requirements (Younes *et al.,* 1992, Younes *et al.,* 1994). The primary advantage of the PAV compared to the CPV, CCV, and tank ventilator systems is that the PAV offers support that is proportional to the subject's inspiratory efforts rather than a fixed set-point for respiratory timing, volume, and pressure to subsequently unload the resistive and elastic burdens (Ambrosino & Rossi, 2002). The PAV system follows the following equation:

$$Pmus = E \times V \times R \times V'$$

The pressure applied by the respiratory muscles (Pmus) to the system is used to overcome the elastic (E) and resistive (R) opposing forces. This is proportional to the volume (V) and the airflow rate (V').

Additionally, in situations that require higher ventilations (i.e. exercise, bouts of exertion), the PAV uses compressed air to deliver pressure. The compressed gas is regulated between 140-480 kPa and is connected to a proportional valve. The proportional valve responds linearly to voltage from the control software and is therefore suitable to a wide variety of exercise intensities where a patient flow needs are continuously changing. Experimentally, the PAV has been successful in reducing the WOB of approximately 30-55% of control values during cycling of workloads between 50-100% (Dominelli *et al*., 2016). However, it is unclear if at lower exercise intensities, reductions in WOB occur.

1.1.3 **Electromyography**

Electromyography (EMG) is an electrodiagnostic medicine technique that is used to evaluate skeletal muscle function. EMG is a representative index that describes the activity based on recording myoelectrical signals. These signals are electric manifestations of the excitation process elicited by action potentials propagating along muscle fibre membranes (Wu et al., 2017). EMG signals, when used for respiratory assessment, provide information regarding the status of the respiratory pump (Alty, Man, Moxham, & Lee, 2008), and respiratory brain stem output (Beloncle et al., 2017). EMG is utilized to automatically adjust ventilator response to varying patient effort (Luo, Moxham, & Polkey, 2008)in a variety of scenarios such as the intensive care unit, patient weaning from ventilators (Barwing *et al*., 2013) and sleep apnea (Luo, Moxham, & Polkey, 2008).

1.1.3.1 Electromyography measurement

EMG can be measured via needle electrodes inserted directly into the diaphragm, via surface skin electrodes (EMG_{sur}) and esophageal electrode catheters in touch with the diaphragm via the cardiac sphincter (EMG_{di}) (Alty *et al*., 2008). Albeit the most direct method, EMG needle electrodes inserted directly into the diaphragm are invasive and largely impractical for most clinical and human studies, and therefore have been used in very few studies (Luo, Moxham, & Polkey, 2008). In contrast, EMG_{sur} has been used as it is the least invasive method. However, with EMG_{sur} there are notable caveats. EMG_{sur} electrodes have high subject variability due to the deposits of the subject's subcutaneous fat, and therefore will reduce the signal strength due to muscle-to-electrode filtering effects (Luo, Moxham, & Polkey, 2008). In addition to the high subject variability while using EMG_{sur}, there is no current standardized method for placing EMG_{sur} electrodes (Luo, Moxham, & Polkey, 2008), making comparisons between subjects and studies difficult.

1.1.3.2 Diaphragm Electromyography

EMG_{di} is recorded using a specialized nasogastric tube catheter equipped with paired electrodes (Barwing *et al.*, 2013; Beloncle *et al.*, 2017). The catheter is placed in the lower esophagus, where is surrounded by the diaphragm (Alty, Man, Moxham, & Lee, 2008) and records from the crual section of the diaphragm (Luo, Moxham, & Polkey, 2008). The EMG_{di} catheter contains nine recording electrode coils and one grounding coil. The nine coils record from 5 pairs (1:5, 2:6, 3:7, 4:8, 5:9) and have an interelectrode distance of 4.4 cm. Multiple recording pairs are required on the catheter to compensate for changes in posture or lung volumes during exercise. The catheter is placed using multiple EMG pairs, such that when the largest amplitude of EMG activity during tidal breaths appears in pairs 1 & 5, in combination with lower amplitudes appearing in pairs 2 & 4, and with the lowest amplitude in pair 3, then the catheter is considered to be at the level of the diaphragm (Luo *et al.*, 2011). Compared to EMG_{sur}, the EMG_{di} is less affected by obesity, and cross talk signals (Luo, Moxham, & Polkey, 2008). However, due to the frequency of EMG_{di}, the signal is segmentally contaminated with signals from the electrocardiogram (ECG) trace (Alty, Man, Moxham, & Lee, 2008). The contaminated EMG_{di} segment is due to the overlap of frequencies between EMG_{di} and ECG. EMG_{di} frequency is between 20-250 Hz, while ECG frequency is between 0-100 Hz (Luo, Moxham, & Polkey, 2008). Another source of artefact is electrode motion, which occurs during voluntary contractions. However, this can be overcome with a high-pass filter (Luo, Moxham, & Polkey, 2008). Despite these challenges, EMG_{di} has been successfully used in conditions of exercise to monitor respiratory drive-in relation to tidal volume (Poulsen *et al.,* 2015).

1.2 SIGNIFICANCE

The use of PAV and the associated reductions in WOB during exercise has largely been limited to exercise in the ‘heavy’ domain rather than submaximal. However, to determine the use of the PAV for possible clinical and rehabilitation practices, or for strictly experimental endeavours, an understanding of reduced WOB in lower exercise intensities is needed in investigating recruitment of the diaphragm. Given that many rehabilitation interventions involve exercise performed at the submaximal level this thesis seeks to further understand the effects of reducing WOB and the associated reductions in diaphragm activity.

1.3 HYPOTHESIS

I. The diaphragm will have significantly lower electrical activity when the work of breathing is reduced via a proportional assist ventilator relative to spontaneous breathing during exercise.

Chapter 2: Experiment

2.1 METHODS

2.1.1 Subjects

Using a previously reported effect size (1.47; Dominelli *et al*., 2016), the calculated number of participants to achieve a power of 0.8 was 9. Males (n = 5) and females (n = 4), between the ages 19-30 years were recruited for this study. Subjects were non-smoking and had self-reported normal pulmonary function (i.e. no history of asthma). Subjects regularly participated in aerobic physical activity (a minimum of 3 times per week, 30 or more minutes). Subjects were excluded if they presented any contradictions to exercise testing (as indicated upon completion of the PAR-Q +, ulcer/tumor in the esophagus, nasal septum deviation, recent nasopharyngeal surgery, or allergies to latex. One subject was completely removed from analysis due to difficulties accepting PAV unloading (n = 8), and another subject was removed from PTP analysis due to gastric balloon problems during experiment (n = 7 for PTP measurements).

2.1.2 Experimental Overview

Testing took place in the Health and Integrative Physiology Lab at the University of British Columbia. All protocols were approved by the Clinical Research Ethics Board at the University of British Columbia, which conforms to the Declaration of Helsinki (H18-03414). Subjects completed two testing sessions, which were separated by a minimum of 48 hours. The first day was a maximal VO_2 exercise test done on a cycle ergometer (Excalibur Sport, Lode, Gronigen, Netherlands), followed by a familiarization session with the PAV. The second day was a continuous cycle test at a wattage corresponding to ten percent less than their gas exchange threshold (10% < GET) determined from the first session. Subjects would continuously cycle at 10% < GET for 6 minutes, while alternating on and off the PAV in one-minute intervals. Every time the subject cycled on to the PAV, the operator would increase the amount of assistance (positive pressure) generated by the PAV (Figure 1).

2.1.3 **Procedures**

2.1.3.1 Day One

Subjects began by resting on the cycle ergometer for five minutes to obtain baseline metabolic and cardiovascular measures. After rest, subjects were instructed to do a five-minute warm-up at a self-selected work rate. Men and women started the test at 120 watts and 80 watts, respectively. Work rate increased in a stepwise fashion by 20 watts every 2 minutes. The test was terminated when cadence dropped below 60 rpm despite verbal encouragement.

2.1.3.2 Day Two

The second day of testing began with the placing of an esophageal balloon-EMG_{di} catheter and surface electrodes on the subject's sternocleidomastoids and scalene muscles. After placement, subjects rested for a total of 5 minutes to record baseline values of heart rate (HR), flow, and EMG_{di}. Subjects were then instructed to do a series of maneuvers to determine maximal diaphragm contraction, including sharp sniffs (SNIFF), maximal inspiratory pressure (MIP), and inspiratory capacity (IC). Subjects completed a 5-minute warm-up at a self-selected work rate on the same electronically braked cycle ergometer (Velotron, RacerMate; Seattle, WA, USA). Subjects then rested briefly until baseline HR was maintained before starting the experimental protocol. Subjects were asked to continuously cycle at a wattage corresponding to 10% lower than wattage where the gas exchange threshold (GET) occurred. While cycling at this intensity, subjects would alternate between using the PAV and spontaneous breathing in minute intervals. Positive pressure unloading created by the PAV would increase with every PAV assistance interval (Figure 1). During spontaneous breathing intervals the PAV generated negligible pressure.

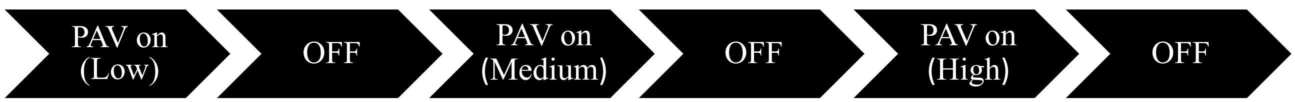

Figure 1. Sequence of experimental protocol

2.1.4 **Measurements**

2.1.4.1 Flow, Volume and Heart rate

Inspiratory and expiratory flow were measured using calibrated and heated pneumotachometer (Model 3813, Hans Rudolph, Kansas City, MO) connected to a two-way-non-rebreathing valve. (Model 2700, Hans Rudolph, Kansas City, MO). Inspiratory and expiratory volumes were measured via integration of inspiratory and expiratory flow. Composition of expired gas was analyzed via a port at the end of a mixing chamber (ML 206; ADInstruments, Dunedin, New Zealand). Heart rate was measured using a chest strap (S610i, Polar Electro, Kempele, Finland). Hear rate was then recorded using PowerLab 16/30 analog-to-digital converter running LabChart Pro Version 8.1 software (ADInstruments, Colorado Springs, CO).

2.1.4.2 Measurement of esophageal pressure, gastric pressure, and EMG$_{di}$

Esophageal pressure, gastric pressure, and EMG$_{di}$ were collected through a EMGdi multi-pair esophageal electrode catheter (Guangzhou Yinghui Medical Equipment LTD., Guangzhou China). A topical anesthetic (Xilocane, Lidocaine Hydrochloride) was applied to the subject's nares and nasal conchae before passing the EMG$_{di}$ multi-pair esophageal electrode catheter to minimize discomfort. Subjects performed a Valsalva manoeuvre while the catheter is open to the atmosphere to empty the balloon. The manoeuvre emptied any pre-existing air filled in the balloons and were filled with 0.5 mL and 1.2 mL of air administered using a syringe to the esophageal and gastric balloons, respectively. Placement was confirmed by positioning the esophageal balloon, in the lower third of the esophagus to measure esophageal pressure by use of a negative inflection in the pressure output during sharp inspirations, once observed, the balloon was retracted a further 10 cm. Validity of the position was assessed using a dynamic occlusion test before being secured in place.

2.1.4.3 **Measurement of SCM, and SCA**

Activation of the SCM and SCA were assessed using surface electrodes (3M, Saint Paul, MN). Placement of the electrodes for the SCM was on the long axis between the medial clavicle and mastoid process (Shadgan, Guenette, Sheel, & Reid, 2011) .Placement for the SCA electrode was positioned at the level of the cricoid cartilage in the posterior triangle of the subject's neck (Segizbaeva et al., 2013).

2.1.4.4 Data sampling and recording

Flow, pressure, tidal volume ($\dot{V}_T$), minute ventilation ($\dot{V}_E$), end-tidal CO_2, expired flow, esophageal pressure, gastric pressure, and EMG_{di} were recorded continuously at 2 kHz. The pressure transducer was calibrated before and after each test using a digital manometer (2021P, Digitron, Torquay UK). All data were recorded using PowerLab 16/30 analog-to-digital converter running LabChart Pro Version 8.1 software (ADInstruments, Colorado Springs, CO). Data were imported and analyzed using Microsoft Excel Version 16.4.

2.1.5 **Data Analysis**

2.1.5.1 EMG of Diaphragm, Scalene and Sternocleidomastoids

Raw EMG_{di} signals were amplified and processed through a notch filter at 60 Hz (RA-8, Yinghui Medical Technology Co. Ltd., Guangzhou, China). EMG signals were further processed through a band-pass filter between 10Hz to 3kHz. Filtered data were then transformed by a root mean square (RMS) and averaged over 0.1 second. EMG_{di}, EMG_{SCM}, and EMG_{SCA} data that were used in analysis were selected during periods of inspiration, and free of cardiac artifact. Since EMG_{di} was measured using a multi-paired catheter (to account for changes during lung volumes during exercise and posture), the highest electrode pair that measured the greatest EMG activity for a specific breath was used in the analysis. Data from the highest pair were then expressed as a percentage relative to the subject's maximal activation from either an IC, SNIFF, or MIP. All three maneuvers were executed at rest.

2.1.5.2 Gas exchange threshold and exercise intensity

Gas exchange threshold (GET) was determined by analysis of the ratio between $\dot{V}O_2$ and $\dot{V}CO_2$ during the maximal exercise test on day one. Methods for determining GET were as described in Schneider, Phillips, & Stoffolano, (1993) and (Weisman & Zeballos, 1994). The cycling wattage which corresponded to the GET was identified, then ten percent of this value was subtracted from the subjects GET wattage and was the intensity used continuously throughout the PAV trials.

2.1.5.3 Calculation of WOB and PTP

The work produced by the respiratory system during this experiment was quantified in two ways: WOB and PTP. Both measures were calculated by averaging flow, volume and pressures over eight breaths which are absent of physiological artefact (i.e. cough, swallow) over a 30 second period. Breaths selected were the same as those used in EMG analysis. WOB was calculated by mouth pressure and esophageal pressure, while PTP was calculated based on esophageal and gastric pressure. From both respective pressures, WOB was calculated via integration of esophageal swings and the volume of air pressure for both inspiration and expiration multiplied by the fb (as described in Dominelli and Sheel (2012)), while PTP was calculated by integrating the area under each pressure curve (P_{eso} ,$P_{di,}$ P_{gas}) during inspiration and multiplying these values by breathing frequency (Guenette *et al.*, 2010) . The quotient of PTP_{di} to PTP_{es} was calculated to determine the contribution of the diaphragm to the total inspiratory muscle pressure production for each condition.

2.1.5.4 Statistical Analysis

Repeated measures analysis of variance (ANOVA) was used to compare the changes in WOB, EMG_{di}, EMG_{SCM}, EMG_{SCA}, PTP_{es}, PTP_{di}, PTP_{gas}, fb, $\dot{V}_E$, and HR. Post-hoc Bonferroni tests were conducted to determine which PAV unloading conditions were considered significant. The level of significance was set at $p \leq 0.05$ for all tests. Statistical analysis was performed using 0.12.1 version of JASP.

2.2 RESULTS

2.2.1 Subject Characteristics

Subjects were healthy male and female students recruited from the University of British Columbia. Subject anthropometric characteristics are shown on Table 1, and subject cardiorespiratory variables at maximal exercise are presented on Table 2. Subjects were of similar age ($p = 0.44$), height ($p = 0.27$), and weight ($p = 0.11$).

Table 1. Subject characteristics

	Subjects (n=8)
Age (years)	26.8 ± 1.0
BMI (kg m^{-2})	22.1 ± 1.9
Height (cm)	173.6 ± 4.6
Weight (kg)	66.7 ± 7.5

Abbreviations: BMI = Body mass index.

Table 2. Cardiorespiratory values at maximal exercise and experimental workloads

	Subjects (n=8)
HR (beats min^{-1})	181.6 ± 10.1
$\dot{V}O_2$ (L min^{-1})	3.6 ± 0.6
$\dot{V}O_2$ (mL $kg^{-1}min^{-1}$)	53.6 ± 7.1
$\dot{V}CO_2$ (L min^{-1})	5.0 ± 1.2
RER	1.1 ± 0.06
$\dot{V}_E$ (L min^{-1})	153.6 ± 32.2
$\dot{V}_T$ (L)	2.6 ± 0.6
fb (breaths min^{-1})	56.4 ± 10.6
$\dot{V}_E/\dot{V}O_2$	42.9 ± 4.0
$\dot{V}_E/\dot{V}CO_2$	37.8 ± 5.0
Power (watts)	285 ± 39.6
GET (L min^{-1})	2.0 ± 0.4
10% < GET WL (watts)	141.3 ± 41.7

Abbreviations: HR = heart rate, $\dot{V}O_2$ = maximum rate of oxygen consumption, $\dot{V}CO_2$ = maximum rate of carbon dioxide production, RER = respiratory exchange ratio, $\dot{V}_E$ = minute ventilation, $\dot{V}_T$ = tidal volume, GET = Gas exchange threshold, 10 % < GET WL = 10% below gas exchange threshold workload.
Values presented as Mean ± S.D

2.2.2 **Work of Breathing**

Work of breathing, fb, $\dot{V}_E$, and HR throughout low, medium, and high PAV unloading's are summarized on Table 3 and shown in Figure 2. The WOB was similar between the lowest unloading of the PAV and unassisted breathing (p = 0.212), but was significantly lower during medium and high PAV unloading compared to spontaneous breathing (~18% mean reduction, p = 0.04 and ~ 37% mean reduction, p < 0.001, respectively). When comparing the WOB between

PAV assistance levels, unloading between low, and medium were not statistically significant compared to high unloading ($p = 0.17$, and $p = 0.38$, respectively), while medium to high unloading were not statistically significant ($p = 0.36$). Across all PAV unloading levels versus spontaneous breathing conditions there were no statistical differences in fb, $\dot{V}_E$, and HR ($p > 0.05$).

2.2.3 **EMG of Diaphragm, Scalene, and Sternocleidomastoids.**

EMG_{di}, EMG_{SCA}, and EMG_{SCM} findings are summarized in Table 3. EMG_{di} was significantly lower in all PAV (low, medium, high) unloading versus unassisted breathing conditions ($p = 0.013$, $p = 0.015$, and $p = 0.009$, respectively; Figure 3). Mean reductions of EMG_{di} between PAV unloading and spontaneous breathing were 9.7%, 9.5%, and 10.3% (low, medium, high, respectively). PAV unloading between low and medium, and low and high were not significant ($p = 0.82$, $p = 0.06$). PAV unloading between medium to high was also not significant ($p = 0.82$).

EMG_{SCA} findings are shown in Figure 4. EMG_{SCA} was insignificant for both low and medium PAV unloading to spontaneous breathing comparisons ($p = 0.5$, $p = 0.65$, respectively). EMG_{SCA} was significantly lower when comparing high PAV unloading to spontaneous breathing ($p = 0.02$).

EMG_{SCM} findings are shown in Figure 5. EMG_{SCM} was not significant for all three PAV unloading to spontaneous breathing comparisons ($p = 0.87$, $p = 0.83$, $p = 0.17$, respectively). When comparing the PAV unloading levels, there were no significance for EMG_{SCA} and EMG_{SCM} activity ($p > 0.05$).

2.2.4 PTP of Esophagus, Diaphragm and Gastric

Findings of PTP_{es}, PTP_{di}, and PTP_{gas} are summarized in Table 3. PTP_{es} was significantly lower on all PAV unloading conditions compared to unassisted breathing ($p < 0.01$). PTP_{di} was significantly lower on all PAV unloading conditions compared to unassisted breathing ($p < 0.05$ low comparison; $p < 0.01$ medium and high comparison). PTP_{gas} was significant only at high PAV unloading to spontaneous breathing comparison ($p < 0.01$). The quotient of PTP_{di} to PTP_{es} are shown in figure 9. No statistical differences were found between any PAV unloading intensities compared to spontaneous breathing.

Table 3. Cardiorespiratory variables, WOB, diaphragm activation, and accessory respiratory muscle activation during experimental protocol

	PAV On (L)	OFF	PAV On (M)	OFF	PAV On (H)	OFF
WOB (J min^{-1})	58.6 ± 25.3	73.5 ± 26.3	76.7 ± 41.9	93.5 ± 39.4 †	72.2 ± 34	114 ± 48.1 ‡
fb (breaths min^{-1})	29.0 ± 1.9	29.0 ± 2.7	29.7 ± 2	27.3 ± 1.9	30.2 ± 1.5	30.0 ± 2.3
$\dot{V}_E$ (L min^{-1})	53.9 ± 6.4	51.4 ± 7	58.5 ± 8.6	57.0 ± 7.9	65.9 ± 8.7	60.3 ± 10.1
HR (beats min^{-1})	133.6 ± 3.3	137.1 ± 3.1	138.2 ± 3.3	141.5 ± 3.7 †	141.2 ± 4	142.9 ± 3.6
EMG_{di} (% normalized)	22.7 ± 10.3	32.41 ± 17.5†	29.7 ± 20.3	39.2 ± 21.9 †	35.68 ± 23.7	46.0 ± 27.5†
EMG_{SCA} (% normalized)	9.8 ± 8.3	9.0 ± 6.9	10.0 ± 6.8	10.5 ± 8.4	10.8 ± 5.3	13.6 ± 4.3†
EMG_{SCM} (% normalized)	12.4 ± 10	12.7 ± 9.4	14.16 ± 12.7	13.8 ± 9.6	15.2 ± 15	17.5 ± 12.1
PTP_{es} (cmH_2O)	537.2 ± 128	667.2 ± 137.7 †	552. 8 ± 132.6	679.7 ± 153.67 ‡	546.4 ± 41.6	724.0 ± 128.0 ‡
PTP_{di} (cmH_2O)	293.0 ± 60.9	329 ± 78.1 †	227.9 ± 59.3	327.0 ± 79.1 ‡	284.4 ± 42.6	347.4 ± 50.0 ‡

PTP_{gas} (cmH_2O)	159.3 ± 60.1	167.0 ± 66.0	144.3 ± 50.1	162.7 ± 82.8	124.0 ± 60.9	177.0 ± 95.0 ‡
PTP_{di}/PTP_{es}	0.55 ± 0.09	0.50 ±0.06	0.55 ± 0.08	0.48 ± 0.08	0.52 ± 0.08	0.48 ± 0.05

Abbreviations: WOB = work of breathing, fb = frequency of breathing, $\dot{V}_E$ = minute ventilation, HR = heart rate, EMG_{di} = electromyography of the diaphragm, EMG_{SCA} = electromyography of the scalene, EMG_{SCM} = electromyography of the sternocleidomastoid, PTP_{es} = pressure time product of esophagus, PTP_{di} = Pressure time product of the diaphragm, PTP_{gas} = pressure time product of the gastric.
Values presented as Mean ± S.D
Significance of p <0.05 between PAV assistance and spontaneous breathing following indicated by †
Significance of p <0.01 between PAV assistance and spontaneous breathing following indicated by ‡

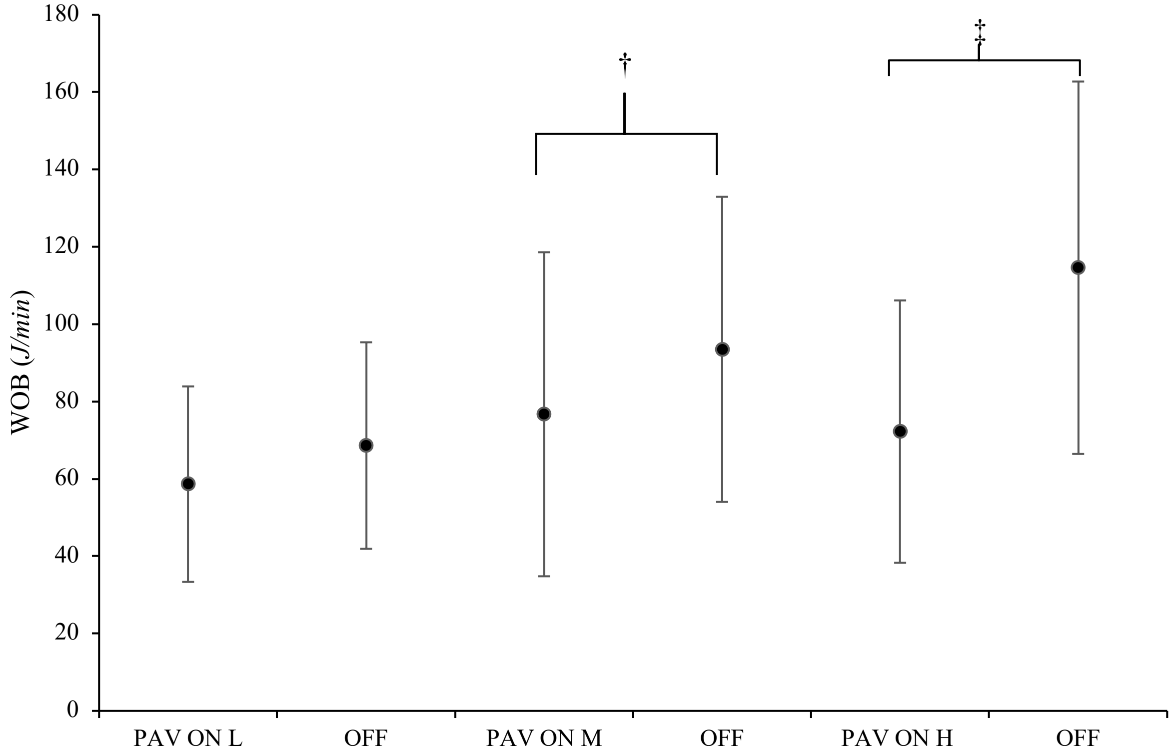

Figure 2. WOB during experimental protocol.
Values presented as mean ± S.D.
† indicates p <0.05 between PAV and spontaneous breathing following.
‡ indicates p < 0.01 between PAV and spontaneous breathing following.

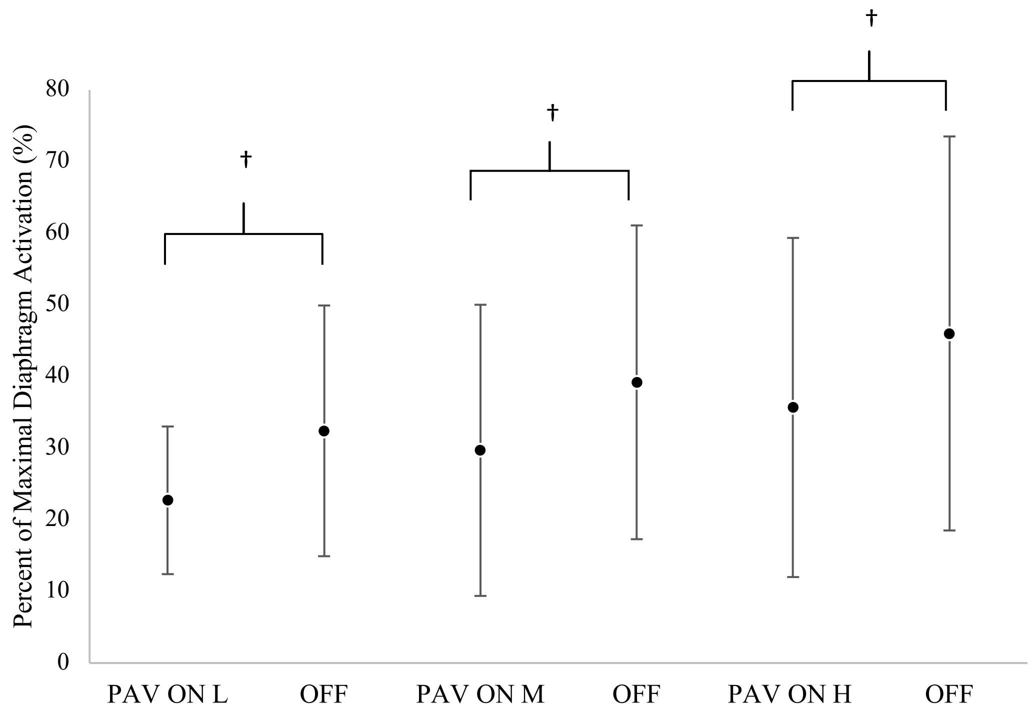

Figure 3. EMGdi during experimental protocol. EMG_{di} is expressed as percent normalized to the subject's maximal respiratory muscle activation (MIP, SNIFF, and IC).
Values presented as mean ± S.D.
Significance of p <0.01 between PAV assistance and spontaneous breathing following indicated by ‡

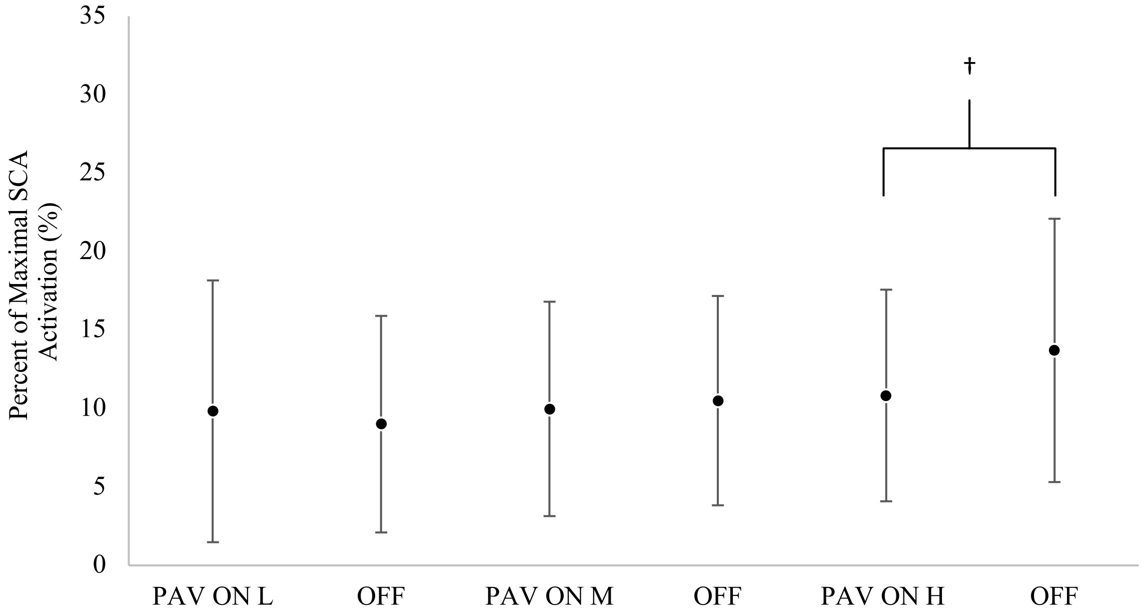

Figure 4. EMG of SCA during experimental protocol.
Values presented as mean ± S.D.
Significance of $p < 0.01$ between PAV assistance and spontaneous breathing following indicated by ‡

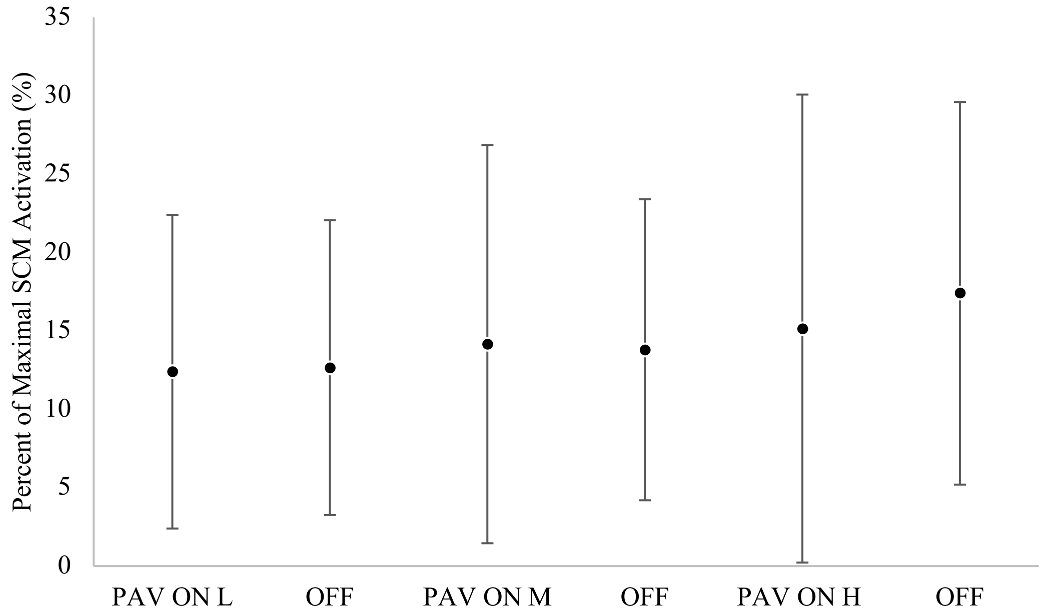

Figure 5. EMG of SCM during experimental protocol.
Values presented as mean ± S.D.
No statistical significance comparing PAV and corresponding off segment.

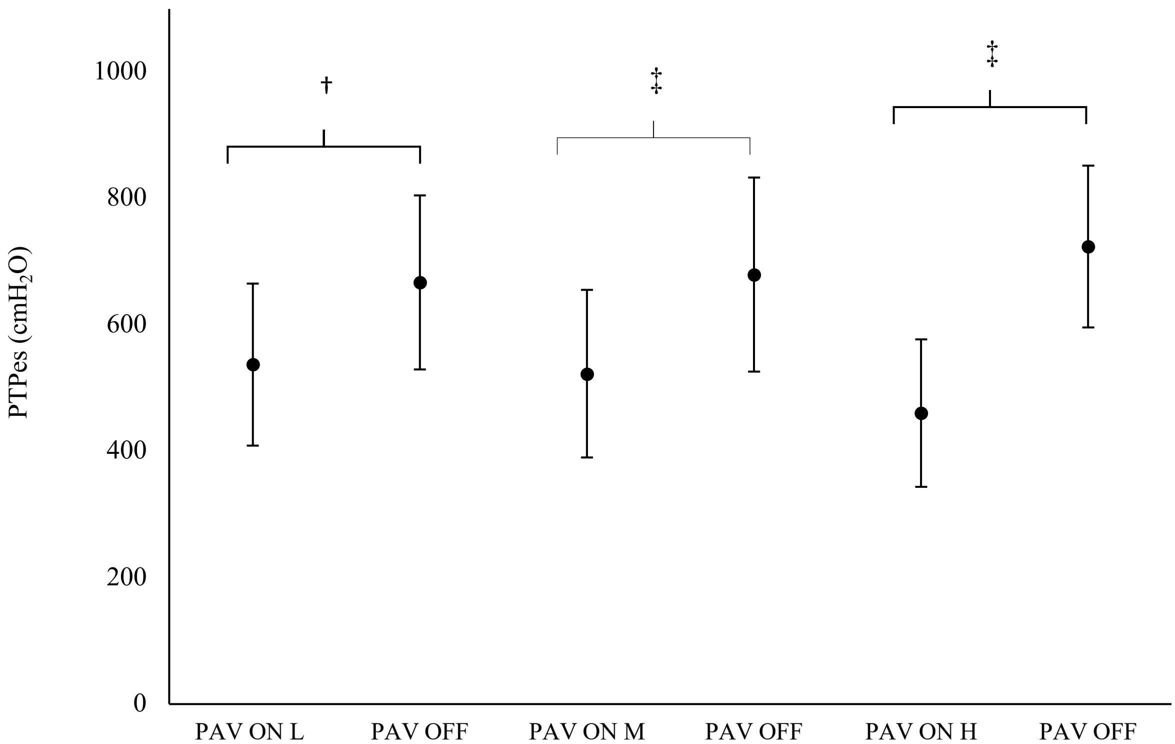

Figure 6. PTP_{es} during experimental protocol.
Values presented as mean ± S.D.
Significance of $p < 0.01$ between PAV assistance and spontaneous breathing following indicated by ‡

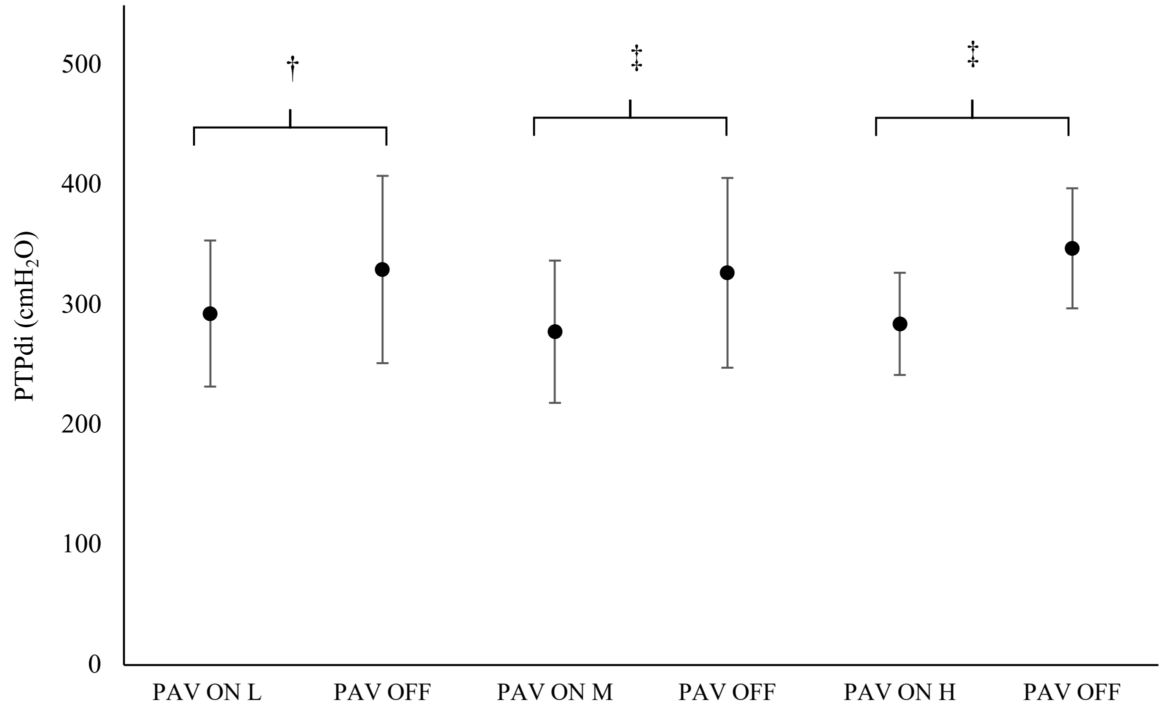

Figure 7. PTP_{di} during experimental protocol.
Error bars represent standard deviation.
Values presented as mean ± S.D.
Significance of $p < 0.05$ between PAV assistance and spontaneous breathing following indicated by †
Significance of $p < 0.01$ between PAV assistance and spontaneous breathing following indicated by ‡

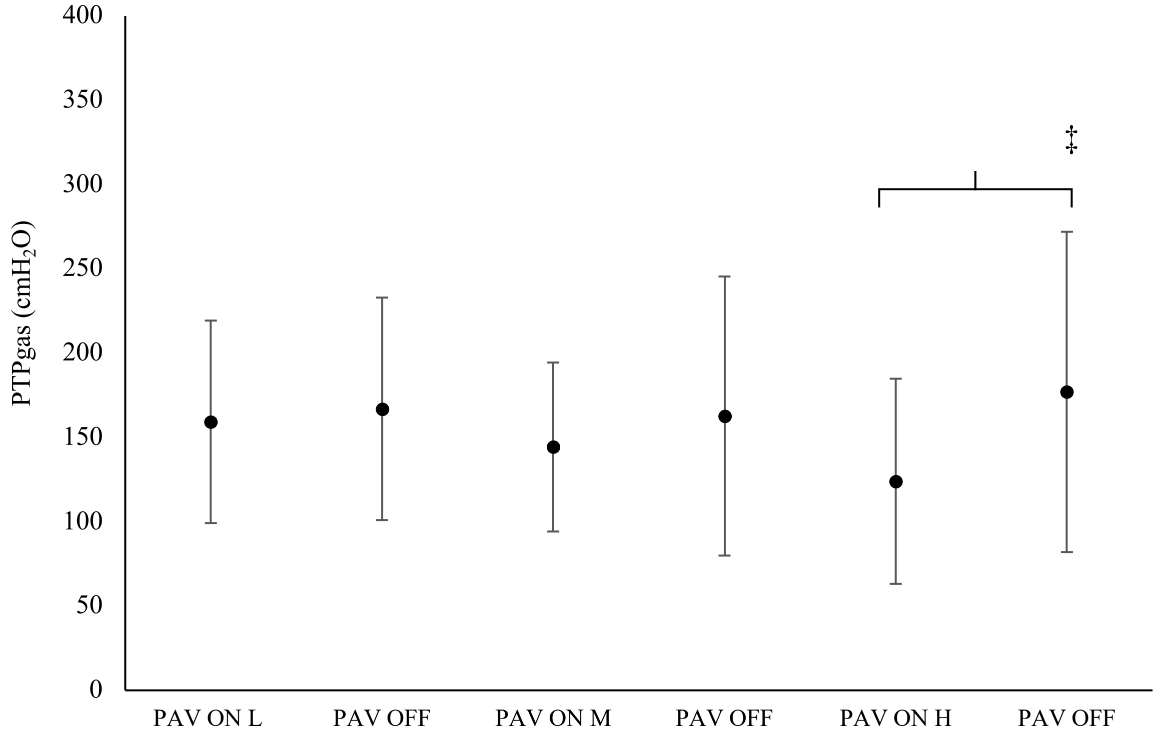

Figure 8. PTP_{gas} during experimental protocol.
Values presented as mean ± S.D.
Significance of $p < 0.01$ between PAV assistance and spontaneous breathing following indicated by ‡

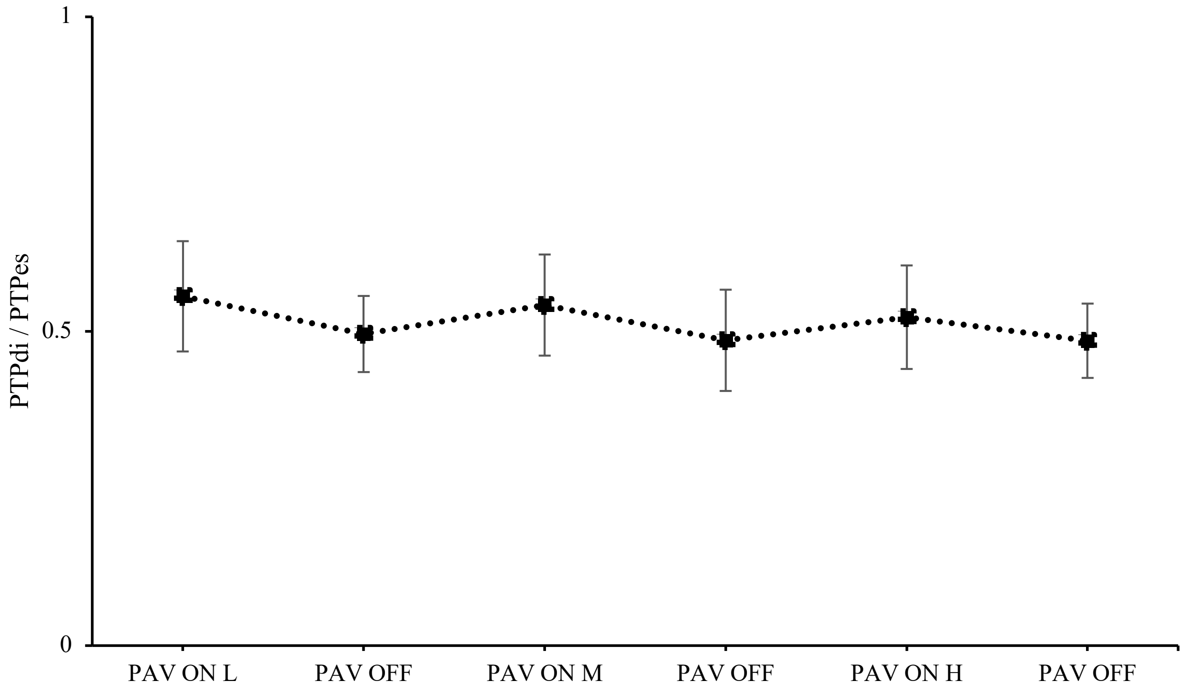

Figure 9. Ratio of PTP_{di} to PTP_{es}.
Values presented as mean ± SD.
No statistical significance comparing PAV and corresponding off segment.

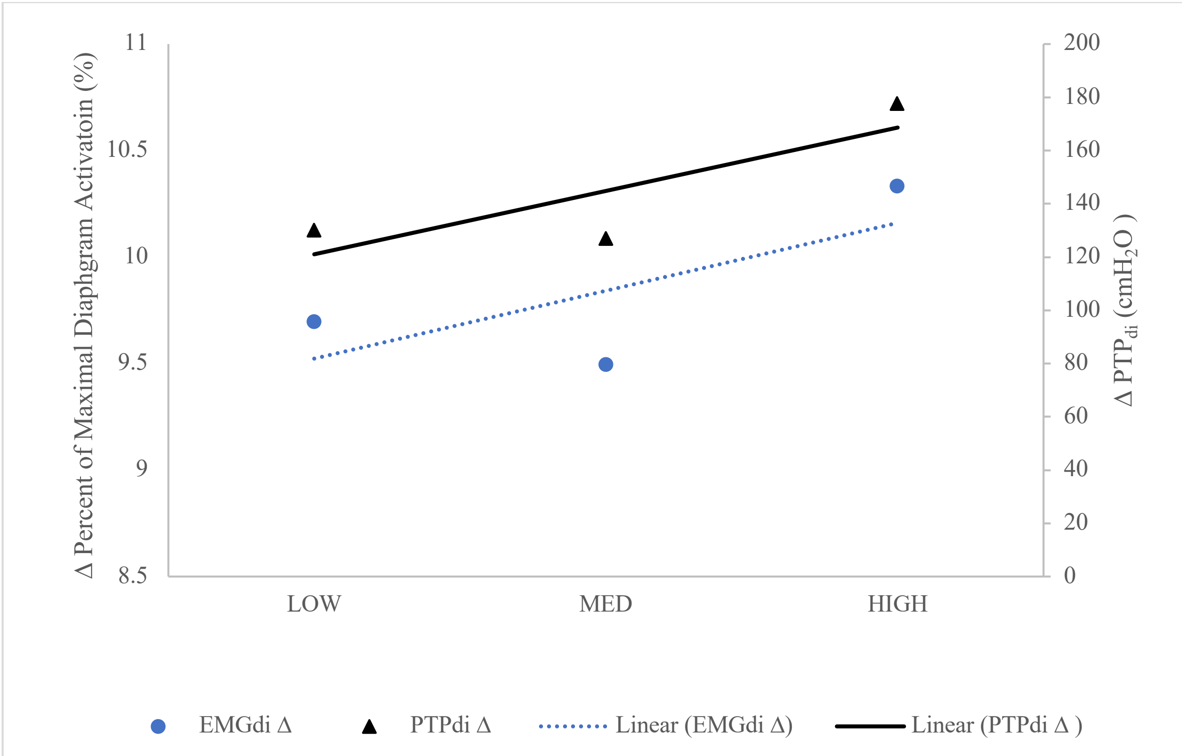

Figure 10. Change in EMG$_{di}$ and PTP$_{di}$ when comparing PAV to spontaneous breathing
X-axis indicates the PAV unloading condition. Change (Δ) calculated by mean value on PAV during unloading minus sponatanous breathing following unloading segment (i.e Low = PAV on L – OFF).

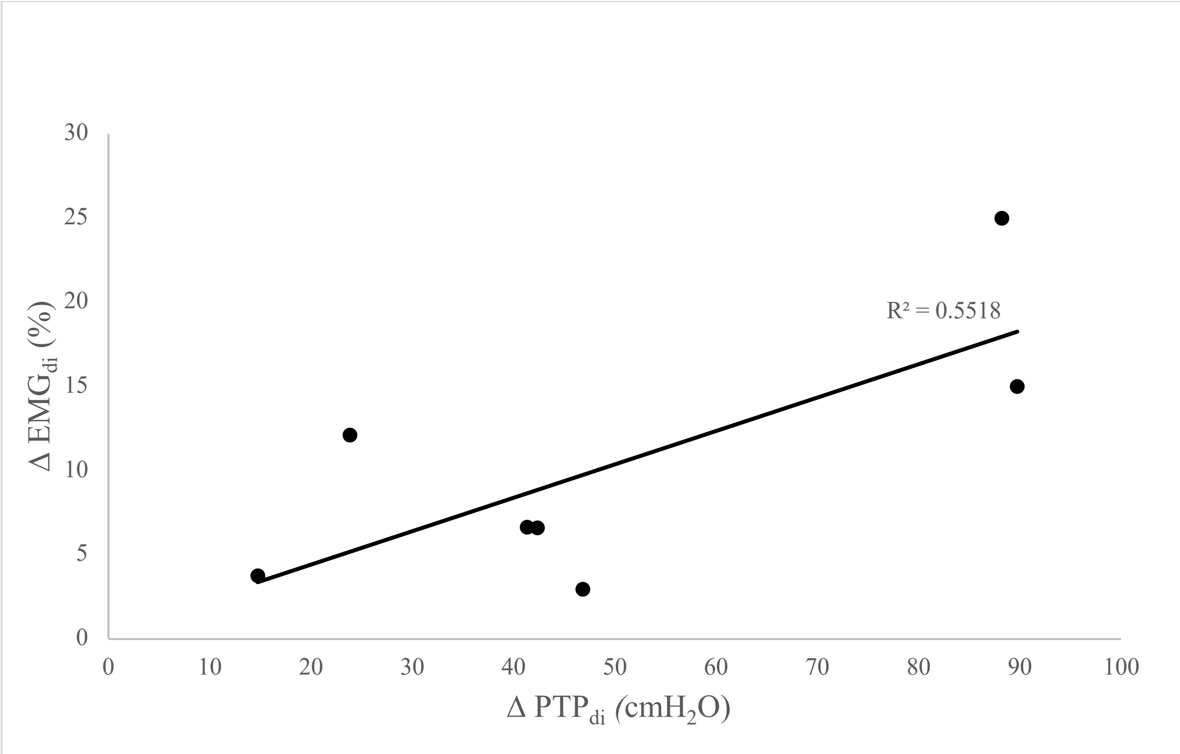

Figure 11. Total change in PTP_{di} vs. change in EMG_{di}.
Change(Δ) for both measured calculated by sponatanous breathing following unloading segment minus PAV unloading condition value (i.e Low = OFF – PAV On L). All three conditions averaged. Each dot represents one subject (n = 7). Participants who failed to allow PAV to unload removed from figure.

Chapter 3: Discussion & Conclusion

3.1 DISCUSSION

This thesis quantified how assisted ventilation lowers the work of breathing and electrical activity of the diaphragm during moderate intensity exercise in healthy humans. It was hypothesized that electrical activity of the diaphragm would be reduced when the work of breathing was experimentally lowered compared to spontaneous breathing. The main findings are two-fold. First, when cycling at a moderate intensity, the work of breathing was significantly lower with assisted ventilation and corresponded to the degree of ventilatory assistance. Second, electrical activity of the diaphragm was significantly lower with ventilatory assist and was proportional to the degree of assistance. The findings of this study show that ventilatory assist during moderate intensity exercise reduces the work of breathing and diaphragm activity. By experimentally reducing the overall work of breathing during exercise the work performed by the diaphragm, as the primary muscle of inspiration, is lowered. Reducing the work, and therefore the metabolic demand of the respiratory musculature allows for greater blood flow towards locomotor muscle. The findings of this study support the use of a PAV at lower exercise intensities and ventilations.

3.1.1 WOB, PTP and PAV

We sought to observe the reductions of WOB during moderate intensity exercise using a PAV. On average, reductions in WOB across all three unloading levels were approximately 25%, while maintaining a constant $\dot{V}_E$ throughout the protocol and cycling at a moderate exercise intensity (10% below GET; approximately < 50% of VO_{2MAX} watts). To our knowledge, this is the first study to examine PAV and diaphragm EMG activity simultaneously under moderate exercise intensities. A similar study by Akoumianaki *et al.,* (2017), which used submaximal exercise, compared pressure support ventilation to PAV in critically ill ICU patients. However, in this study there was no direct measurement of WOB, and an index of breathing efficiency was used ($\Delta VO_2/W$) instead. Akoumianaki *et al.,* (2017) reported that use of PAV during 15 minute exercise at 60% VO_{2MAX} doubled the breathing efficiency, when compared to pressure support ventilation. Despite the absence of a measure of the WOB, the findings of Akoumianaki *et al.,* (2017) agree with the current thesis – namely, PAV is able unload the respiratory system under conditions of submaximal exercise. Using the same apparatus, previous work done in our laboratory has shown reductions in WOB via PAV by approximately 30-55% of control during high intensity cycling (Dominelli *et al.* 2016), while other studies using moderate to near maximal workloads have reported reductions in WOB ranging from 40-80% (Amann *et al.*, 2007; Dominelli *et al.*, 2017; Harms, 1997; Romer, 2006; Wetter *et al.*, 1999).

Reductions in WOB for the current study align with the reductions seen by Dominelli *et al.* (2016). Smaller reductions in WOB compared to the existing literature are likely due to the low $\dot{V}_E$ associated with moderate exercise, the effect of low $\dot{V}_E$ on the compartments of WOB, and the PAV assistance level unloading with between subject variability (Dominelli *et al.,* 2016). For example Wetter *et al.,* (1999), had highly trained male subjects cycle at 50% VO_{2MAX} in 10-15 minute bouts where $\dot{V}_E$ was 79 L•min^{-1}, fb = 27 (breaths• min^{-1}) and the reductions in WOB via PAV were 40%. In the current study, we found that $\dot{V}_E$ ~ 59 L•min^{-1}, fb = 29, and the reductions in WOB were 20-30% (depending on PAV unloading level). Since fb between the current study and Wetter *et al.,* (1999) are similar, its likely that the subjects in the current thesis had smaller V_T, thus contributing to the smaller reduction in WOB. Further, differences in the

WOB reductions could be accounted for by the variation between subjects and their ability to accept the unloading of the PAV. Amann *et al*., (2007) observed subjects cycling at constant workload trials at roughly 80% of peak watts while using a PAV to maximally unload participants. Reported variation in reductions in WOB ranged from 35-80% (Amann *et al*., 2007) highlighting the inconsistency between subjects to accept unloading of the PAV. Additionally, the PAV unloads only during inspiration and cannot unload during expiration. As such, the degree to which the subject will allow the PAV to assist them is crucial in determining the reductions in WOB. Since the current study attempted to unload subjects in gradual assistance levels instead of maximally throughout the entire experimental trial, this contributed to the lower average of WOB reductions. When specifically looking at the highest unloading PAV comparison, reductions were approximately 40%, which align with the unloading values reported in Amann *et al.* (2007) Dominelli *et al.*(2015; 2016; 2017); Harms (1997); Romer (2006); and Wetter *et al.*(1999).

To further understand where reductions in WOB occurred we conducted PTP analyses. PTP is used to estimate respiratory muscle oxygen consumption and is broken into three areas: esophageal, diaphragm, and gastric. PTP_{es} provides a general estimate of the entire respitatory system, while PTP_{di} provides an estimate of the diaphragm, and PTP_{gas} estimates the contribution of the abdominal muscles. The ratio between PTP_{es} to PTP_{di} estimates the contribution of the diaphragm to the total respiratory muscle generation. In the current thesis, significant reductions in PTP_{es} and PTP_{di} (Figures 6 & 7) were shown for each PAV unloading to spontaneous breathing comparison. However, when analyzing the quotient of PTP_{di} to PTP_{es}, there is no significant differences in diaphragm contribution between conditions. This suggests that the PAV was successful at unloading both the respiratory muscles and the diaphragm proportionally.

3.1.2 **EMG_{di} and PAV**

The current study showed significant reductions in EMG_{di} during exercise while on the PAV. In addition, the largest reductions in EMG_{di} and WOB compared to spontaneous breath occurred at the highest PAV unloading (Table 3). However, there were similar absolute changes in EMG_{di} for each unloading comparison (Figure 10). It has been demonstrated that changes in EMG_{di} have a significant correlation to changes in PTP_{di} (Molgat-Seon *et al*., 2018), however, in the current thesis there were similar absolute changes for each unloading comparison. Other studies which have similar absolute changes in EMG_{di} include Luo *et al.* (2011), which investigated EMG_{di} in clinically stable COPD patients in constant versus incremental exercises tests at 80% VO_{2MAX}, while using EMG_{di} catheters. Their study showed at constant load exercise, EMG_{di} increases initially followed by a plateau during constant work rate (Luo *et al*., 2011). Reasons for this plateau may be due to neural inhibition from reduced diaphragm force induced by increased inspiratory load (i.e. exercise) (Bigland-Ritchie, Rice, Garland, & Walsh, 1995). Albeit in the current study the experimental trial was conducted under a constant workload, it is unlikely there was a plateau since the change in EMG_{di} across all PAV unloading comparisons very small (~9-10%; Figure 10), and because there are only three absolute values to compare. Further, Luo *et al*. (2011) study was conducted on COPD patients, where the current study was done on young, healthy individuals.

In other animal models the relationship between EMG, PTP and ventilatory assist has been examined. Beck *et al.,* (2007) investigated EMG_{di}, PTP_{di} with neurally adjusted pressure support ventilators (NAVA) in 3 kg lung injured rabbits. Although this study did not use a PAV, fundamentally NAVA accomplishes the same goals as PAV via a nasogastric tube to measure diaphragmatic EMG and moderate gas delivery in efforts to reduce wasted inspiratory efforts. Like the current findings, Beck *et al.,* (2007) found with NAVA decreased EMG_{di} and PTP_{di}.

3.1.3 PAV and Accessory Muscles

EMG_{SCA} showed significant reductions in the high unloading PAV comparison (p = 0.02). However, EMG_{SCM} was similar amongst all PAV unloading and spontaneous breathing comparisons. It is likely accessory respiratory muscles were not as recruited during these exercise intensities compared to accessory muscle recruitment in maximal exercise (Breslin, 1992).

Studies that have investigated the relationship of positive pressure support ventilation with accessory respiratory include Schmidt *et al.,* (2013), which examined high- versus low-pressure support ventilation on EMG of extra diaphragmatic inspiratory muscles in intubated intensive care unit patients. EMG_{SCA} was found to be reduced during high pressure support ventilation compared to low pressure support ventilation (Schmidt *et al.,* 2013). Like the current thesis, reductions in EMG_{SCA} were significant only at the highest level of PAV assistance. These findings are valuable since in pulmonary rehabilitation populations (such as COPD), there is an increased reliance on accessory respiratory muscles such as the scalene and sternocleidomastoids at low ventilations to lift the chest wall during inspiration (Sarkar, Bhardwaz, Madabhavi, & Modi, 2019).

3.1.4 Significance and Future Directions

What do these findings add to the current literature? It is known during exercise that there is an ongoing competition for blood flow between respiratory musculature and locomotor muscles. As respiratory muscle work increases with greater exercise intensity, sympathetic activity increases from the diaphragm, causing localized blood flow constriction of the locomotor muscles, and redistribution to respiratory musculature (Aaker & Laughlin, 2002). Using this metaboreflex framework, PAV has been used in numerous studies to assess WOB influences on locomotor muscles blood flow during high intensity exercise. Findings include: 1) prevention of diaphragm fatigue (Babcock, Pegelow, Harms, & Dempsey, 2002) and locomotor fatigue (Romer, 2006); 2) increased exercise duration in normoxia, hypoxia, and in chronic heart failure patients (Harms *et al.,* 2000; Amann *et al.*, 2007; O'Donnell *et al.,* 1999, respectively); and 3) reduced leg discomfort and dyspnea ratings (Harms *et al.*, 2000).

In the current study, we successfully unloaded the respiratory muscles, shown via reductions in WOB, PTP, and lowered diaphragm electrical activity. As such, these findings demonstrate that PAV can reduce mechanical work of the respiratory muscles at moderate intensity exercise with lower ventilations, and without applying maximal unloading.

Why is this important? This study showed that by reducing the WOB via a PAV, the activity of the diaphragm (via EMG_{di}) was reduced (Figure 11). This adds to the current body of literature by showing; 1) the PAV is suitable in a wider range of ventilations (i.e. lower exercise intensities), and 2) the PAV is capable of reducing the activity of the diaphragm, the largest contribution respiratory muscle to a spontaneous breath, even during submaximal PAV unloading. As such, these results suggest that the PAV would be a suitable intervention in clinical populations where there is reduced capabilities in exercise as outlined in Ambrosino & Rossi (2002). Specifically, reductions in WOB and EMG_{di} from a PAV would be favorable in applications such as sleep apnea, improving cardiac index (Kondili *et al.* 2006), improved dyspnea scores (Ambrosino et al., 1997), promotion of exercise in critically ill patients, and patient ventilator weaning (Barwing *et al*., 2013; Yuan Ming Luo *et al.*, 2008). However, more information of how the PAV influences heart-lung interactions is needed to determine if the PAV is a viable intervention for clinical populations. In addition, follow up studies including other positive support ventilators such as a PSV, and NAVA should be investigated to determine study repeatability and generalizability.

3.1.5 **Limitations**

3.1.5.1 WOB and PTP

Calculations for WOB used in this study were a conservative estimate. WOB was calculated based on mouth and esophageal pressure, while PTP was calculated via esophageal and gastric pressure via the EMG_{di} multipair electrode esophageal catheter. Esophageal pressure is used as a surrogate for pleural pressure, however there are limitations to this method which include regional differences in ventilation, and the effects of subjects posture to esophageal pressure due to mediastinal weight (Milic-Emili *et al*., 1964; Washko, O'Donnell, & Loring, 2006). Further, due to the positive pressure generated by the PAV it is difficult to compartmentalize the individual components of breathing (i.e. elastic and resistive components). Lastly, the presented values are not considering the work done by distorting the chest wall and the stabilization of the abdomen (Goldman, Grimby, & Mead, 1976). Given these limitations, the estimates of WOB and PTP in this thesis are likely underestimated.

3.1.5.2 EMG

Due to the frequency of EMG_{di}, the signal is contaminated with signals from the ECG trace (Alty, Man, Moxham, 2008). EMG_{di} frequencies are between 20-250 Hz, while ECG frequencies ore between 0-100 Hz (Luo, Moxham, Polkey, 2008). Despite best efforts it is possible that ECG trace was captured during analysis of EMG_{di}.

3.1.5.3 PAV

The sensation of positive pressure at the mouth during inspiration on the PAV is arguably different from spontaneous breathing. To achieve optimal unloading, the subject must accept the positive pressure support generated by the PAV. As such, subjects become more aware of their breathing pattern and coaching is required to maintain relaxation of the respiratory muscles and not dampen the inspiratory assistance. Despite our best efforts to provide subjects with familiarization sessions, and coaching while conducting the experiment, subjects may have not fully accepted the PAV during this study. As such, the PAV may have been unable to fully unload subjects, reducing the value between unloading to spontaneous breathing comparisons.

We aimed to use low, medium, and high PAV unloading conditions as a gradient for maximal subject unloading to analyze if there was a “all or nothing” response in reductions of WOB, PTP, and EMG. Maximal PAV unloading was determined subjectively by incrementally increasing the assistance throughout the trial and fine tuning via the absence or presence of coughing, swallowing, or subjects becoming asynchronous with the PAV. As a result, we were unable to quantify the magnitude of unloading.

3.1.5.4 Experimental Design

This study attempted to unload subjects as much as they could tolerate using a PAV. As mentioned previously, a characteristic of the PAV is to provide the subject with pressure in proportion to their instantaneous effort, as such it has no preselected target volume or pressure. However, a caveat of having no preselected volume or pressure is that the subject needs to cooperatively work with the PAV operator. Subsequently, we were unable to blind the subjects to the condition they were under. During the study, subjects 1) needed to listen to the PAV operator to achieve unloading and synchronicity, 2) heard the pneumonic valves opening and closing, and 3) could feel the positive pressure at their mouths.

We aimed to use low, medium, and high PAV unloading conditions as a gradient for maximal subject unloading to analyze if there was a "all or nothing" response. Maximal PAV unloading was determined subjectively by incrementally increasing the assistance throughout the trial and fine tuning via the absence or presence of coughing, swallowing, or subjects becoming asynchronous with the PAV. As a result, we were unable to quantify the magnitude of unloading and there is potential for a carryover effect between low, medium, and high unloading comparisons.

3.1.6 **Conclusion:**

Among healthy subjects, the use of PAV during moderate exercise intensities and ventilations lowers both the WOB and EMG_{di}. Reductions in WOB occurred in a similar magnitude to those of diaphragm activity, suggesting that the PAV is successful in reducing diaphragm activity. In the context of the current body of literature, the reductions in WOB,

PTP_{es}, PTP_{di} and EMG_{di} suggest that PAV would be suitable for rehabilitation applications proposed by Ambrosino & Rossi (2002).

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Appendix: Questionnaires

THE UNIVERSITY OF BRITISH COLUMBIA

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Tel: (604) 822-3838
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Electrical activity of diaphragm when lowered work of breathing during exercise

Subject Identifier:

Medical History

To the best of your knowledge please circle or answer the following:

1. Are you in good general health? YES/ NO
   If no, please specify: ____

1. Are you currently taking any medications (excluding oral contraceptives)?

   Please list: ____

2. Do you currently smoke? YES/NO

3. Do you have a history of smoking? YES/NO

4. When was the last time you had a cold? __________________

5. Do you have asthma, other lung problems or significant illness? YES/NO
   Please list: ____

6. Have you had recent nasopharyngeal surgery? YES/NO

7. Do you have an ulcer or tumour in your oesophagus? YES/NO

8. Are you sensitive to local anaesthetics or if you have allergies to latex? YES/NO

9. Has a doctor told you that you have high blood pressure? YES/NO

10. Have you ever had a heart attack? YES/NO

11. Has a doctor told you that your cholesterol is at a high risk-level? YES/NO

    If yes, please specify: ____

12. Do you have diabetes or has a doctor told you that you have pre-diabetes? YES/NO

    If yes, please specify: ____

Version 2 February 21, 2019 [H18-03414] 1

Physical Activity History

Type of Physical Activity: ____

Average Duration: ____

Average Frequency: ____

Medical Screening Form

Diaphragm electrical activity during manipulation of work of breathing and exercise intensities

Subject ID # : __________

Age: _____ (years)

To the best of your knowledge:

1. Are you in good general health?
Please circle one. yes 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 or has a doctor told you that you have pre-diabetes?
Please circle: yes or no

If yes, please specify: ______________________________________