THE EFFECT OF DIFFERENT INTERVENTIONS ON THE SENSORY AND AFFECTIVE DIMENSIONS OF DYSPNEA IN PATIENTS WITH COPD DURING EXERCISE

by

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Abstract

Background: Dyspnea is a complex sensation that has been recognized as a similar entity to the sensation of pain. Research has shown that dyspnea can be caused by a variety of diverse mechanisms and can be interpreted differently by each individual. Hyperoxia, heliox, and BiPAP are able to reduce dyspnea in patients with COPD but it is unknown how they specifically influence the affective (A_1) and sensory (S_I) dimensions of dyspnea during exercise. The aim of this study was to examine the extent to which hyperoxia, heliox and BiPAP alter A_1 and S_I scores and if changes in these dimensions of dyspnea are associated with improvements in exercise capacity.

Methods: 10 patients with moderate to severe COPD (post-bronchodilator FEV_1/FVC <0.7, 30%< FEV_1 < 80% pred, >10 pack year history of smoking) who were exacerbation-free for at least six weeks prior to the study performed constant-load cycling at 75% of maximal work rate breathing air, hyperoxia (40% O_2, 60% N_2), heliox (21% O_2, 79% He), or BiPAP (pressure optimized for each individual).

Results: At an isotime during exercise, hyperoxia reduced the sensory intensity of dyspnea (p=0.033). The change in A_1 and S_I were also significantly reduced compared to air with both hyperoxia (p=0.033, p=0.025, respectively) and heliox (p=0.047, p=0.041, respectively) but not with BiPAP. The A_1/S_I ratio was unchanged with all interventions compared to air. There were no significant changes in the sensory qualities of dyspnea with any intervention, except for the sensation of breathing a lot (rapidly, deeply, or heavily), which was significantly reduced with heliox at isotime. There were no significant differences in dyspnea measures or ventilatory parameters at end exercise.

Conclusions: Hyperoxia and heliox altered the affective and sensory dimensions of dyspnea during exercise, leading to improvements in exercise time with hyperoxia. There were considerable individual differences in the reported quality of dyspnea scores, as well as exercise time. These findings suggest that phenotyping patients based on their specific type of dyspnea to a particular therapy before an exercise intervention may be warranted to enhance the known benefits of exercise for patients with COPD.

Preface

Chapter 2 is based on work conducted at the Pulmonary Function Laboratory at the Kelowna General Hospital by Ms. S Perry, Dr. N Eves, and Dr. D Rolf. Ms. Perry was responsible for recruiting all patients for the study, conducting all testing sessions, and analyzing all the data. Dr. N Eves was responsible for overseeing and supervising the project, while Dr. D Rolf was responsible for ensuring patient safety and screening any exercise contraindications during the cardiopulmonary exercise tests. Mr. G Koelwyn was a valued research assistant and helped to collect data during the exercise tests.

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List of Terms

A	Affective Dimension
A_1	Immediate Feelings of Unpleasantness
A_2	Long-term emotions
ACCP	American College of Chest Physicians
ANOVA	Analysis of Variance
A-H	Air Hunger
ATS	American Thoracic Society
BDI	Baseline Dyspnea Index
BiPAP	Bi-level Positive Airway Pressure
CLT	Constant Load Test
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CPET	Cardiopulmonary Exercise Test
CVD	Cardiovascular Disease
D_LCO	Diffusion Capacity of the Lung for Carbon Monoxide
D_{LCO}/V_A	Diffusion of the lung for carbon monoxide corrected for alveolar ventilation
ECG	Electrocardiogram
EELV	End Expiratory Lung Volume
EFL	Expiratory Flow Limitation
EILV	End Inspiratory Lung Volume
ERV	Expiratory Reserve Volume
FEV_1	Forced Expired Volume in One Second
FVC	Forced Vital Capacity
FRC	Functional Residual Capacity
Heliox	Helium-Oxygen Gas
HR	Heart Rate
IC	Inspiratory Capacity
IRV	Inspiratory Reserve Volume
KGH	Kelowna General Hospital
M-E	Muscular Effort
MDP	Multidimensional Dyspnea Profile
mMRC	Modified Medical Research Council Dyspnea Scale
MVV	Maximal Voluntary Ventilation
OCD	Oxygen Cost Diagram
$PaCO_2$	Partial Pressure of Carbon Dioxide in the Blood
PaO_2	Partial Pressure of Oxygen in the Blood
PEEPi	Intrinsic Positive End Expiratory Pressure
PO	Power Output
R_{aw}	Airway Resistance
RER	Respiratory Exchange Ratio
RR	Respiratory Rate
RV	Residual Volume
SaO_2	Oxyhemoglobin Saturation as Measured by Blood Analysis

S_PO_2	Oxhemoglobin Saturation as Measured by Pulse Oximeter
ΔS_PO_2	Change in Oxyhemoglobin Saturation From Resting Values to Peak Exercise
S_I	Sensory Intensity
SOBQ	Shortness of Breath Questionnaire
T_E	Time for Expiration
T_I	Time for Inspiration
T_{TOT}	Total Respiratory Cycle Time
TLC	Total Lung Capacity
VAS	Visual Analog Scale
VC	Vital Capacity
V_E	Ventilation
VO_2	Volume of Oxygen Uptake
VO_{2peak}	Peak Oxygen Uptake
V_T	Tidal Volume
W-E	Work-Effort
W_{max}	Workload Maximum
WOB	Work of Breathing

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The amount of support and motivation for this project from my committee members, family, and friends has been astounding. In particular, I would like to thank Dr. N Eves for his continued reassurance and his scientific aptness, both of which were crucial to the success of this project. The encouragement from my family and friends has been my driving force to complete this thesis, and without them this project would not have been possible. I cannot begin to express how much I appreciate everyone who helped to make this project possible.

CHAPTER 1

Introduction

1.1 Chronic Obstructive Pulmonary Disease (COPD)

Chronic Obstructive Pulmonary Disease (COPD) refers to a number of preventable chronic respiratory conditions characterized by partially reversible airflow limitation, cough, sputum production and dyspnea [2]. Chronic bronchitis and emphysema are the two primary conditions of this disease [3] and are associated with persistent inflammation of the lung [4]. Chronic bronchitis is defined as excessive tracheobronchial mucus production, sufficient to cause cough, and with expectoration for at least three months of the year [5]. Emphysema refers to the destruction of alveolar parenchymal tissue and the subsequent loss of lung epithelial cells, endothelial cells, and interstitial mesenchymal cells [6]. The loss of alveoli and surrounding attachments causes a loss of lung elastic recoil, which produces airway collapse upon expiration. Chronic inflammation results in mucus plugging, inflammatory narrowing, and the loss of small airways, which consequently results in airway obstruction [4] and can cause accelerated lung aging [7]. Furthermore, emphysema can cause the loss of the pulmonary vascular bed, which can have direct repercussions on pulmonary resistance [8]. Inhaled toxic particulate matter (primarily from tobacco smoke in the Western world) is believed to trigger this abnormal inflammatory response that damages the small and large airways, the lung parenchyma, and the pulmonary vasculature [4, 9].

In 2005, 754,700 Canadian adults over the age of 35 were diagnosed with COPD [10]. It is likely that this number greatly underestimates the actual number of people living with the disease, since many people likely remain undiagnosed. In Vancouver

alone, it is predicted that 9.3% of the population over 40 years of age is living with moderate to severe forms of this disease [11]. COPD is currently the fifth leading cause of death worldwide and is predicted to be the fourth by 2030. The economic burden of COPD is huge and is also projected to increase due to the aging population and the number of individuals smoking over the last 30-50 years [12] .

It is well documented that patients with COPD exhibit a considerably reduced exercise capacity compared with that of healthy, age, and sex matched controls [13, 14]. Exercise intolerance has considerable implications as it is a primary predictor of prognosis and mortality in this population [15, 16]. The causes of exercise limitation in patients with COPD is multifactorial in nature and is due to a combination of factors including dyspnea, dynamic lung hyperinflation, decreased ventilatory reserve, respiratory and peripheral muscle dysfunction [14], and a decline in cardiac function [17].

1.2 Pulmonary Function in Healthy Aging

The human respiratory system ages just like many other organ systems in the body. Some of the changes that occur to the respiratory system, such as pulmonary elastic and resistive properties, and maximum expiratory flow have been described and studied for several decades [18]. Other changes that have been commonly observed in the aging respiratory system include fewer, but larger, alveoli [19], lower respiratory muscle strength [20], increased calcification of intrathoracic joints [21] and an increase in the diaphragmatic contribution to ventilation, particularly during exercise [21].

More recently, studies have begun to investigate changes in operational lung volumes that occur with aging. These studies have illustrated that maximal lung volume

(or size) does not change throughout the aging process, and that ultimately total lung capacity (TLC) remains the same [22]. Increases in functional residual capacity (FRC) and residual volume (RV) do typically occur and, and as a result, inspiratory capacity (IC) and vital capacity (VC) tend to decrease [22]. These changes in lung volume are primarily due to a decrease in the static recoil of the lungs with aging [23, 24]. Reduced transmural pressures are another factor that can lead to increases in RV because they raise the tendency for airway collapse at low volumes. This increases static lung compliance [22] and these changes are similar to what is seen in patients with emphysema [18].

As subjects age, declines in lung function measured by the forced expired volume in one second (FEV_1) and the maximum flow at various lung volumes are typically observed. These changes may be a result of a diminished VC, and, in healthy subjects are due primarily to the decrease in static recoil pressure to drive flow, and less likely a result of narrowing of the airways [23, 25]. A study by De Bisschop (2005) [26] showed that expiratory flow limitation (EFL) was common at rest in old age, and that EFL was found in some elderly subjects with dyspnea in the absence of overt cardiopulmonary disease.

In 2004 Chaunchaiyakul et al. explored the effects of aging and habitual physical activity on static respiratory work [21]. One of the primary findings of this study was that the elastic work of the lung changed significantly with age [21]. In the older participants, there was a shift from energy being stored primarily during expiration to energy being stored during inspiration and this energy was helping to drive expiration both at rest and during exercise [21]; this observation is opposite of what is typically observed in younger populations.

1.3 Pulmonary Function in COPD

Changes to the respiratory system occur in the presence of illness and can compound the already-mentioned changes that occur in the respiratory system with age. Individuals with obstructive lung disease are usually able to maintain normal driving pressures during expiration [27] but problems often arise as a result of mucus and inflammation in the airways that are compounded by emphysema. This leads to expiratory flow limitation and gas-trapping, and as a result patients with obstructive lung disease must create greater negative pleural pressure on inspiration to maintain normal inspiratory flow rates. They also tend to breathe with a greater alveolar ventilation than in healthy individuals due to an increase in physiological deadspace [27]. Additionally, emphysema causes the lungs to become more compliant and decreases the static recoil to drive expiratory flow. In COPD, the loss of static recoil combined with the reduction of airway radius as a result of the chronic bronchitis increases the resistive drop of pressure as exhalation proceeds and consequently causes the pressure to equalize between the inside and the outside of the smaller airways that are anatomically cartilage deficient [28]. When these equal pressure points occur, the smaller airways become compressed and eventually collapse, causing air to get trapped in the lung and for lung volumes to increase. When the amount of inflammation and airway resistance reaches high enough levels, flow limitation will occur.

EFL is hallmark of COPD and can occur even at rest in patients with more advanced disease [9]. EFL often results in gas trapping and an increase in end-expiratory lung volumes above FRC, forcing patients to breathe at higher lung volumes than healthy

individuals. Breathing at these higher volumes is necessary in order to prevent airway collapse and increase expiratory flow rates, and is termed hyperinflation. Hyperinflation can be divided into two subcategories: static and dynamic, each caused by different pathological features [29].

Static hyperinflation is defined as an abnormal increase in the volume of gas in the lungs at the end of tidal expiration [30]. This can be identified by an increase in RV, FRC, or a decrease in expiratory reserve volume (ERV) [29, 30]. Lung hyperinflation is virtually universal in patients with airway obstruction, but to different levels [30].

Dynamic hyperinflation usually occurs at rest in patients with moderate-to-severe airflow obstruction, but it increases during exercise [30] as the rate of respiration increases. During exercise, the respiratory drive to breathe increases as a result of a higher oxygen demand [1]. As the time to expire decreases, patients often start the next inspiration before they have fully expired, leading to dynamic gas trapping and an increase in end-expiratory lung volume (EELV). At lower levels of dynamic hyperinflation, patients are often able to increase their tidal volume (V_T) by increasing end-inspiratory lung volume (EILV). However, as EILV nears TLC further increases in V_T are impossible. In this situation, further increases in ventilation (V_E) can only occur via increases in respiratory rate (RR), which further decreases time for expiration (T_E) and compounds the initial problem. This also increases the demand on the respiratory muscles, and as lung volumes continually increase, these muscles get placed at disadvantaged lengths for producing optimum tension for muscle contraction. Once EILV is within approximately 500mL of TLC dyspnea usually increases at an exponential rate and patients curtail exercise very quickly [31]. At this stage, the work of breathing

becomes intolerable due to the combination of the increased RR compounded by respiratory muscle weakness.

1.4 Definition and Mechanisms of Dyspnea

For almost half a century it has been postulated that dyspnea is not one single entity. In 1963 Campbell and Howell [32] stated that there was no unique explanation for dyspnea. Over the past 50 years many individuals have tried to give this concept a single definition. For example, Comroe [33] states that "[dyspnea] is difficult, labored, uncomfortable breathing; it is an unpleasant type of breathing, though it is not painful in the usual sense of the word. It is subjective and, like pain, it involves both perception of the sensation by the patient and his reaction to the sensation". The American Thoracic Society (ATS) describes dyspnea as "a term used to characterize a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioral responses" [34]. Others have acknowledged that there can not be one unique definition for this construct, but offer insight into its understanding. For example, Tobin [33] states that "there is no universally accepted definition of dyspnea, but everybody has experienced the sensation and thus has an intuitive understanding of the phenomenon". Others have a more skeptical view on the matter stating that "a respiratory physiologist offering a unitary explanation for breathlessness should arouse the same suspicion as a tattooed archbishop offering a free ticket to heaven" [32].

Many researchers and clinicians have hypothesized that the different experiences of dyspnea likely arise from different pathological mechanisms [34]. The causes of dyspnea are plentiful and are not necessarily of a pulmonary or cardiac origin. Even when focusing on the pulmonary causes of dyspnea, changes to the airways, pleura, chest wall, parenchyma, or neuromuscular disease can all create sensations of dyspnea. In COPD specifically, dyspnea may be a result of changed ventilatory mechanics, respiratory muscle weakness, or a perceived mismatch between respiratory effort and air supply. Gas exchange abnormalities such as hypercapnia or hypoxemia may also contribute to the sensation of dyspnea and can compound the above-mentioned problems. In patients with COPD, it is important to note that these problems often arise in the absence of cardiovascular disease (CVD), which in itself tends to cause dyspnea.

As COPD is a heterogeneous disease, there are a multitude of potential sensory mechanisms that contribute to the sensations of dyspnea including disturbance of chemosensitivity, increased pulmonary and respiratory muscle receptor activity, and outgoing respiratory motor command which all can be based on the type and severity of disease.

When chemosensitivity is disturbed in a patient with COPD, it is likely a result of an increase in the partial pressure of carbon dioxide in the blood ([$PaCO_2$], hypercapnia) or a decrease in partial pressure of oxygen in the blood ([PaO_2], (hypoxemia). These changes may be a result of gas trapping, diffusion limitation, and/or or hypoventilation, all of which are a common result of obstructive pulmonary disease. Small increases in $PaCO_2$ and/or large decreases in PaO_2 will increase ventilation. The rate of ventilation can have a direct effect on the feeling of shortness breath in COPD patients by increasing

the recruitment of respiratory and accessory muscles and subsequently increasing oxygen demand. As a result, as respiratory rate increases, it may accentuate feelings of the urge to breathe (air hunger) and/or the work of breathing.

Respiratory control is a unique process because it is both autonomic and voluntary. Respiration can be altered by metabolic, chemical, and mechanical events. As mentioned, changes in $PaCO_2$, PaO_2, and pH will be sensed by central and peripheral chemoreceptors and will alter respiration accordingly. In health, respiration is largely determined by $PaCO_2$ that feeds back to the respiratory control centers in the brain. As CO_2 diffuses across the blood-brain barrier, it gives off a H^+ and an HCO_3- molecule. The brain senses an increase in $[H^+]$ and stimulates the drive to breathe [35]. Peripheral chemoreceptors also can sense changes in $[H^+]$ and can change respiration rates very rapidly. In patients with COPD, the levels of $PaCO_2$ can be chronically high and the kidney will attempt to neutralize the acidosis by increasing HCO3- levels. Eventually the brain becomes less receptive to high $PaCO_2$ levels and the drive to breathe is primarily a function of the PaO_2 [35]. Usually, the PaO_2 will only stimulate respiration if arterial levels fall below 50-60 mmHg. When hypercapnia and hypoxia occur simultaneously, the drive to breathe is further enhanced [35].

The mechanical drive to breathe arises primarily from stimulation of pulmonary receptors. There are many different types of receptors in the lung and tracheobronchial tree. Among these are the rapidly adapting pulmonary stretch receptors, slowly adapting pulmonary stretch receptors, and juxta-alveolar receptors. Rapidly adapting pulmonary receptors respond to irritants (such as cigarette smoke) and send information to the respiratory centers of the brain which causes an increase in airway resistance, reflex

apnea, cough [28] and at times, rapid shallow breathing [28, 36]. Reductions in ventilation and increases in airway resistance may lead to the sensation of shortness of breath; however, with a sustained stimulus, the activity of these receptors rapidly decreases [28, 36].

Mechanical stimulation, in particular from lung inflation, activates slowly adapting pulmonary receptors. These receptors are located in the smooth muscle of the bronchial walls and respond to changes in transmural pressure [36]. When activated, there is a delay in the onset of inspiration and this allows for a greater expiratory time. This is beneficial for patients with COPD as it minimizes expiratory effort and allows for greater amounts of air to be expired over a longer period of time. These reflexes are not very active in the normal, healthy adult, but become more active when tidal volume increases above 1.0L [28]. The stimulation of these slowly adapting pulmonary receptors is hypothesized to lead the sensation of dyspnea by creating a stretch reflex response that is interpreted as being inappropriate by the respiratory centre of the brain [28, 36].

The juxta-alveolar receptors (J-receptors) are the endings of nonmyelinated c-fibers [35] located in the lung parenchyma and respond to both chemical and mechanical stimulation [36]. They act in response to large inflation of the lungs, forced deflation, pulmonary vascular congestion, edema, and inflammatory chemical mediators [28]. When they are stimulated they cause the larynx to close, breathing to become rapid and shallow, bradycardia, and hypotension, which can consequently lead to feelings of shortness of breath.

Respiratory muscle receptors, also known as somatic receptors, respond to changes in the length or tension of the respiratory muscles and provide information about

lung volume. When lung volumes increase, these receptors play a role in terminating inspiration to prevent these volumes from getting too high [28]. If inspiration is terminated before adequate amounts of air are present for gas exchange, then dyspnea may occur. The sense of breathing effort (the conscious awareness of the voluntary activation of both peripheral skeletal and respiratory muscles [1]) can also be interpreted by these receptors. When stimulated during fatigue, these receptors activate type IV afferent fibres and relay information to the central nervous system [21]. As would be expected, when expiratory flow limitation is present, expiratory work becomes greater and the recruitment of expiratory muscles is increased [21]. Generally, dyspnea is proportional to the amount of expiratory flow limitation that is present [21] and may be due to the mismatch between respiratory muscle work and output of the pulmonary system.

Studies have shown that the tension generating capacity of the respiratory muscles is reduced as lung volumes increase above FRC. More specifically, the ability to generate tension declines linearly by 1.7% for each 1% of TLC increase in volume above the FRC, and by 5% for each 1L/second increase in inspiratory flow [21]. As the velocity of shortening of respiratory muscles increases, the respiratory muscles' maximal capacity of producing pressure is reduced [21]. This decrease in respiratory muscle contractility and increase in inspiratory operational pressure during exercise has been shown to increase the sense of effort [34] that is perceived which can, again, induce dyspnea.

Outgoing respiratory motor command in the brainstem from the medulla and the pons refers to the activity of the motor neurons that is sent to the respiratory muscles, and which is monitored by the medulla. There are groups of medullary neurons that determine

the appropriateness of any sensory information originating from the respiratory muscles before making adjustments to respiratory muscle output to alter the ventilatory response [28]. When ventilation is increased voluntarily, motor command is increased to the respiratory muscles [37]. A copy of this signal, called "central corollary discharge" is also sent from the motor cortex to the sensory cortex [37]. A secondary corollary discharge is sent from the brainstem to the sensory cortex. This signal is related to metabolic changes associated with breathing and it is less strong than the central corollary discharge. It has been hypothesized that this signal is associated with the perception of air hunger [38] which can be one sensation associated with shortness of breath.

Neuromuscular uncoupling has been the term coined to describe the increased perception of dyspnea in patients with COPD as a result of a disparity between respiratory motor output and mechanical response of the system [21, 39]. More specifically, this term refers to the scenario in which patients with COPD must increase their ventilation and consequent motor drive to meet respiratory demands, but due to altered ventilatory mechanics in these patients, continuing chemostimulation, and a restriction of further increases in lung volume there is an inconsistency between supply and demand [39].

1.5 Causes of Exertional Dyspnea

Dyspnea is commonly reported as the primary symptom causing exercise cessation in patients with COPD [40]. Although dyspnea can be present at rest, exercise often significantly exacerbates their sensations of shortness of breath. The mechanisms

for dyspnea during exercise may be due to the same factors responsible for producing dyspnea at rest, but changes in the chemosensitivity, firing rate of the pulmonary and respiratory muscles receptors, and motor output are usually augmented during exercise.

As ventilatory demand increases with exercise, patients with COPD have only minimal ability to increase tidal volume so predominantly rely on an increase in breathing frequency. As the rate of respiration increases the time for expiration decreases and patients often start breathing in before they have completed expiration. This causes an increase in the amount of gas trapped in the lung and leads to a rise in end-expiratory lung volume, a phenomena known as dynamic hyperinflation. Dynamic hyperinflation, results in a decrease in dynamic lung compliance [41] and when combined with an increase in airway resistance results in a marked increase in the pleural pressure needed maintain adequate airflow into the lung. In addition to the changes in lung compliance, dynamic hyperinflation results in an increased alveolar pressure at the start of inspiration which causes intrinsic positive end expiratory pressure (PEEPi) [42]. PEEPi acts as an inspiratory threshold load that also needs to be overcome before any inspiratory flow can be generated [31, 43]. This can only be achieved by further decreasing pleural pressure, and, as a result, the inspiratory work of breathing in patients with COPD becomes very pronounced [15]. The influence of PEEPi becomes more pronounced as exercise intensity is increased, and at exhaustion, inspiratory work due to PEEPi can account for over 50% of the total inspiratory work in these patients [42].

During exercise as the work of breathing increases, patients with COPD receive altered peripheral sensory information. This sensory information is conveyed through mechanoreceptors that sense a change in pressure in the lung and its associated

musculature due to hyperinflation (see Figure 1.1). As this sensory information is increased, it signals that there is an inefficient ventilatory response for the effort being expended [31]. This mismatch represents the neuromechanical dissociation, or uncoupling, previously mentioned and is likely the primary cause of dyspnea during exertion in these patients [31].

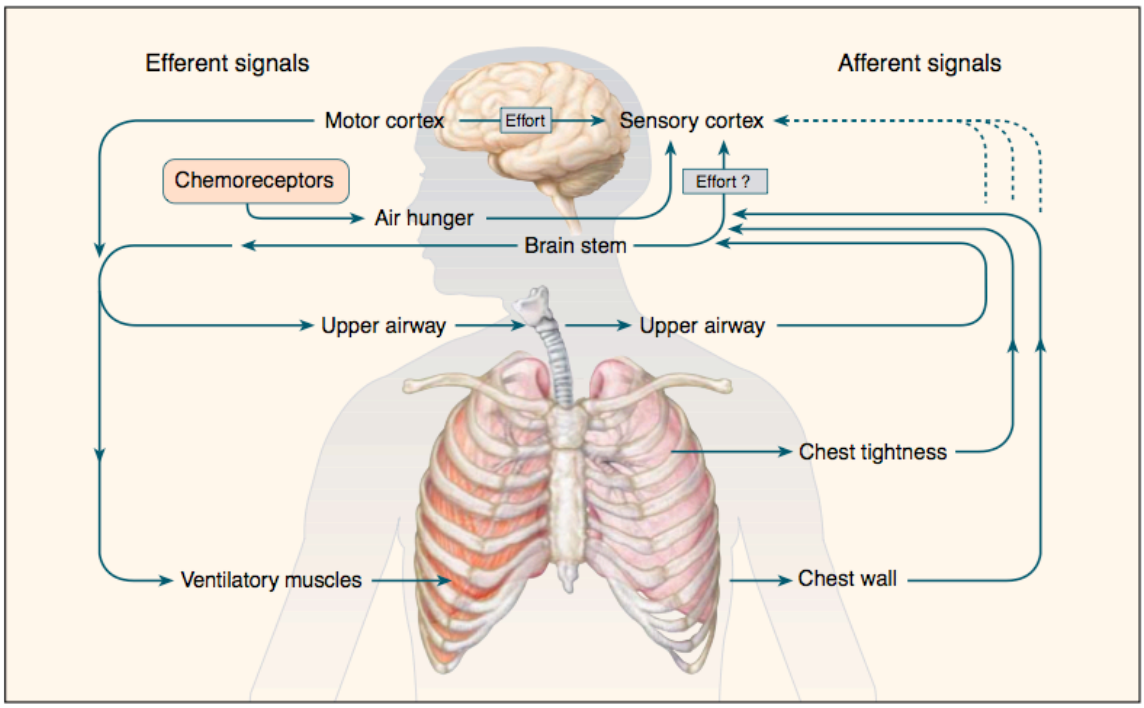

Figure 1.1: Suggested mechanism for the sensation of dyspnea from Manning and Schwartzstein (1995)

1.6 Measuring Dyspnea

As previously mentioned the sensation of shortness of breath has interested clinicians and researchers for many decades. As such, there are many instruments that have been created for this purpose, such as the Visual Analog Scale (VAS), the modified Medical Research Council Dyspnea Scale (mMRC), the Oxygen Cost Diagram (OCD), the Baseline Dyspnea Index (BDI), and the Shortness of Breath Questionnaire (SOBQ) [44] to measure dyspnea at rest. One of the few scales developed for measuring shortness

of breath during exercise is the modified 10-point Borg scale which was traditionally used to get an overall representation of the amount of shortness of breath a patient is experiencing at any given moment [45]. When using this scale, patients are asked to choose a score between 0 and 10 (0 being "no shortness of breath", and 10 being "the maximal amount of shortness of breath they have ever felt or could imagine experiencing") to indicate their dyspnea levels. This method of measuring dyspnea during rest and exercise is widely used, but it does not provide any specific information regarding the precise sensation of dyspnea that a patient is experiencing.

The concept of pain has been the focus of ample research over the past few decades and scientists have made great headway into understanding its mechanisms; how sensations are relayed to the brain; where they are processed; how they are perceived; and the associated emotional implications. Pain is the result of many different stimuli, which can be sensed and interpreted differently. Scientists have separated pain into two dimensions; an affective and a sensory dimension. The affective dimension (A) refers to immediate feelings of unpleasantness (A_1) and the long-term emotions that arise as a consequence of these feelings (A_2) [46]. The intensity, location, time course, and quality of the pain are all components of the sensory dimension (S_I) [46]. Although the affective and sensory dimensions are related, the affective dimension can vary for a given sensory input, which can be dependent on psychological or environmental factors.

Similar to pain, there are different sensations of dyspnea. These different sensations are the result of the quality of the experience, the stimuli that evoke them, and different afferent pathways [46]. Over the years, and as the result of many studies [47-52], researchers have broken down the most common sensations of dyspnea into three major

categories; air hunger, the work of breathing, and chest tightness. Thus, it follows that there should be a measurement tool that can portray information about these separate sensations and the corresponding affective feelings that accompany them. These affective feelings have been shown to have a significant relationship with respiratory-related impairments that are described in patients with COPD. Recently, studies have demonstrated that subjects are capable of differentiating between the affective and sensory dimensions of dyspnea [53]; therefore, it follows that a more thorough multidimensional dyspnea profile (MDP), as proposed by Lansing et al. [46] has great promise and practicality as a new measurement tool for dyspnea.

1.7 The Multidimensional Dyspnea Profile (MDP)

The MDP questionnaire was created by the Lansing *et al*. [46] laboratory group from Harvard University in 2009 with the goal of presenting a testable model for multidimensional dyspnea [46]. The MDP was based on ideas about the multidimensionality of dyspnea, and its content was adapted from similar questionnaires used to measure pain [54-57]. The MDP used the main elements from these pain questionnaires; sensory quality, sensory intensity, unpleasantness, and emotional impact [46] to try and gather a more representative and complete picture of dyspnea sensations. The MDP is divided into three different sections; one to measure the unpleasantness of breathing sensations (i.e. the immediate affective dimension), one to measure the intensity of five different breathing sensations (i.e. the sensory dimensions), and one to measure the lasting or residual emotional impacts of dyspnea (i.e. the long-term affective dimension). Each section has its own separate questionnaire, all of which ask subjects to

rank the specific unpleasantness or intensity of breathing sensations using a scale from 1-10 (See Appendix A).

The MDP is a valid and reliable tool [58] that has been mostly used by the Banzett lab group where it was created [53]. However, to date, there have only been a handful of studies that have published data using the MDP, or variations of it, to measure dyspnea at rest or during exercise. For example, Banzett et al. [53] have studied how healthy volunteers rate dyspnea using the MDP when they are subject to different stimuli intended to induce distinctive sensations of dyspnea. They reported that the MDP was able to distinguish between the different sensations of dyspnea, and that air hunger was commonly the most unpleasant sensation that participants experienced. A variation of the MDP was also used by Bianchi et al. [59] to test the effects of a pulmonary rehabilitation program for patients with COPD on measures of both the intensity and qualitative descriptors of dyspnea. That study found, following the rehabilitation program, patients reported a lower intensity of dyspnea (i.e. S_I score) at a given inspiratory reserve volume (IRV) but that the affective and qualitative descriptors they used to describe the sensations of dyspnea did not change. This finding suggests that it is possible to modify the intensity of dyspnea that patients experience, but that the contributing mechanisms and feelings associated with dyspnea are less likely to be altered. More recently, it has been reported that patients with COPD are able to distinguish between the affective and sensory dimensions of dyspnea during exercise [60]. These two dimensions are typically rated differently among patients during exercise, with the gap between the two increasing near the end of exercise [60]. In order to ensure that the affective dimension reported by patients during exercise is a valid representation about the distress or anxiety associated

with their shortness of breath, research by the same group revealed that the affective score of dyspnea is a distinct measurement and is not associated with state anxiety, anxiety about the exercise test, or negative affect [60].

1.8 Interventions to Reduce Dyspnea

There are several interventions that have been used during exercise to reduce the sensations of dyspnea in patients with COPD. These adjunct therapies have a positive effect on exercise tolerance by allowing patients to perform a greater volume or intensity of exercise, thus providing a greater stimulus for physiological adaptations. Oxygen gas, heliox gas, and non-invasive bi-level positive airway pressure (BiPAP) are examples of a few of these interventions, all of which affect shortness of breath by a number of different mechanisms.

1.8.1 Hyperoxic gas

Studies have shown that when non-hypoxemic patients with COPD breathe hyperoxia during exercise it helps to reduce the RR and in turn allows for a greater time for expiration. The increase in PaO_2 and SaO_2 can also improve O_2 delivery, reduce metabolic acidosis, and blunt chemoreceptor stimulation which act together to reduce breathing frequency [61]. By providing more time to expire air both dynamic hyperinflation and the work of breathing are reduced, consequently leading to reductions in dyspnea [61-63]. O'Donnell *et al*. [61, 64] demonstrated that hyperoxia does not change the maximal flow-volume envelope but improves lung emptying, and in turn maintains EELV closer to resting levels. These changes in lung volume can reduce or

delay sensations of dyspnea independent of whether a patient is dyspneic before the administration of this gas. Therefore, supplemental oxygen during exercise reduces exertional breathlessness and improves exercise tolerance by reducing ventilatory demand and by reducing the feelings of a conscious perception of the urge to breathe, a feeling that has been described as "air hunger".

1.8.2 Helium-Oxygen (heliox) Gas

When a lower density gas, such as helium, replaces nitrogen in room air expiratory flow rates can be increased as a result of decreased airway resistance and maintenance of laminar flow. This helps to reduce expiratory flow limitation, maintain EELV, reduce dynamic hyperinflation, maintain tidal breathing at lower lung volumes [62, 65, 66], increase peak ventilation [17, 65] and improve SaO_2 [17] in patients with COPD. Furthermore, both Palange *et al*. [65] and Eves *et al*. [62] have shown that the extent of dynamic hyperinflation in patients with COPD during exercise can be reduced when breathing heliox gas compared to room air. By decreasing dynamic hyperinflation, heliox reduces the elastic and resistive work of breathing during constant load exercise. In both of these studies, participants reported lower dyspnea scores throughout exercise and these reductions in dyspnea were correlated to improvements in exercise time. Decreasing the work of breathing is likely the primary reason for reduced dyspnea scores during exercise [62]. However, since heliox allows patients to reach higher peak ventilations, at end exercise it is possible that reductions in the sensation of air hunger also allows more exercise to be performed.

1.8.3 Bi-level Positive Airway Pressure

Non-invasive bi-level positive airway pressure (BiPAP) generates a positive pressure at the mouth that increases airflow into the lungs. It can reduce inspiratory muscle effort and the work of breathing by increasing the driving pressure for inspiration and creating inspiratory flow without muscle work, which reduces the sensation of dyspnea [67, 68]. Maltais *et al*. [69] has showed that only 11 cmH_2O of inspiratory pressure support reduces both inspiratory effort and dyspnea in severe chronic airflow obstruction patients performing constant workload cycling. O'Donnell [70, 71] found similar results using a continuous positive airway pressure (CPAP) machine and showed that CPAP was able to unload respiratory muscles which resulted in decreased central respiratory output, decreased inspiratory effort, and decreased dyspnea in patients with chronic airflow obstruction. Therefore, BiPAP and CPAP can markedly reduce the effort required to breathe, which is their primary mechanism for lowering reported dyspnea scores.

1.9 Research Questions

To date, no study has examined the effects of directly manipulating the sensory and affective dimensions of dyspnea in patients with COPD during exercise. As such, this thesis investigated: 1) the extent to which three different interventions (hyperoxia, helium-oxygen, or BiPAP) - aimed at reducing air hunger and/or the work of breathing - alter the A_1 and S_I dimensions of dyspnea, 2) the extent to which changes in the affective and sensory dimensions of dyspnea are associated with exercise tolerance, 3) how changes in operating lung volume with each intervention are associated with

improvements in the affective and sensory dimensions of dyspnea.

1.10 Primary Aim and Hypothesis

The primary aim was to examine the absolute change in ratings of the A_1 and S_I dimensions of dyspnea using the MDP during, and at the cessation of exercise, in patients with COPD using interventions that are known to reduce air hunger and the work of breathing. *It was hypothesized that all interventions would decrease ratings of* A_1 *and* S_I *compared to room air. However, the interventions that primarily decrease air hunger (*O_2 *and* HeO_2*) would have a greater effect on* A_1 *and* S_I *than BiPAP.*

1.11 Secondary Aim and hypothesis

To examine the effects of decreasing A_1 and S_I on the time to symptom limitation during exercise in patients with COPD and the association between improvements in operational lung volumes and changes in A_1 and S_I. *It was hypothesized that isotime changes in* A_1 *and* S_I *would be associated with the improvement in exercise time for each intervention. It was also hypothesized that improvements in operational lung volumes would be associated with reductions in* A_1 *and* S_I*.*

1.12 Relevance

One of the major goals of COPD treatment is dyspnea reduction [44]. Dyspnea is a symptom that commonly leads to activity limitation, and as a result, skeletal muscle deconditioning and an impoverished quality of life [40]. Poor exercise capacity is an important clinical problem, which has been associated with reduced health-related quality

of life and poor prognosis in patients with COPD.

The mechanisms of exercise limitation in COPD are still not fully understood but are likely multifactorial in nature. This study will be the first to investigate the direct effects of reducing air hunger and the work of breathing on the sensory and affective dimensions of dyspnea in patients with COPD during exercise. The information obtained will allow us better understanding of how dyspnea presents in patients with COPD and how that contributes to exercise limitation within this population. Furthermore, it will allow investigation of how commonly used adjuncts to exercise in patients with COPD reduce different dimensions of dyspnea, which is important for better understanding the heterogeneity of responses seen with these therapies.

CHAPTER 2

The Effect of Different Interventions on the Sensory and Affective Dimensions of Dyspnea in Patients with COPD During Exercise*

2.1 Introduction

Dyspnea is an unpleasant symptom that affects the majority of patients with chronic obstructive pulmonary disease (COPD) during activities of daily living and/or exertion. It is commonly the primary reported symptom limiting activity [40] and presents a significant barrier for patients to obtain the known benefits of exercise. Structured exercise training as a component of pulmonary rehabilitation is a well established "standard of care" for patients with COPD and is known to improve exercise capacity and health related quality of life. Growing evidence also supports the benefits of exercise for reducing the rate of morbidity and mortality in these patients [15, 16]. As such, the inability to be able to exercise due to dyspnea has many negative consequences for these patients.

Dyspnea is a complex sensation that has been recognized to be a similar entity to the sensation of pain. Research has shown that shortness of breath can be caused by a variety of diverse mechanisms and can be interpreted differently by each individual [46]. It has been proposed [46, 48, 51-53, 59], that similar to pain, dyspnea is a multidimensional entity that has both affective and sensory dimensions that govern not only the unpleasantness and intensity of the symptom but also the emotional impact and immediate and long term behavioral responses [60]. From these studies it has been

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immediate and long term behavioral responses [60]. From these studies it has been identified that dyspnea can be categorized into three major categories: air hunger, the work or effort of breathing, and chest tightness, all of which result from different stimuli and different afferent pathways [46]. Although these sensory and affective dimensions of dyspnea are related, research has shown that it is possible to alter these dimensions to different degrees within the same individual, and that the affective dimension (i.e. how unpleasant the patient perceives dyspnea to be) has a relationship both to respiratory-related impairments but also to exercise adherence or avoidance [47].

A number of interventions have been shown to reduce dyspnea in patients with COPD throughout clinical, rehabilitation, and research settings. For example, breathing an increased fraction of oxygen (hyperoxia) can help to slow the rate of respiration and allow for a greater time for expiration which improves lung emptying, reduces dynamic hyperinflation and the work of breathing [61-63]. Hyperoxia can also reduce the conscious urge to breathe, a sensation that has been described as "air hunger". Helium-oxygen gas (heliox), which is less dense than room air, can also increase expiratory flow rates, decrease dynamic hyperinflation, and in turn, maintain tidal breathing at lower lung volumes [62, 65, 66]. During constant load exercise this approach can reduce the work of breathing compared to room air and likely also lead to reductions in air hunger. Finally, non-invasive bi-level positive airway pressure (BiPAP) helps to relieve dyspnea by increasing the driving pressure for inspiration, reducing inspiratory muscle effort, which directly reduces the work of breathing [67, 68].

All of these interventions have shown promising results in terms of reducing dyspnea in patients with COPD but how they specifically affect the sensory and affective

dimensions of these sensations during exercise remains be studied. As a result, the aim of this study was to examine the extent to which hyperoxia, heliox and BiPAP affect the affective and sensory dimensions of dyspnea and to determine if improvements in A_I and S_I scores are associated with ameliorations in exercise capacity. We hypothesized that all interventions would decrease ratings of A_I and S_I compared to room air but that interventions that primarily decrease air hunger (hyperoxia and heliox) would have a greater effect on A_I and S_I than BiPAP. We also hypothesized that changes in A_I and S_I during exercise would be correlated with improvements in exercise time and that improvements in operational lung volumes would be associated with reductions in A_I and S_I.

2.2 Methodology

2.2.1 Patients

Patients were recruited from the Pulmonary Rehabilitation Program at the Kelowna General Hospital and from a COPD exercise program at the Parkinson Recreation Centre. Inclusion criteria included moderate to severe COPD (post-bronchodilator FEV_1/FVC <0.7, 30%< FEV_1 < 80% pred, >10 pack year history of smoking), and exacerbation-free for at least six weeks prior to the study. Patients with cardiovascular contraindications to exercise or musculoskeletal limitations to exercise (i.e. knee pain, leg pain, osteoarthritis) were excluded. Any patients with exertional hypoxemia (oxygen saturation measured with pulse oximetry [SpO_2] <85% during exercise) were also excluded. All patients volunteered to participate and signed an informed consent that had received institutional and Interior Health ethics board approval.

2.2.2 Study Design

The study used a randomized single-blind crossover design, which required patients to visit the Pulmonary Function Laboratory at the Kelowna General Hospital (KGH) on three separate occasions. During the first visit, patients underwent a routine pulmonary function test to confirm the severity of airflow obstruction and a symptom limited incremental cardiopulmonary exercise test (CPET) to screen for cardiovascular contraindications to exercise and to provide appropriate exercise intensities for the constant load exercise trials. During this visit, baseline dyspnea scores were also assessed with the multidimensional dyspnea profile (MDP) questionnaire (see Appendix A).

Patients performed two constant load cycling tests (CLTs) during both the second and third visits, at 75% of their workload maximum (W_{max}), which was previously determined from the CPET during Visit 1. Patients breathed compressed air (21% O_2, 79% N_2), heliox (21% O_2, 79% He), hyperoxia (40% O_2, 60% N_2), or received non-invasive continuous positive airway pressure (BiPAP), in a randomized order. All tests were performed on an electronically braked cycle ergometer (Ergoline, ErgoSelect, Cardinal Health, Vaughan, ON). The tests were separated by at least one hour during which time the patient rested. The gases were delivered to the participants from a large reservoir bag through a standard low resistance two-way breathing valve mouthpiece (Figure 2.1 *and* Appendix C.1). The BiPAP was delivered to the patients from a portable BiPAP machine (Respironics System One, Respironics Inc, Murrysville, PA) connected to a pneumatic valve in series with a standard low resistance two-way breathing valve mouthpiece (Figure 2.1 *and* Appendix C.2). Prior to the exercise test with the BiPAP, patients were familiarized to the BiPAP machine at rest so that the pressure support could

be titrated to an optimal level (i.e. set to a high but tolerable level of support) for each individual during the CLTs. Patients exercised until symptom limitation and were asked not to talk during, or for a short period after exercise due to the change in vocal tone with helium.

2.3 Specific Methodology

2.3.1 Pulmonary Function Testing

To confirm the severity of disease and to determine lung volumes, routine spirometry, single-breath diffusion capacity for carbon monoxide (D_LCO) and constant-volume body plethysmograph (6200 Autobox; SensorMedics, Yorba Linda CA) were performed according to American Thoracic Society (ATS) criteria [72-77]. Established reference equations were used to determine predicted values for spirometry, lung volumes, and diffusing capacity.

2.3.2 Incremental Exercise Test

A physician-supervised incremental exercise test to symptom limitation was performed using current ATS/ACCP recommendations [78]. More specifically, patients exercised on an electrically braked cycle ergometer and expired gases were collected and analyzed using a calibrated metabolic measurement system (Sensormedics Vmax 29C, SensorMedics, Yorba Linda, CA). The exercise load started with unloaded peddling and was increased by 10 $W.min^{-1}$ until symptom-limitation. During the exercise test, oxyhemoglobin saturation and heart rate were monitored continuously using pulse oximetry (Radical 7, Maximo, Irvine, CA) and ECG (CardioSoft™, GE Healthcare,

Waukesha, WI) respectively. Blood pressure (manual sphygmomanometry) and inspiratory capacity maneuvers were measured every two minutes. Patient symptoms were measured every four minutes, and as close to the end of exercise as possible, using both the Borg scale (dyspnea and leg discomfort) and the MDP questionnaire (dyspnea). At the end of exercise patients were asked what symptom was the primary reason for exercise termination.

2.3.3 Constant-Load Exercise Tests

Participants completed four constant-load cycling trials to symptom limitation at 75% Wmax while breathing the three experimental gases or receiving ventilatory assistance from BiPAP. The respiratory therapist determining the constant load trial end points and providing encouragement throughout the tests was naïve to the gas mixture used. A heated pneumotachograph (Fleish Model 7322, Phipps and Bird, Richmond VI) was placed on either side of a low resistance standard two-way valve (Hans Rudolph Model 2700, Hans Rudolph, Shawnee, KS) to measure both the inspiratory and expiratory flow rates. The pneumotachs were calibrated with the appropriate test gas mixture (i.e. air, heliox, hyperoxia) before each test using a 3L syringe to compensate for the different physical properties of each gas. The pneumotachs were attached to separate pressure transducers (ADInstruments Spirometer unit, ADInstruments, Colorado Springs, CO) and signals from the pressure transducers were converted to a digital signal using a data acquisition system (Powerlab 16/35, ADInstruments, Colorado Springs, CO). The inspiratory and expiratory flow signals were integrated to obtain volume and the volume

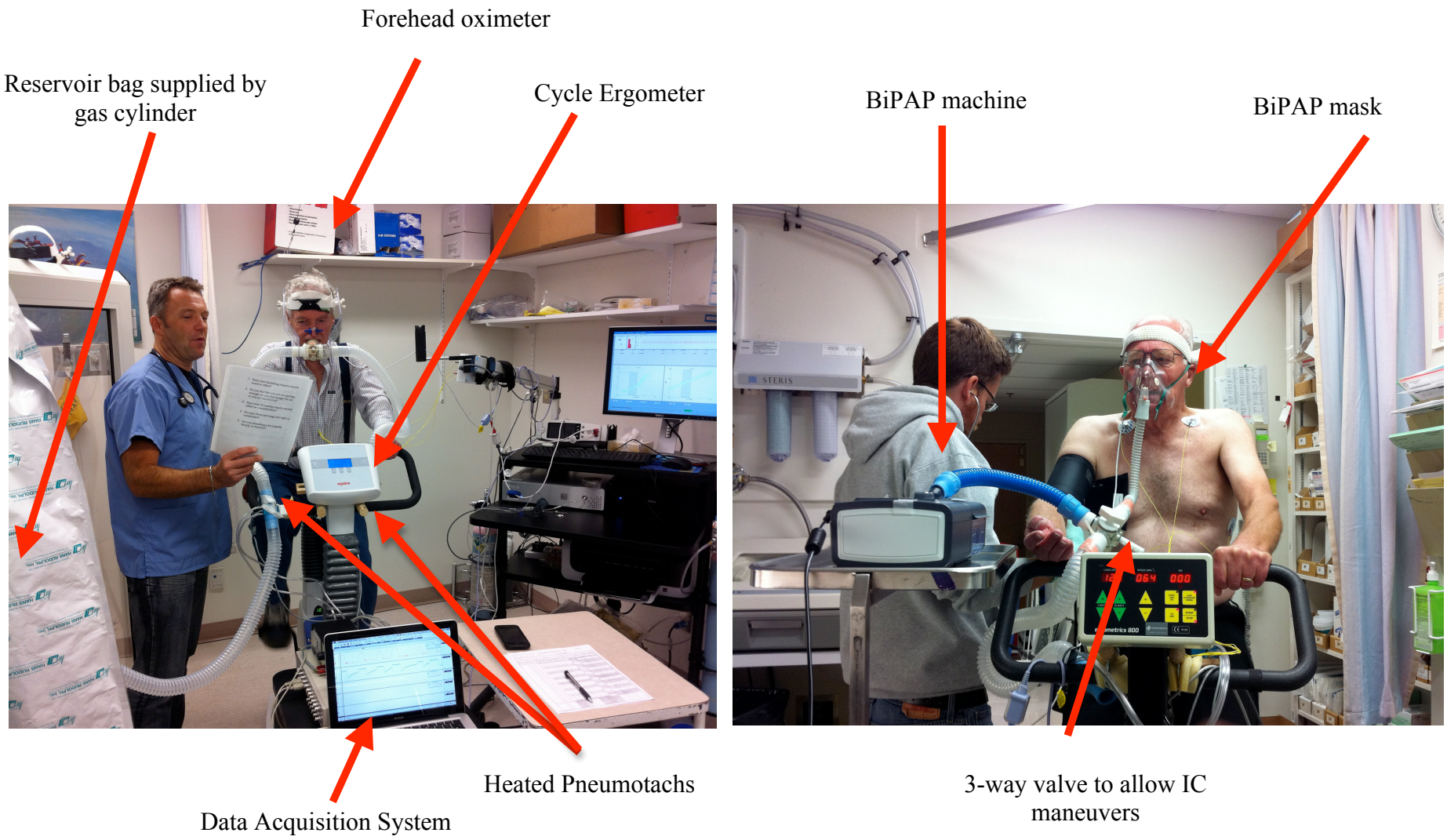

Figure 2.1 – Experimental set up for gas interventions (left) and for BiPAP (right)

signals were combined. All data was sampled at 1KHz and stored on a computer for analysis at a later date.

Oxyhemoglobin saturation and heart rate were monitored continuously throughout each test while dyspnea, blood pressure and inspiratory capacity maneuvers were performed every two-minutes. During the BiPAP trials, the BiPAP machine was turned off to the patient by blocking flow with a 3-way valve immediately preceding the IC measurement and turned back on immediately after the IC was complete. This allowed inspiratory volume measurements to be made without the effect of positive pressure from the BiPAP on the inspiratory pneumotach.

2.3.4 Measurement of Dyspnea

During the constant load tests, patients were asked to describe and rate their sensations of dyspnea using the MDP questionnaire prior to, every two minutes during, and immediately after the exercise tests. For each measurement, patients were asked to select the unpleasantness of their breathing sensations on a scale from 1-10 and to rank the intensity of five common shortness of breath descriptors that most accurately described their dyspnea at the given moment, also on a scale from 1-10. In order to differentiate these components of dyspnea for our participants we read them a "Script for first time use" courtesy of Lansing *et al*. This script describes the intensity of dyspnea as "how much breathing sensation you feel", whereas unpleasantness is "how bad it feels". Patients were given an analogy of radio to further clarify these differences. Both the volume and the content of the sound on a radio can change, and one can ask how loud the sound is or how unpleasant it is. Music that you hate can be unpleasant even at low

volumes and will become more unpleasant as the volume increases. But, music that you like will not be unpleasant, even if the volume increases. Therefore, the intensity of breathing is like sound volume and the unpleasantness of breathing depends not only on intensity but also on how good or bad the sensation is. See Appendix A for the complete MDP with instructions. After an adequate recovery period post exercise, patients were given another short questionnaire having them rank the intensity, on a scale from 1-10, of seven emotions related to their breathing sensations during the exercise test.

2.3.5 Measurement of Operational Lung Volumes

Assuming that total lung capacity (TLC) does not change with exercise [79, 80], repetitive inspiratory capacity maneuvers (IC) were performed to track changes in EELV (TLC - IC). This technique has been reported to be reliable for measuring end-expiratory lung volume in this population [80, 81]. Subjects performed a minimum of two IC maneuvers at rest and every two minutes during each of the constant-load trials. To ensure IC maneuvers were performed accurately during exercise tidal breathing was continuously displayed on a computer monitor. At the end of a normal expiration the patient was asked to breathe-in without warning and to give an additional effort on top of a maximal inspiration [80].

2.3.6 Outcome Measures

The primary outcomes of this study were the absolute ratings of the affective and sensory dimensions of dyspnea measured at an isotime during exercise, which was defined as the time at symptom limitation in the shortest constant-load exercise trial

(usually the air trial). Secondary outcomes included the change in operational lung volumes (specifically IC, IRV, and EELV) measured at isotime and end-exercise during the constant-load trials, as well as exercise tolerance measured as the time to symptom limitation during each exercise trial.

2.4 Statistical Analysis

For all primary and secondary outcomes variables, one-way repeated measures analyses of variance (ANOVAs) were performed. When the ANOVA detected a significant effect, a Fisher post-hoc multiple comparisons test was utilized to determine differences between conditions. To test for associations between the change in exercise time and changes in measurements of dyspnea, ventilatory parameters, and operational lung volumes simple regression analysis using Pearson correlations were performed. For all analyses and post hoc comparisons the alpha level was set *a priori* at 0.05.

2.5 Sample Size Calculations

Before this pilot study, no previous study had used the MDP questionnaire in patients with COPD during exercise and no study had assessed how any of the interventions used in this study independently alleviate the sensory and affective dimensions of dyspnea. However, as the interventions being used are known to greatly reduce dyspnea (measured with the Borg scale) during exercise we used this previous data to estimate a sample size. Eves *et al*. [62] reported that at an isotime during exercise, Borg dyspnea scores decreased from 5.8 to 2.7 when breathing hyperoxia compared to room air, and 5.8 to 3.1 when breathing heliox compared to room air. Similarly, Johnson

et al. 2002 [82] also reported a significantly lower Borg scale value for dyspnea at an isotime during exercise, when patients received continuous positive airway pressure compared to room air (5.3 vs. 7.3, respectively). Considering the A_1 and sensory S_I dimension of dyspnea are measured on a similar 10-point scale and assuming that heliox and hyperoxia will have a greater effect for changing A_1, whereas continuous positive airway pressure will have a greater effect for changing S_I we can make the following calculations:

With a similar magnitude change in A_1 with heliox and hyperoxia compared to that seen with the Borg Scale at an isotime during exercise, a sample size of 5 would be needed to detect a 2.7 unit difference with heliox and a sample size of 6 would be needed to detect a 3.1 unit difference with hyperoxia compared to room air. These calculations were performed utilizing measured standard deviations of the change score from previous work by our laboratory of 1.0 and 1.4, respectively, a power of 0.8 and a two-tailed alpha of 0.008 (adjusted for multiple comparisons). Similarly, considering a similar change in S_I with CPAP to that previous reported in the literature, a sample of 6 would be need to detect a 2.0 unit difference compared to room air assuming a standard deviation of the change score of 1.0 and a similar power and alpha to that previously mentioned. As such, we estimated that a sample size of 10 would be adequate to detect a change in our primary outcome variables even with multiple comparisons used for this study.

2.6 Results

2.6.1 Patients

Participant flow through the study is presented in detail in Figure 2.2. Patients were enrolled between May and July 2011. Fifty-eight patients had a clinical diagnosis of COPD and were potentially eligible for the study, however thirty of these patients were not interested in participating, and ten others were excluded because they did not meet study inclusion criteria. Eighteen participants were recruited and screened for the study, and eight of these participants were further excluded for either a positive test for ischemia (n=1), pulmonary function tests not confirming a COPD diagnosis (n=4), and for a variety of other reasons (n=3). A total of 10 patients were enrolled in the study, six were male and four were female. During testing, two patients displayed exercise-induced hypertension. These patients were referred for further clinical investigations and were cleared for exercise by their physician following pharmaceutical intervention.

Subject characteristics are presented in Table 2.1. On average, subjects demonstrated a moderate degree of airflow obstruction, evidence of gas trapping, a moderate decline in diffusion capacity and a greatly increased airway resistance, all of which are consistent with a diagnosis of COPD.

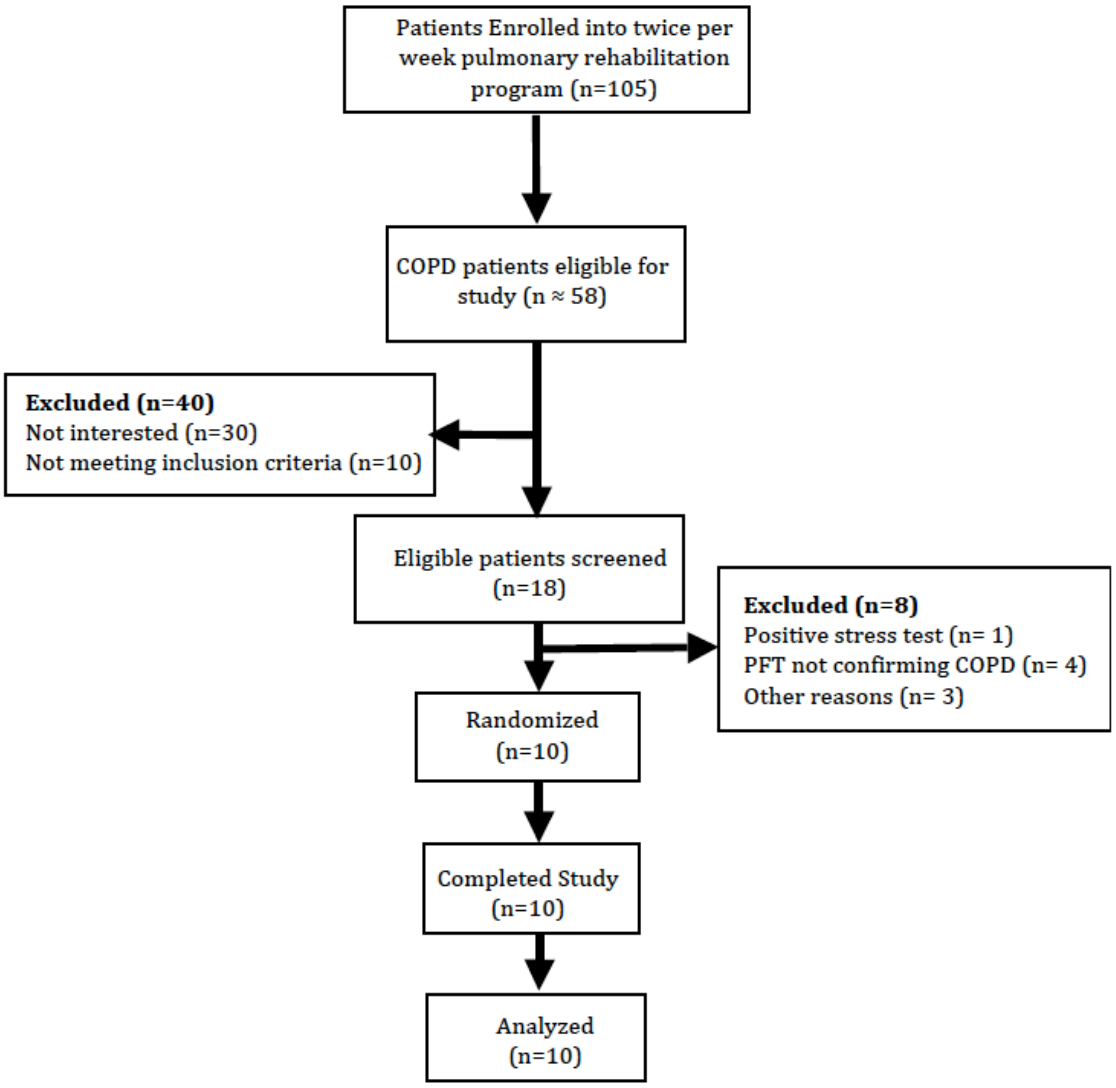

Figure 2.2: Study Flow

Table 2.1: Patient Characteristics

Characteristic	Value	% Pred
Age, yr	71 ± 7	
Height, cm	171 ± 10	
Mass, kg	78 ± 10	
Body mass index, $kg \cdot m^2$	27 ± 5	
MRC Dyspnea	2.6 ± 2.6	
FEV_1, L	1.5 ± 0.6	56 ± 24
FVC, L	3.5 ± 0.7	100 ± 16
FEV_1/FVC, %	44 ± 17	
TLC, L	7.1 ± 2.0	113 ± 23
RV, L	3.6 ± 1.7	155 ± 61
FRC, L	4.9 ± 2.0	139 ± 45
IC, L	2.2 ± 0.4	
D_{LCO}, $mL \cdot mmHg^{-1} \cdot min^{-1}$	14.1 ± 4.7	61 ± 20
D_{LCO}/V_A, $mL \cdot mmHg^{-1} \cdot min^{-1} \cdot L^{-1}$	3.1 ± 0.9	78 ± 21
Raw, $cmH_2O \cdot L^{-1} \cdot sec^{-1}$	4.4 ± 2.6	195 ± 115

Abbreviations: FEV_1 = Forced expiratory volume in 1 second, FVC = Forced vital capacity, TLC = Total lung capacity, RV =Residual volume, FRC =Functional residual capacity, IC = Inspiratory capacity, D_{LCO} = Diffusion of the lung for carbon monoxide, D_{LCO}/V_A = Diffusion of the lung for carbon monoxide corrected for alveolar ventilation, Raw =airway resistance, Values = mean ± SD, n=10.

2.6.2 Incremental Exercise Test Results

Responses to the graded exercise tests are presented in Table 2.2. The average peak oxygen uptake (VO_{2peak}) for the patients in this study was 16.8 ± 5.6 $ml \cdot kg^{-1} \cdot min^{-1}$ at a mean power output of 82 ± 40W. These findings were equivalent to 74 ± 22% and 66 ± 35% of the age and sex predicted norms for sedentary individuals, respectively. At peak exercise mean saturation was 93 ± 4%, which was a decrease of 5 ± 3% from resting values. A maximal effort, defined as the achievement of ventilatory limitation (ventilatory reserve<11L or a V_{Emax}/MVV of >0.85) or a maximal heart rate of >90% of predicted [78], was achieved by three and two patients respectively. Four patients achieved both criteria. Only one patient did not achieve what was considered a maximal effort. Three patients reported dyspnea as their primary reason for stopping the

incremental exercise test, four reported leg fatigue, two reported a combination of the two, and one participant ended their tests for other reasons (i.e. feeling too hot).

Table 2.2: Responses at Symptom Limitation to Incremental Exercise

Characteristic	Value	% Pred
VO_2, $ml \cdot kg^{-1} \cdot min^{-1}$	16.8 ± 5.6	74 ± 22
VO_2, $L \cdot min^{-1}$	1.32 ± 0.52	
PO, W	82 ± 40	66 ± 35
HR, $beats \cdot min^{-1}$	134 ± 21	90 ± 16
S_PO_2, %	93 ± 4	
ΔS_PO_2, %	5 ± 3	
RER	0.99 ± 0.11	
V_E, $L \cdot min^{-1}$	48 ± 17	95 ± 20
V_T, L	1.42 ± 0.43	
RR	34 ± 5	
Dyspnea		
Unpleasantness (A_1)	3.2 ± 1.7	
Sensory Intensity (S_I)	3.3 ± 1.2	
Ratio (A_1/S_I)		
Muscle Work	3.0 ± 2.2	
Air Hunger	3.5 ± 2.3	
Mental Effort	2.4 ± 2.2	
Chest Tightness	2.0 ± 2.5	
Breathing a lot	4.2 ± 1.8	
Leg Discomfort	3.5 ± 1.3	
Reason for Stopping Exercise		
Dyspnea	3	
Leg discomfort	4	
Dyspnea + Leg Discomfort	2	
Other	1	

Abbreviations: VO_2 = Volume of oxygen uptake, PO = Power output, HR =: Heart rate, S_PO_2: Oxhemoglobin saturation, ΔS_PO_2 = change in oxyhemoglobin saturation from resting values to peak exercise, RER = Respiratory =exchange ratio, V_E = Minute ventilation, V_T =Tidal volume, RR =Respiratory Rate. Values = mean ± SD, n=10.

2.6.3 Multi-Dimensional Dyspnea and Ventilatory Responses at an Isotime During Exercise

Figure 2.3A demonstrates the effect of each intervention on the sensory and affective dimensions of dyspnea. At isotime during exercise, no intervention reduced the affective dimension of dyspnea (p=0.09, p=0.11, p=0.64, for hyperoxia, heliox and BiPAP, respectively) and only hyperoxia reduced the sensory intensity of dyspnea (p=0.033). Heliox also reduced S_I but the results did not reach statistical significance (p=0.052). The change scores for both the affective and sensory dimensions of dyspnea compared to air were reduced with both hyperoxia (p=0.033 and p=0.025, respectively) and heliox (p=0.047 and p=0.041, respectively) but not with BiPAP. The A_I/S_I ratio was unchanged with any of the interventions compared to air as depicted in Figure 2.3B. There were also no significant changes in the sensory qualities of dyspnea compared to air (Figure 2.3C), except for the sensation of breathing a lot (rapidly, deeply, or heavily), which was significantly reduced with heliox (p= 0.043).

At the exercise isotime, absolute values of minute ventilation, tidal volume and respiratory rate were not altered with any intervention (Table 2.4). However, there was a +6.1 L change in V_E with heliox, which was significantly different from the V_E change with air (p=0.001) and hyperoxia (p=0.00005). The change in V_E was not accompanied by significant changes in V_T (+0.18 L, p=0.1947) or in breathing frequency (+0.13 breaths·min^{-1}, p=0.91). Even though the -2.0L change in V_E with hyperoxia was not statistically significant compared to air (p=0.24), the 2.7 breaths·min^{-1} reduction in breathing frequency with hyperoxia was significantly different from both air (p=0.022) and heliox (p=0.016). This change in breathing frequency with hyperoxia was accompanied by an increased inspiratory (0.09 ± 0.13s) and expiratory time (0.11 ±

0.18s) compared to air, although only the inspiratory time reached statistical significance (p=0.028 and p=0.101, respectively). S_pO_2 was unchanged from air with heliox and BiPAP, but was different from all other conditions with hyperoxia (p<0.01).

At exercise isotime, IC was greater with heliox (p=0.046) compared to air but not with hyperoxia (p=0.58) or BiPAP (p=0.62). The difference in IC was also significant between heliox and BiPAP (p=0.0145). In the air trial, all patients dynamically hyperinflated (i.e. EELV increased >200ml) between rest and isotime during exercise. In accordance with the changes observed in IC, EELV was decreased at the isotime in exercise with heliox by 0.32 ± 0.15 L (p= 0.0007) but not with hyperoxia or BiPAP. EELV was also decreased with heliox compared to hyperoxia (p=0.010) and BiPAP (p<0.001).

Table 2.3: Dyspnea and Ventilatory Parameters at an Isotime During Constant Load Exercise.

	Air	Hyperoxia	Heliox	BiPAP
Unpleasantness	4.1 ± 1.7.	2.6 ± 1.7	2.7 ± 2.2	3.7 ± 1.9
Sensory Intensity	4.6 ± 1.6†	3.0 ± 1.4*	3.1 ± 1.9	3.7 ± 1.5
Muscle Work	3.7 ± 1.8	2.6 ± 2.1	2.6 ± 2.4	2.9 ± 2.2
Air Hunger	4.4 ± 1.7	3.2 ± 2.4	3.4 ± 2.7	4.1 ± 2.6
Mental Effort	4.0 ± 2.0	2.7 ± 2.5	3.0 ± 2.8	3.2 ± 2.6
Chest Tightness	3.8 ± 2.6	2.8 ± 2.5	2.7 ± 2.1	2.8 ± 2.2
Breathing a lot	5.5 ± 1.5‡	4.1 ± 2.1	3.7 ± 2.1*	4.8 ± 1.9
V_E, L·min^{-1}	34 ± 13	32 ± 12	39 ± 14	-
V_T, L	1.06 ± 0.35	1.09 ± 0.35	1.24 ± 0.35	-
RR, breaths·min^{-1}	32 ± 6	29 ± 5	32 ± 5	-
T_I, s	0.71 ± 0.13†	0.80 ± 0.22*	0.72 ± 0.13	-
T_E, s	1.20 ± 0.36	1.32 ± 0.31	1.21 ± 0.33	-
T_I/T_{TOT}	0.38 ± 0.07	0.38 ± 0.06	0.38 ± 0.06	-
V_T/T_E, L·s^{-1}	0.97 ± 0.49	0.91 ± 0.44	1.10 ± 0.48	-
IC, L	1.43 ± 0.37‡	1.52 ± 0.39	1.76 ± 0.39*	1.35 ± 0.26
EELV, L	5.67 ± 2.14	5.58 ± 2.13	5.35 ± 2.05*†‡	5.76 ± 1.94
S_pO_2, %	92 ± 6†	100 ± 1*‡§	94 ± 3†	94 ± 6†
HR, beats·min^{-1}	121 ± 19	113 ± 20	118 ± 19	117 ± 19

Abbreviations: V_E = Minute ventilation, V_T: Tidal volume, RR = Respiratory Rate, T_I = Inspiratory time, T_E = expiratory time, T_I/T_{TOT} = Duty cycle (inspiratory time / total respiratory cycle time), V_T/T_E = Tidal volume / expiratory time, IC = inspiratory capacity, EELV = end-expiratory lung volume, S_PO_2 = oxyhemoglobin saturation, HR = heart rate. Values = mean ± SD, n=10. * = $p<0.05$ vs. Air; † = $p<0.05$ vs. Hyperoxia; ‡ = $p<0.05$ vs. Heliox; § = $p<0.05$ vs. BiPAP.

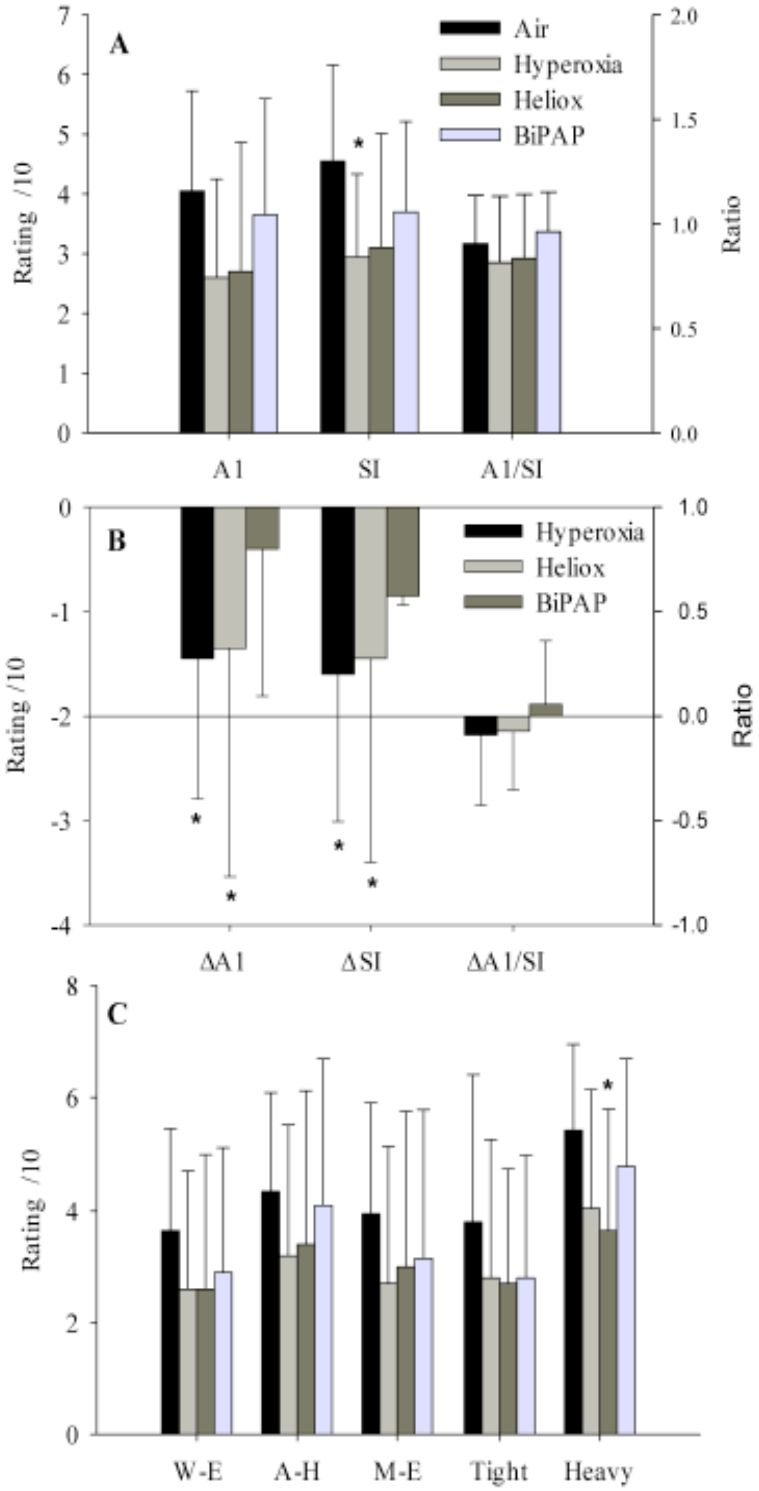

Figure 2.3: A) A_1 and S_I during constant load exercise at isotime. B) A_1/S_I ratio during constant load exercise isotime C) Ratings of the dimensions of dyspnea: work-effort (W-E), air hunger (A-H), muscular effort (M-E), chest tightness, and heavy breathing at isotime. Values = mean ± SD, n=10. * = p<0.05 vs. Air.

Table 2.4: Dyspnea and Ventilatory Parameters at End-Exercise

	Air	Hyperoxia	Heliox	BiPAP
Unpleasantness	5.0 ± 1.3	4.4 ± 1.8	4.4 ± 2.3	4.3 ± 1.8
Sensory Intensity	4.3 ± 1.6	3.9 ± 2.1	4.2 ± 2.3	4.4 ± 2.0
Muscle Work	3.8 ± 2.5	3.5 ± 2.4	4.0 ± 2.8	3.6 ± 2.6
Air Hunger	4.7 ± 1.8	4.5 ± 2.5	4.9 ± 2.7	5.0 ± 2.3
Mental Effort	4.5 ± 2.1	3.2 ± 2.9	4.2 ± 2.7	4.2 ± 3.1
Chest Tightness	4.3 ± 2.9	3.6 ± 3.1	4.1 ± 2.2	3.6 ± 2.4
Breathing a lot	6.0 ± 1.7	5.3 ± 2.2	5.5 ± 2.2	5.8 ± 1.8
V_E, $L \cdot min^{-1}$	32.6 ± 11.5	32.8 ± 12.6	37.4 ± 13.3	-
V_T, L	1.04 ± 0.35	1.02 ± 0.30	1.17 ± 0.36	-
RR, $breaths \cdot min^{-1}$	32 ± 7	32 ± 5	33 ± 7	-
T_I, s	0.72 ± 0.13	0.71 ± 0.13	0.69 ± 0.12	-
T_E, s	1.21 ± 0.37	1.18 ± 0.28	1.13 ± 0.24	-
T_I/T_{TOT}	0.39 ± 0.07	0.38 ± 0.06	0.38 ± 0.06	-
IC, L	1.44 ± 0.38	1.51 ± 0.39	1.73 ± 0.46§	1.30 ± 0.28‡
EELV, L	5.66 ± 2.14	5.59 ± 2.09	5.37 ± 2.09	5.76 ± 1.99
S_pO_2, %	91 ± 6†	99 ± 4*‡§	93 ± 5†	93 ± 6†
HR, $beats \cdot min^{-1}$	123 ± 20	120 ± 19	122 ± 20	116 ± 21
Reason for Stopping Exercise				
Dyspnea	5	4	5	4
Leg Fatigue	2	4	4	4
Both	2	1	1	2
Other	1	1	1	0

Abbreviations: See Table 2.3 Values = mean ± SD, n=10. Values = mean ± SD, n=10. * = $p<0.05$ vs. Air; † = $p<0.05$ vs. Hyperoxia; ‡ = $p<0.05$ vs. Heliox; § = $p<0.05$ vs. BiPAP.

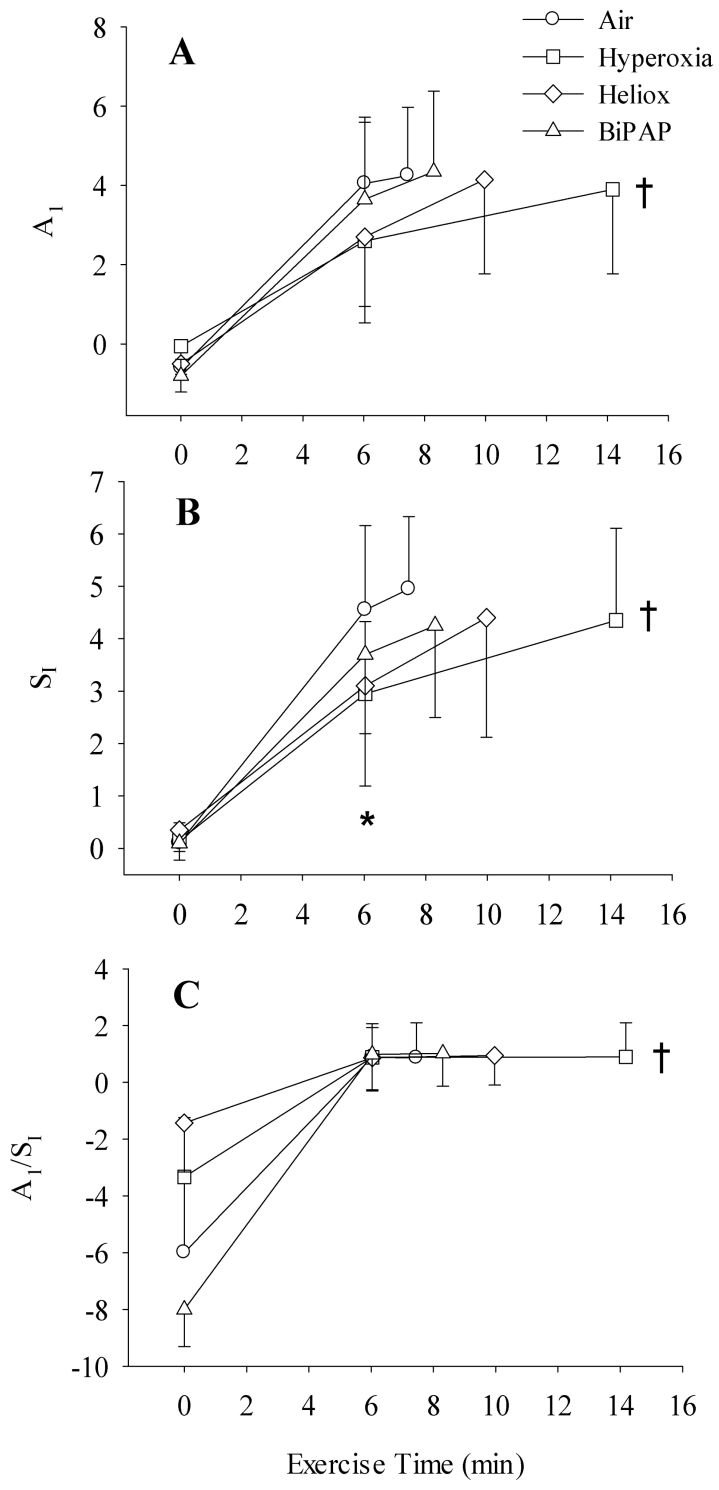

Figure 2.4: A) Immediate unpleasantness (A_1), B) Sensory intensity (S_I) and C) A_1/S_I ratio during constant load exercise tests breathing room air, hyperoxia, heliox and BiPAP. n=10, * = p<0.05, vs. Air for S_I , † = p<0.05, vs. Air for exercise time

2.6.4 Multi-Dimensional Dyspnea and Ventilatory Responses at End-Exercise

At end-exercise, there were no significant differences between any of the interventions for A_1, S_I, or the A_1/ S_I ratio as depicted in Figures 2.4 A, B, and C as well as Figure 2.6A. There were no significant differences in the sensory qualities of dyspnea that were reported between each intervention as shown in Figure 2.6B. Ventilatory parameters were also similar between tests at end-exercise (Table 2.4 *and* Figure 2.7). However, there was a trend toward greater IC with heliox compared to air ($p=0.099$) and IC was significantly increased with heliox compared to BiPAP ($p=0.017$). S_PO_2 was significantly greater at the end of the hyperoxia trial compared to the three other interventions ($p<0.05$). When assessing the affective emotional responses to dyspnea following exercise (Figure 2.6C) there were also no significant differences between interventions for the negative feelings of depression, anxiety, frustration, anger and fear.

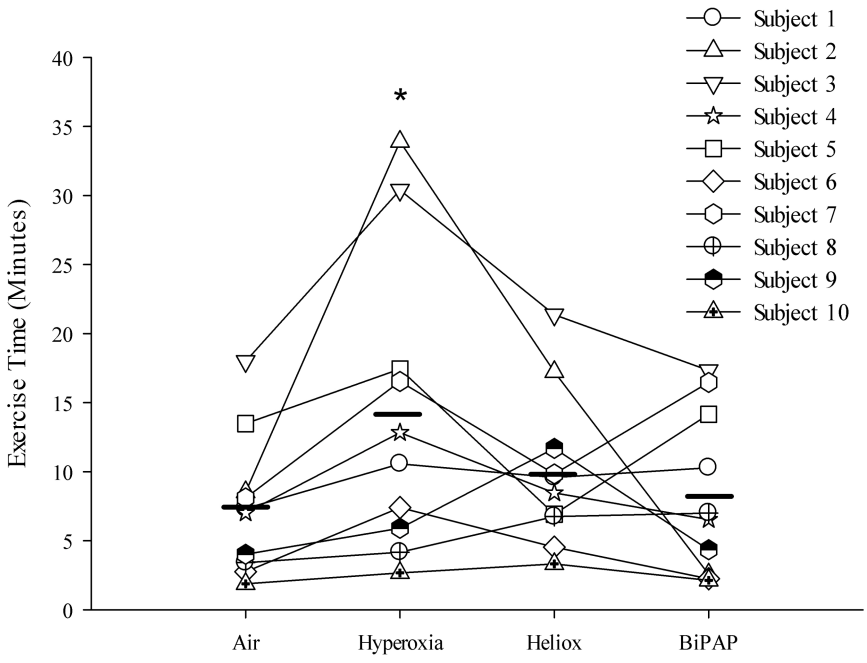

Figure 2.5: Individual exercise responses to the four interventions. Line represents mean exercise time for each intervention. n=10, * = p<0.05, vs. Air

Exercise time to symptom limitation, was significantly increased with hyperoxia ($p = 0.043$), almost doubling the mean exercising time from 7.5 ± 5.1 min with air to 14.2 ± 10.7 min (Figure 2.4). All ten patients increased their exercise time with hyperoxia. The change in exercise time with hyperoxia was also significantly different to air ($p=0.003$) and BiPAP ($p=0.008$). Breathing heliox, 9 out of 10 participants increased their exercise time, and the mean exercise time was increased by 58 ± 65% to 10.0 ± 5.6 min. However this increase in exercise tolerance with heliox was not statistically significant ($p=0.439$). BiPAP increased exercise time in 6 of 10 participants but the mean exercise time of 8.3 ± 5.9 min was not significant ($p=0.792$). The symptoms responsible for stopping exercise were similar between the four interventions (Table 2.4).

Table 2.4: Dyspnea and Ventilatory Parameters at End-Exercise

	Air	Hyperoxia	Heliox	BiPAP
Unpleasantness	5.0 ± 1.3	4.4 ± 1.8	4.4 ± 2.3	4.3 ± 1.8
Sensory Intensity	4.3 ± 1.6	3.9 ± 2.1	4.2 ± 2.3	4.4 ± 2.0
Muscle Work	3.8 ± 2.5	3.5 ± 2.4	4.0 ± 2.8	3.6 ± 2.6
Air Hunger	4.7 ± 1.8	4.5 ± 2.5	4.9 ± 2.7	5.0 ± 2.3
Mental Effort	4.5 ± 2.1	3.2 ± 2.9	4.2 ± 2.7	4.2 ± 3.1
Chest Tightness	4.3 ± 2.9	3.6 ± 3.1	4.1 ± 2.2	3.6 ± 2.4
Breathing a lot	6.0 ± 1.7	5.3 ± 2.2	5.5 ± 2.2	5.8 ± 1.8
V_E, $L \cdot min^{-1}$	32.6 ± 11.5	32.8 ± 12.6	37.4 ± 13.3	-
V_T, L	1.04 ± 0.35	1.02 ± 0.30	1.17 ± 0.36	-
RR, $breaths \cdot min^{-1}$	32 ± 7	32 ± 5	33 ± 7	-
T_I, s	0.72 ± 0.13	0.71 ± 0.13	0.69 ± 0.12	-
T_E, s	1.21 ± 0.37	1.18 ± 0.28	1.13 ± 0.24	-
T_I/T_{TOT}	0.39 ± 0.07	0.38 ± 0.06	0.38 ± 0.06	-
IC, L	1.44 ± 0.38	1.51 ± 0.39	1.73 ± 0.46§	1.30 ± 0.28‡
EELV, L	5.66 ± 2.14	5.59 ± 2.09	5.37 ± 2.09	5.76 ± 1.99
S_pO_2, %	91 ± 6†	99 ± 4*‡§	93 ± 5†	93 ± 6†
HR, $beats \cdot min^{-1}$	123 ± 20	120 ± 19	122 ± 20	116 ± 21
Reason for Stopping Exercise				
Dyspnea	5	4	5	4
Leg Fatigue	2	4	4	4
Both	2	1	1	2
Other	1	1	1	0

Abbreviations: See Table 2.3 Values = mean ± SD, n=10. Values = mean ± SD, n=10. * = $p<0.05$ vs. Air; † = $p<0.05$ vs. Hyperoxia; ‡ = $p<0.05$ vs. Heliox; § = $p<0.05$ vs. BiPAP.

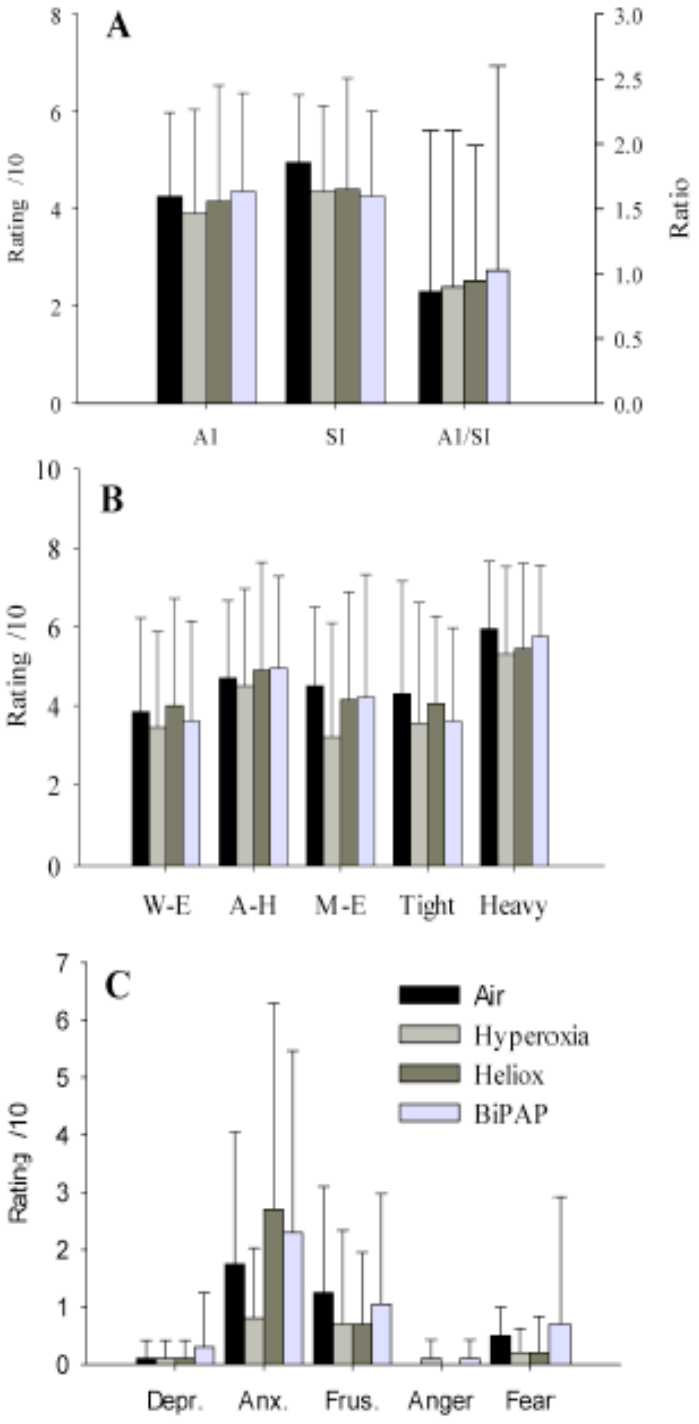

Figure 2.6. A) A_1, S_I, and the A_1/S_I ratio at end exercise B) Rankings of the Dimensions of Dyspnea at end-exercise. C) Ratings of A_2. Values = mean ± SD, n=10

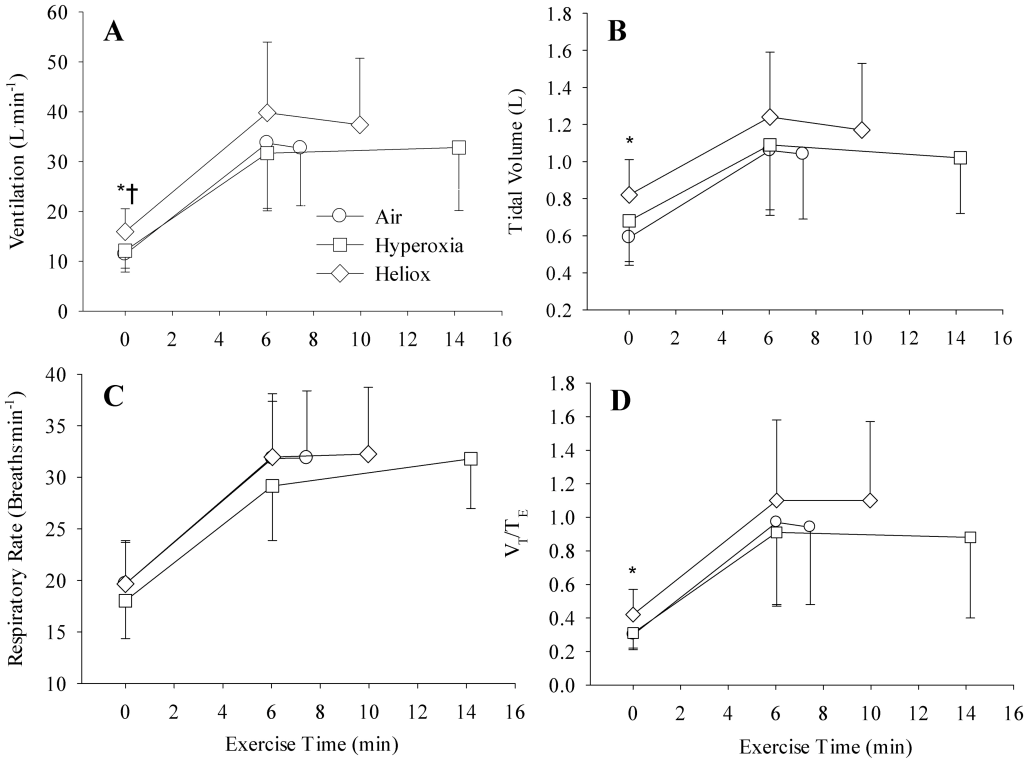

Figure 2.7: Ventilatory Parameters Measured Throughout the Constant Load Exercise Trials. V_T/T_E = tidal volume/expiratory time which is equivalent to mean expiratory flow. Values = mean ± SD, n=10. * = p<0.05 heliox vs. air; † = p<0.05 heliox vs. hyperoxia

Table 2.6 Correlates of Improved Exercise Time

	Hyperoxia (R= ±0.67- 0.90)	Heliox (R=± 0.67)	BiPAP
Respiratory Rate	↓	↓	-
Time for Inspiration	↑	↓	-
Time for Expiration	↑	-	-
Inspiratory Capacity	↑	-	-
Air Hunger	↓	-	-

Table 2.7 Correlates of Changes in the Dimensions of Dyspnea

	Hyperoxia (R= -0.58-0.79)	Heliox (R= 0.64- 0.88)	BiPAP (0.63-0.84)
Inspiratory Capacity	↑ A_1	↑ A_1/S_I	↑ A_1/S_I
End-Expiratory Lung Volume	-	↓ A_1/S_I	↓ A_1
Work or Effort	↓ A_1, S_I	↓ A_1, S_I	↓ A_1
Air Hunger	-	↓ A_1, S_I	-
Breathing Heavy	-	↓ S_I	↓ A_1

2.6.5 Correlates of Improved Exercise Tolerance

The increase in exercise time to symptom limitation with hyperoxia significantly correlated with the isotime decrease in breathing frequency ($r = -0.74$, $p=0.016$), the decrease in the sensation of air hunger ($r = -0.67$, $p=0.036$), the increase in IC ($r = 0.70$, $p=0.026$), and the lengthening of inspiratory ($r = 0.90$, $p=0.0005$) and expiratory time ($r = 0.74$, $p=0.014$) as seen in Table 2.6. The increase in exercise time with heliox correlated with the change in isotime breathing frequency ($r = -0.66$, $p=0.036$) and the decrease in isotime inspiratory time ($r = 0.66$, $p=0.040$) (Table 2.6). There were no significant correlations between improvements in exercise time with BiPAP and any dyspnea or ventilatory measure. However, there was a trend toward correlations between the increase in exercise time and the isotime reductions in the sensation of breathing effort ($r = -0.67$, $p=0.089$) and air hunger ($r = -0.59$, $p=0.073$) (Table 2.6).

2.6.6 Correlates of Changes in the Dimensions of Dyspnea

There was a trend toward a significant correlation between the change in A_1 and the change in IC (r=-0.58, p=0.077) with hyperoxia (Table 2.7). There were also correlations between the change in A_1 and the perceived change in the work to breathe (r=0.79, p=0.007), and S_I and the change in the perception of muscular effort to breathe (r=0.75, p=0.013) (Table 2.7). However, the changes in S_I with hyperoxia at isotime during exercise were not significantly correlated with changes in IC or EELV.

There were also no significant correlations between the changes in A_1 and S_I with heliox and operational lung volumes. Nevertheless, the changes in A_1/S_I were correlated with the changes in IC (r=-0.77, p=0.009) and EELV (r=0.77, p=0.025). The change in A_1 was correlated with changes in the sensory qualities of air hunger (r=0.88, p=0.007) and muscle effort (r=0.70, p=0.025). The changes in S_I were also correlated with changes in the sensory qualities of air hunger (r=0.75, p=0.013), muscular effort (r=0.64, p=0.047) and the sensation of breathing heavily, rapidly or deeply (r=0.78, p=0.008) (Table 2.7).

At isotime, changes in A_1 with BiPAP were significantly correlated with changes in EELV (r=0.63, p=0.050) and the changes in A_1/S_I significantly correlated with the changes in IC (r=-0.64, p=0.046). There were also apparent correlations between the changes in A_1 and the sensory quality of muscular effort to breath (r=0.84, p=0.002) and the sensory quality of breathing heavily, rapidly or deeply (r=0.76, p=0.010).

2.7 Discussion

This is the first study to investigate how hyperoxia, heliox, and BiPAP alter the affective and sensory dimensions of dyspnea during exercise in patients with COPD. The primary novel findings of this study were that at an isotime during exercise, both hyperoxia and heliox reduced the unpleasantness and the sensory intensity of dyspnea as demonstrated by the significant changes in A_1 and S_I. Heliox also significantly reduced the sensation of breathing heavily, rapidly or deeply at isotime. Secondary findings included significant correlations between the affective and sensory dimensions of dyspnea with changes in operational lung volumes with all three interventions. There was also a correlation between the change in the sensory quality of air hunger and the improvement in exercise tolerance with hyperoxia. Collectively, these findings highlight the multidimensionality of dyspnea and demonstrate that it is possible to improve different sensations of breathlessness during exercise, which leads to enhanced exercise tolerance.

2.7.1 Hyperoxia, Heliox, and BiPAP and their Effects on the Affective and Sensory Dimensions of Dyspnea.

The changes in the absolute A_1 and S_I scores observed in this study only partially supported our primary hypothesis that all interventions would decrease the A_1 and S_I ratings compared to room air. More specifically, none of the absolute A_1 scores were decreased at the isotime during exercise; however the change in A_1 with hyperoxia and heliox were significantly different from air. Even though these findings were not statistically significant, they could be of clinical relevance as hyperoxia and heliox

reduced A_1 from 4.1 to 2.6 (p=0.09) and 2.7 (p=0.11), respectively. This magnitude of change in the affective dimension of dyspnea is associated with a change in the perception of breathing unpleasantness from "annoying" to "slightly unpleasant". It is possible that patients may be more inclined to perform further exercise or be able to complete a greater volume of tasks related to activities of daily living when exertion is only "slightly unpleasant".

The absence of statistically significant results may be due to the relatively small sample size and/or the large amount of individual variation that existed with regards to the perception of the affective and sensory dimensions of dyspnea with each participant. Lansing *et al*. [46] reported that some individuals find it difficult to separate the A_1 and S_I dimensions when using the rating scales even though their verbal descriptors may suggest a difference between these two parameters, while other participants have less difficulty ranking these scores more liberally. This variation in rating pattern may have affected some of the A_1 scores that we observed. However, the magnitude of change of an A_1 score correlates proportionally with changes in S_I scores (i.e. $\Delta A_1 \cong \Delta S_1$). A change greater than 1 point is considered the minimal clinically important difference for the S_I score (see below), thus the hyperoxia and heliox trials that reduced the A_1 score by greater than one point (1.45 and 1.35, respectively) would have clinical importance.

To our knowledge, no study has investigated the role of different interventions for reducing A_1 in patients with COPD during exercise. The interventions we used may have decreased the feeling of unpleasantness for our participants by decreasing the sensation of suffocation or the urge to breathe (air hunger) and by diminishing the amount of respiratory work/effort required during exercise. As mentioned above, hyperoxia directly

reduces the drive to breathe by maintaining the PaO_2 at appropriate levels and by reducing metabolic acidosis. By lowering the demand of the respiratory system, breathing sensations may have been sensed as less unpleasant. Heliox reduces expiratory flow limitation and maintains tidal breathing at lower lung volumes [66] which may reduce the feeling of suffocation but may also decrease the work of breathing, both of which would reduce the unpleasantness of breathing. Finally, BiPAP is designed to improve V_E by maintaining the patency of the airways and promoting airflow to the patient with minimal respiratory work. We had expected that unloading the respiratory muscles would have made breathing more pleasant, but it is possible that participants found the BiPAP facemask and/or "blasts" of air uncomfortable, which could have translated into higher A_1 scores. Again, our results support our hypothesis that the interventions that primarily decrease air hunger would have a greater effect on A_1 and S_I ratings compared to those primarily targeted at the work of breathing.

Hyperoxia was the only intervention that significantly reduced the absolute rating of the sensory dimension of dyspnea at isotime during constant load exercise. In support of our hypothesis, both hyperoxia and heliox were able to produce a significant change in S_I. Furthermore, decreases in the S_I score were positively correlated with perceived muscular work during the hyperoxic trial and with perceptions of breathing heavy, muscle effort, and air hunger during the heliox trial. Lansing *et al*. [46], have demonstrated that the sensation of air hunger is positively correlated with the automatic drive to breathe and negatively correlated with pulmonary ventilation. Since hyperoxia reduces ventilatory demand and improves lung emptying by increasing expiratory time, it is not surprising that this intervention had the greatest effect on air hunger and subsequent

S_I scores. The sensation of air hunger may be decreased when breathing heliox by increasing airflow through the obstructed airways and promoting ventilation. This may explain the negative correlation between air hunger and pulmonary ventilation that we observed during this trial. It is possible that BiPAP could lead to reductions in air hunger by increasing passive inflation of the lung and decreasing vagal afferent stimulation. Nevertheless these mechanisms may have had less of an effect on ventilation and the drive to breathe in our participants based on the effectiveness of BiPAP delivery as well as the degree of dynamic hyperinflation present in each patient, and we did not observe any decreases in air hunger or any correlations of dyspneic symptoms with air hunger in this condition.

The measure of S_I is the dimension of dyspnea that is most reasonably comparable to the commonly used Borg dyspnea scale. Many studies have shown that decreasing the work of breathing can reduce the reported Borg score. In particular, since hyperoxia and heliox are able to reduce EELV and PEEPi, the work required to inspire is lowered and other studies have shown a decrease in the Borg ratings of dyspnea [61-63, 65]. Again, since Borg is likely analogous to the sensory dimension of dyspnea, based on these studies it would be expected that a lower work of breathing may reduce S_I scores. Many studies have also demonstrated the ability of positive airway pressure to reduce the sensation of dyspnea as a result of a lower work of breathing [67-71], but we did not observe these changes in our study.

Even though the heliox and BiPAP trials did not decrease the absolute ratings of S_I to statistically significant levels, similar to the reductions in A_1 that were clinically significant, it is also likely that the average reduction in S_I is of clinical relevance. It is

well accepted in the literature that a change of 1 point on the Borg scale is a minimal clinically important difference in COPD [83]. For example, a change of one point is "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side-effects and excessive cost, a change in the patient's management" [84]. During the heliox trial, we observed reductions in S_I of ~1.5 points.

The A_I/S_I ratio was not significantly different among interventions at isotime during exercise. However, since we were able to decrease both A_I and S_I to similar extents throughout the exercise bouts, it makes sense that the ratio would stay similar despite these changes. There was a correlation between the A_I/S_I ratio with changes in the IC and EELV during the heliox trial, which suggests that reducing dynamic hyperinflation has favourable effects for altering dyspnea perception. Reducing this ratio indicates that patients are perceiving their dyspnea to be less unpleasant for a given sensory intensity. Consistent with [46], and as mentioned above, different patients report varying levels of A_I ratings in conjunction with S_I scores, leading to a large amount of individual variability in this ratio. As a result, this ratio can be useful in monitoring within individual changes, but may be limited in its ability to compare between individuals and between groups [46].

The descriptors for dyspnea (muscle work-effort, air hunger, mental effort, chest tightness, and heavy breathing) were not significantly different among trials, except for breathing heavily, rapidly or deeply, which was significantly reduced with heliox at isotime. Interestingly, patients perceived they were breathing less heavily even though they were breathing at a significant increased V_E during this condition. While, RR or V_T

did not change to statistically significant levels, the primary reason for the increase in V_E was due to an increase in tidal volume, due to a significant reduction in EELV. This is consistent with the previous studies [62][65]. The perception of decreased breathing despite actual increases in ventilation suggest that dynamic hyperinflation and the inability to increase tidal volume contribute to the sensation of heavy breathing, and changes in these operational lung volumes can change this important sensory quality in patients with COPD.

At end exercise, there was no effect of any intervention on either the affective or sensory dimensions of dyspnea. As a result, the A_I/S_I ratio was also not changed significantly among trials. However, our data indicate that during the BiPAP and air trials the A_I/S_I ratio remains constant at a certain value once the A_I score reaches a critical or threshold level. This could imply that unpleasantness may be more important in terms of dyspnea sensation than the sensory intensity of dyspnea perception, and may be the reason why patients curtailed exercise in these conditions. It is also possible that since the interventions allowed participants to exercise for longer periods of time, their sensations of dyspnea were delayed throughout exercise, but ultimately as exercise progressed they reached the same level of exertional symptoms. This is in keeping with previous studies that have shown that once patients reach a certain level of dyspnea, exercise cessation will occur [39]. The prolongation of exertional symptoms was particularly true during the hyperoxia and heliox exercise conditions, where the amount of exercise that was performed was ultimately increased.

There were no changes in the emotional responses to dyspnea with any intervention. Hyperoxia tended to reduce anxiety post-exercise, which may be an

important finding to investigate further. Anxiety is a common emotion described in patients with COPD that is also associated with their level of disability [85]. Long-standing emotional feelings can affect patient's behaviour. When patients associate negative feelings with their dyspnea, they tend to make lifestyle choices that to avoid dyspneic sensations all together, which makes adherence to an exercise program difficult [46]. These are important considerations when planning an exercise program for a patient with a chronic disease, especially when exercise in this population has been proven to have considerable effects on the prognosis of disease and overall health-related quality of life.

2.7.2 Hyperoxia, Heliox, and BiPAP and their Effects on Exercise Time

The time to symptom limitation was significantly increased during the hyperoxia trial ($p = 0.043$), increasing mean exercise time by 6.73 minutes, a 91 ± 85% (range: 22-298%) improvement. This is similar to that previous reported by others [61-63]. Eves [62] reported that breathing 40% hyperoxia increased exercise time from 9.4 ± 5.2 min to 17.8 ± 5.8 min compared to air. Similarly, O'Donnell [61] reported an increases of 4.7 ± 1.4 minutes with 60% oxygen compared to air (mean exercise time during the air trial = 4.1 ± 0.9). Additionally, Somfay [63] demonstrated that hyperoxia (O_2 30%, and O_2 50%) increased exercise time compared to air by 92 ± 20% and 157 ± 20%, respectively, which shows there is an increasing dose response effect up to 50% O_2. The improved exercise time in these studies was correlated with exercise isotime changes V_E, RR [62], changes in the slope of V_E/time and in the slope of lactate/time [61], and with increases in IC, IRV and mean expiratory time [63]. These findings are in agreement with our data that

showed a decrease in RR, and increases in IC, T_I, and T_E to be correlated with the improvements in exercise time. Our study furthers these findings since we demonstrated that a decrease in air hunger at isotime also was associated with this increase in exercise time. As discussed, air hunger may have been a factor involved in reducing the S_I score at isotime during this condition and may have played a role in producing more favourable A_1 values since this sensation is usually described as being very uncomfortable for participants [53].

While breathing heliox, the mean exercise time for all patients was prolonged by 2.52 minutes, a 57 ± 65% (range: -49-+191%) improvement. This finding is similar to studies by Eves [62], Palange [65], and Chiappa [86] who demonstrated improvements with 21% O_2, 79% He of 16.7 ± 9.1 min compared to 9.4 ± 5.2 min with air, 9.0 ± 4.5 min from 4.0 ± 2.0 min on air, and 640 ± 95 seconds from 371 ± 100 seconds with air, respectively. Although we observed a modest increase in mean exercise time, it was not to the same extent as other previous studies. Several characteristics of our patient population may have played a role in this finding. First, our study included four female participants and six males. All other studies included only men as their testing subjects. To our knowledge, no study has investigated if sex differences could play a role with regards to a response with heliox. Furthermore, the mean age and the average FEV_1 (% pred) of our patients was slightly higher in our study compared to others. This difference in pulmonary function could suggest that heliox may be better suited for those with more advanced disease.

The only significant correlates that we observed with the change in exercise time with heliox were a decreased RR and T_I at isotime, however participants did report

decreased dyspnea scores at isotime and the changes in A_1 and S_I compared to air were significant. Correlations found in this study also agree with previous findings that reported similar changes in operational lung volumes and breathing patterns associated with changes in exercise tolerance [62, 65, 86]. As mentioned above the changes in A_1 were associated with decreased perceptions of both air hunger and muscle effort, indicating that targeting these sensations of dyspnea can have positive repercussions for exercise tolerance.

Again, the interventions that have a greater effect on the "air hunger" component of dyspnea showed the greatest improvements on exercise time. The clinically relevant change in exercise time for patients with COPD has been accepted as ~1.75 minutes [87]. As such, breathing hyperoxia or heliox during exercise in these patients is potentially of clinical importance and when utilized in pulmonary rehabilitation as an adjunct to exercise training to reduce the unpleasant sensations of dyspnea could improve the volume of exercise that can be performed [88, 89].

BiPAP only increased the exercise time for 6 of the 10 participants but the mean improvement was not statistically meaningful. The mean time change was only 0.86 minutes compared to air, but there was a considerable range among participants from -5.95 to + 8.37 minutes (-40 to +104%). We expected all participants to respond to the BiPAP, but to a lesser extent than to the hyperoxia and heliox gas mixtures. We did not anticipate that the BiPAP would have any negative effect on exercise tolerance as previous studies have reported exercise improvement in patients with COPD while using non-invasive positive pressure ventilation (NIPPV) [90-93]. However, Johnson et al. [82] have observed that patients who exercised with NIPPV initially performed worse and had

lower exercise times than without the machine. After six weeks of training with NIPPV, patients exercised more than 2.5 minutes longer and at higher workloads than those who trained without the machine, which still provides some encouragement for the use of BiPAP as an adjunct to exercise training in patients with COPD.

2.7.3 Hyperoxia, Heliox, and BiPAP and their Effects on Operational Lung Volumes

As previously reported by our group [62, 88] and others [61, 63, 65, 70], operational lung volumes can change between the interventions and throughout the exercise trials. The change in V_E compared to room air, was significantly different at isotime between the hyperoxia and heliox trials. We also observed an increase in the change in V_E at isotime with heliox compared to hyperoxia.

Hyperoxia has the known effect for reducing ventilatory demand during exercise, even in non-hypoxemic patients, which has favourable effects on operational lung volumes and dyspnea [61]. We observed a similar effect, as there was a significant reduction in RR that was accompanied by a lengthening of inspiratory and expiratory time, which supports previous studies [61-63]. At isotime, the absolute IC did not change significantly with hyperoxia as might be expected. O'Donnell [61, 64] has shown that hyperoxia lengthens T_E and improves lung emptying which in turn maintains EELV closer to resting levels. EELV was decreased for 9/10 participants during the hyperoxia trial and as a result, a lower EELV should translate into a greater IC. However, this was not the case. Our results do show a small increase in IC, but again, the small sample size and extreme variation among individuals may have contributed to the statistically nonsignificant result. Although the change in IC was not statistically significant, there

was a trend (p=0.077) toward a decrease in IC and lower A_1 scores. This correlation is supportive of the idea that patients may experience a decrease in unpleasant sensations during exercise with lowered dynamic hyperinflation.

In contrast, V_E was significantly increased with heliox, primarily as a result of the increased V_T. However, neither Eves [62] nor Palange [65] observed a change in V_E at isotime with heliox, but Eves did observe a significant increase in V_T. As mentioned above, the demographic of our participants varied in terms of sex, age, and FEV_1 to other comparable studies with heliox and these factors may have affected how our participants responded to this gas mixture. Heliox, due to its lower density, should help improve airflow and lung emptying which would explain why the majority of participants did exhibit an increased V_T at isotime. Compared to room air, the mean IC of our participants was increased significantly when breathing heliox (p= 0.046), which is consistent with the literature. This is likely due to heliox's ability to increase maximal expiratory flow rates, reduce dynamic hyperinflation [65], and reduce EELV at isotime compared to air [62, 65]. Every participant in our study had a lower EELV at isotime during the heliox trial. Furthermore, these changes in EELV and IC correlated with a change in the A_1/S_I ratio, implying once again the role of dynamic hyperinflation with the perception of the various dimensions of dyspnea.

The mean IC at isotime, when breathing with BiPAP was not significantly changed compared to room air and only two participants had a lower EELV during the BiPAP trial at isotime. Very few studies have attempted to measure IC during exercise with BiPAP due to the methodological difficulties with this measure. However, we did observe a correlation between the change in A_1 score with the change in EELV, and also

between the A_I/S_I ratio and changes in IC. These findings, again, identify dynamic hyperinflation as a potential mechanism for the cause of respiratory unpleasantness during exercise.

One of the most interesting findings of this study was the magnitude of variation between reported dyspnea scores and how the perceived dimensions of dyspnea had the capacity to change with each intervention. Many participants preferred the interventions that reduced the sensation of air hunger, but others thrived (best trial for one participant, and second best trial for three participants) when using the BiPAP during exercise. This suggests that it may be clinically important and beneficial to try and match the intervention to the patient based to the type and sensation of dyspnea that they experience during exercise. Although COPD is a single diagnosis, it is a very heterogeneous disease and the extent and type of lung damage as well as the severity of expiratory airflow obstruction varies between patients. There are different phenotypes of COPD; some patients are statically inflated, while others dynamically hyperinflate. Some patients desaturate during exercise, while some have more emphysema than chronic bronchitis and vice versa. For patients with hyperinflation, hyperoxia may be better for reducing the sensory and affective dimensions of dyspnea by increasing T_E and promoting greater lung emptying, thus reducing the amount of pulmonary stretch and decreasing the amount of gas trapping. Heliox may be better for those with reduced ventilatory capacity as it increases expiratory flow rates through the large and mid size airways allowing greater tidal volumes to be achieved while maintaining EELV closer to resting levels. For patients with moderate-severe emphysema, BiPAP may help by reducing the tendency of their untethered alveoli to collapse and consequently keeping their airways inflated and

ventilated. It is intuitive then that, based on an individual's pathophysiology compounded by many other psychosocial factors, each patient will respond differently to each intervention. Therefore, it is warranted for future studies to investigate phenotyping patients before exercise training or a pulmonary rehabilitation program so that the appropriate adjunct to exercise can be prescribed to optimally reduce the unpleasantness of dyspnea. This would allow all patients to get the optimal benefits out of an exercise rehabilitation program, which could greatly enhance the known benefits of this routine therapy.

2.7.4 Limitations

A primary limitation of the study was the setup of our BiPAP machine since the continuous positive pressure altered the ability of the differential pressure transducers to accurately measure flow. As such we were unable to measure ventilatory parameters and during the inspiratory maneuvers with the BiPAP trial, we manually switched the machine off to the patient with a 3-way valve immediately before the IC maneuver, and switched it back on immediately after. This was a highly reproducible maneuver but could have affected our measurement if the timing was not flawless. Furthermore, it is possible that since we optimized the BiPAP settings for each patient during rest, these pressures were not ideal during exercise. The pressures could have been inadequate to reduce the work of breathing and subsequent dyspnea scores during exercise, but it is also plausible that for some patients, the pressures that were optimal at rest may have been too high during exercise.

The relatively small sample size of this pilot study may also have lead to the potential of a type 2 error. In the measurements made there was considerably more

variation than was originally predicted and caution needs to be taken when interpreting the data accordingly. Although this study shows some promising trends, a larger more comprehensive study is now needed to try and address the specific mechanistic responses for changes in the affective and sensory dimensions of dyspnea and to try and understand how to best match phenotypes of COPD to interventions that will provide them with the most benefit from performing exercise.

2.7.5 Conclusions

This study demonstrated that hyperoxia and heliox were able to alter the sensory intensity and the immediate affective dimension of exertional dyspnea. A number of strong correlations between the affective and sensory dimensions of dyspnea with changes in ventilatory parameters and operational lung volumes in patients with COPD during exercise further our understanding of the potential causes of this unpleasant breathing sensation and how different interventions may positively alter it. We were also able to demonstrate that reductions in air hunger measured at an exercise isotime while breathing a hyperoxic gas correlated with improvements in exercise time. Finally, this was the first study to document the considerable individual variation between the qualities of shortness of breath described by individuals with a clinical diagnosis of COPD. The magnitude of individual variation suggests the benefits of providing patients with an adjunct to exercise that is best suited to their needs during a rehabilitation program. This may allow patients to perform more exercise training, which could result in long-term benefits to their health related quality of life and overall health status.

CHAPTER 3

Extended Discussion

Dyspnea is an extremely common clinical presentation. It is seen most commonly among patients with cardiovascular and respiratory disease [39], but can also be present in patients who are anemic, obese, or in those with gastro-intestinal, musculoskeletal, or psychosocial, conditions [94], to name a few. In patients with COPD, dyspnea is the symptom that is most frequently described at rest and during exercise [39]. It limits exercise capacity and is usually the primary reason that prompts referral to a pulmonary rehabilitation program for patients with COPD [34]. Dyspnea usually progresses with the severity of disease and is one of the strongest prognostic indicators in patients with COPD [95]. Dyspnea presents a huge burden of disease, yet remains a symptom that is still relatively misunderstood.

There are several reasons that may explain this lack of understanding, but one of the more plausible reasons stems from the fact that there are many different definitions for the term “dyspnea”. Shortness of breath can describe feelings of distress, increased respiratory effort, not getting enough air, feeling smothered, and experiencing chest tightness, to name a few. It is clear that overall shortness of breath represents respiratory discomfort, but the exact sensations that each patient may be experiencing can vary.

The complexity of dyspnea is further enhanced because there are many different physiological mechanisms that can induce the sensation of dyspnea and each mechanism can cause shortness of breath to be perceived differently. Respiratory dyspnea can be caused by changes in pulmonary musculature, vasculature, receptor sensation, volume,

airway resistance, chest wall displacement, as well as activation of central and peripheral chemoreceptors [94].

The above mechanisms can act independently to create sensations of dyspnea, but more commonly the mechanisms are multifactorial, especially during exercise. When patients exercise, their drive to breathe is increased to provide adequate oxygen delivery to their working muscles. Increasing either tidal volume or respiratory rate can increase the amount of ventilation. The amount of increase in V_T is largely determined by each patient's degree of dynamic hyperinflation. During mild and moderate exercise intensities there may be room for an increase in V_T, but as exercise progresses and patients become dynamically hyperinflated they are restricted in their ability to further increase their V_T as it becomes fixed on the non-compliant portion of the pressure-volume curve of the respiratory system [39]. This restriction also impedes IC, which is closely related to the amount of dyspnea that patients experience, so that smaller ICs are associated with greater sensations of dyspnea [39]. As ventilatory demands continue to increase during exercise and V_T is restricted, patients will increase their RR to meet the demand. However, as RR increases the T_E will subsequently decrease and in patients with COPD who are expiratory flow limited, this leads to further gas trapping [39].

As described by O'Donnell *et al*. [39], dynamic hyperinflation increases the load on the inspiratory muscles and leads to an increased work of breathing. The increase in lung volumes also places these muscles at disadvantaged lengths for producing muscle contraction, which further reduces the respiratory muscles' ability to achieve the work required to maintain alveolar ventilation [39]. As previously mentioned, at high lung volumes and high respiration rates, patients are largely unable to increase their ventilation

to supply enough oxygen to meet the demand of the body. Furthermore, a worsening V/Q mismatch within their lungs compounds the ventilatory limitation of many of these patients. Decreasing ventilation will increase the amount of CO_2 retained in the body [39], and will promote the drive to breathe. The increased drive to breathe resulting from afferent stimulation of pulmonary mechanoreceptors and chemoreceptors and subsequent inability to increase ventilation is termed neuromechanical dissociation and can create very strong sensations of dyspnea [39].

There were several interesting findings in this study related to the ability of the interventions to change the A_1, A_2, and S_I, scores during the constant load exercise trials. First, we found that the change in A_1 and S_I scores was significantly reduced during the hyperoxia trial. The changes in A_1 and S_1 were both correlated with changes in the reported sensation of respiratory muscle work/effort. Hyperoxia was able to increase exercise time to both clinically and statistically significant levels, and this increase in exercise time was positively correlated with a lower RR, increased IC, T_I, and T_E, as well as lower ratings of air hunger at isotime. The anxiety component of the A_2 score was also reduced during this intervention, although not to a statistically significant level.

As previously mentioned, hyperoxia suppresses ventilation by decreasing the firing rates of peripheral chemoreceptors and patients tend to adopt a slower breathing pattern during exercise when compared to room air [39]. This slower pattern of respiration helps to decrease EELV and hyperinflation, which likely lead to the reductions in the sensory dimensions of dyspnea. Maintaining SaO_2 and lower lung volumes reduces the sensory afferent inputs from muscle mechanoreceptors and metaboreceptors and may in turn enhance the ventilatory output for a given ventilatory

effort (termed neuromuscular coupling) [39]. By sustaining a greater contribution of ATP production from aerobic metabolism at the level of the muscle tissue for a longer amount of time than would be observed when participants were breathing room air (and potentially beginning to desaturate), there would be less byproducts of anaerobic metabolism. This may reduce fatigue and lower the amount of central motor command to ventilate [39], leading to further improvements in neuromuscular coupling. The participants in our study were not hypoxemic, so the primary mechanism involved in decreasing S_I was likely the change in V_E.

The mechanisms for the ability of hyperoxia to reduce the sensation of air hunger relate back to the processes described above. Air hunger is thought to occur as a result of afferent stimulus through corollary discharge to the sensory areas of the forebrain, and by the stimulation of chemoreceptors being sensed by the forebrain [39]. The intensity of air hunger is determined by the excitatory stimulus (the drive to breathe) and by ongoing inhibition from mechanoreceptors that signal the current level of pulmonary ventilation [39]. Air hunger is usually associated with negative affective emotions, such as distress [46]. The increase in exercise time with hyperoxia was correlated with decreases in air hunger at isotime, so follows that our A_1 scores should also significantly decrease during this condition, as we observed. Furthermore, hyperoxia tended to reduce the anxiety portion of the A_2 score, which may be due to the decreases in A_1 and S_I during the exercise test.

Neurologically, effort is sensed by corollary discharge from motor cortical centers that drive voluntary breathing [39]. Increased corollary discharge can be interpreted as abnormal and can create negative threat-related affective responses [39]. Changes in the

firing of pulmonary mechanoreceptors and metaboreceptors may also play a role in the sensation of work or effort [39]. Muscular effort is sensed when there is increased loading and functional weakening of inspiratory muscles as a result of dynamic hyperinflation. Again, since hyperoxia has been shown to reduce EELV, hyperinflation, and the resultant PEEPi [61-63, 65], this gas mixture may have also affected the work of breathing and sense of effort during the constant load exercise test. Overall, we did not observe significant changes in these ventilatory parameters, but this may be due to the large amount of individual variability that we observed between participants. Several subjects had quite a prominent response to hyperoxia, whereas this response was modest in others (see Appendix C Individual Scores). Had this response been more comparable among individuals, overall we may have seen a bigger effect on mean ventilatory parameters and dyspnea scores. Reducing the work of breathing and effort may have also led to decreases in corollary discharge and could have contributed to the reduction in A_I scores that we observed in this condition.

Heliox was able to evoke a clinically significant change in exercise time, as well as a significant increase in V_E at isotime, while the sensation intensity of dyspnea related to heavy breathing was significantly decreased. The increase in exercise time was correlated with decreases in the RR and T_I at isotime. The changes in A_I and S_I scores were also significantly decreased when breathing heliox, and were associated with variations in the sensory qualities of dyspnea. For example, changes in air hunger and respiratory muscle work/effort were both correlated with alterations in the A_I and S_I scores. The sensation of breathing a lot (either rapidly or heavily) was also associated

with the S_1 value and changes in the A_1/S_1 ratio were correlated with changes in IC and EELV.

Heliox may have decreased the sense of air hunger and effort by affecting the same neurological pathways as discussed for hyperoxia, although the means to achieve these reductions are likely different. Since heliox increases expiratory flow rates it reduces the extent of expiratory flow limitation, dynamic hyperinflation [65], and maintains lung volumes close to FRC during exercise [62, 65]. Heliox is also able to maintain lower lung volumes as a result of less gas trapping [66] and an increase in ventilation causing less CO_2 being retained and less stimulation of chemoreceptors being sensed by the forebrain [39]. The reduction in lung volume also decreases the work of breathing due to a decrease in the loading of inspiratory muscles. The lower work of breathing may have decreased the amount of corollary discharge from motor cortical centers that drive voluntary breathing [39], reduced the sense of effort, and helped to normalize the neuromechanical dissociation. Additionally, we did observe a significant increase in V_E during this trial, and the increase in V_E was mostly due to an increase in V_T. Again, pulmonary stretch receptor information is capable of relieving air hunger [39] and this increase in V_T may have led to the lower S_I scores that we observed. Studies have also shown that increasing tidal volume can relieve air hunger [39] and this may be another mechanism by which heliox reduces this sensation. As air hunger is associated with negative affective emotions and since it is likely that air hunger was targeted with the use of heliox, the two mechanisms described above probably both contribute to the change in A_1 score that we observed.

We did not observe any changes in the affective or sensory dimensions of dyspnea during the BiPAP trial. We expected BiPAP to decrease the WOB and sense of effort by reducing the load on the muscles of inspiration and preventing any functional weakening. BiPAP could have also improved V_E by maintaining the patency of the airways and promoting airflow to the patient, which could have affected the sensation of air hunger. The BiPAP settings were optimized for each patient, but unfortunately many patients did not tolerate this condition very well. It is possible that patients required a longer trial period with the BiPAP to feel more comfortable with its use. Other reasons may include the slight positive pressure on expiration that patients had to work against, and the fact that patients were titrated on BiPAP at rest. These pressures may have been too overwhelming during exertion, and in the future the optimal BiPAP settings should be titrated during an exercise familiarization trial.

Regardless, many of the findings of this study have clinical relevance and practicality. Increases in exercise time can increase the volume of training in pulmonary rehabilitation and provide significant physiological adaptations that help to improve quality of life [88, 89]. Decreases in the A_1 sensation during exercise may allow for less negative feelings to be associated with exercise in this population and may improve exercise adherence. Similarly, the fact that some patients were less anxious following the hyperoxia trial suggests that we may need more trials with a longer follow up period to see if we can reduce the A_2 component to significant levels- a finding which could present considerable benefits for patients with COPD and promote greater adherence to exercise regimes.

3.1 Future Studies

This initial pilot study has provoked many areas for future investigation. First, although we did see many changes in A_1 and S_I scores, the descriptors of dyspnea did not vary to the extent that we had anticipated. We observed considerable individual variation throughout the exercise tests, so in order to get a more accurate representation of the mean values of these scores, a study with a much larger sample size powered on these initial findings is now warranted.

Similarly, although we observed many changes in the sensory and affective dimensions of dyspnea using the MDP, if this questionnaire is going to be used more commonly in clinical practice the minimal clinically significant changes should be studied in the future. This includes changes in the immediate unpleasantness scores, long-term emotional feelings, and the descriptors of dyspnea.

Third, once we have determined the significant change in the long term affective dimension (A_2), it would be interesting to investigate if changes in this marker could influence exercise adherence. If patients left an exercise session with a lower amount of negative feelings, then it is likely that they would be more willing to continue to participate in these exercise regimes. As mentioned, exercise has considerable implications for this population and anything that might encourage adherence should be thoroughly investigated.

Finally, as outlined in Chapter 2, phenotyping patients to match an adjunct therapy to exercise to their quality or type of dyspnea may play a very large and important role in promoting valuable physiological changes by allowing patients to increase their volume of exercise participation. Maximizing the benefits of an exercise

rehabilitation program by facilitating exercise volume and optimizing affect during, and after exercise, could greatly impact the quality of life of these patients. COPD is a systemic disease that presents primarily with lung manifestations. The benefits that exercise can offer to the multitude of systemic effects and consequences of this disease still remain unmatched by any pharmaceutical agent.

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Appendix A: The Multidimensional Dyspnea Profile

A.1 MDP Stipulations

Standard Stipulations for MDP use – these must be followed unless written exception is made

1. Permission must be obtained from the authors for use of the MDP for each study in which it is used. There is no charge for use.
2. Copyright status must be indicated in publications and public presentations.
3. Acknowledgement must be given to the authors of the MDP in publications and public presentations.[1]
4. The MDP must be used unaltered.
   - Rating scales must appear grouped on pages as in the original.
   - The instruction scripts should be read to subjects in their entirety.
   - Additional questions for clarification or additional information should come after the completion of the questionnaire as it stands (because addition of items to a list is known to have the potential to alter the response to other items).
5. Investigators using the MDP are expected to consult the latest "Suggestions for Administering the MDP" for guidance.
6. If requested, de-identified data will be made available to the MDP team for analysis of psychometric characteristics of the MDP (reliability estimates, factor analysis). MDP data with Age, Gender, Diagnosis, and Condition (e.g., rest, end exercise etc.) are required. The data would be combined with data from other sources, and all sources will be acknowledged. No analysis or conclusions regarding the purpose of the original research will be attempted by the MDP team.

[1] Publication of the MDP is expected in 2009. Please contact the authors for update on reference information. For presentations prior to the publication, refer to "Multidimensional Dyspnea Profile – version ___. RB Banzett, RW Lansing, RM Schwartzstein, PM Meek, MB Parshall. ©2009"

A.2 Suggestions for administering the MDP

Uniformity in the administration of the MDP permits comparison of results among different research groups and, for a given study, among subjects, and experimental trials and sessions. Following the suggestions below can help preserve that uniformity. If departures from these suggestions are scientifically necessary, investigators should consider discussing the departures in reports of results.

Instructions to the subject

Written instructions are provided for each section explaining to subjects which aspect of their breathing sensations is to be rated and how they are to use the rating scales. These can be read by the subjects themselves, or by the examiner and have proven to be sufficient to complete the MDP. In our experience the questionnaire, including explanations, was usually accomplished in less than 5 min, and subsequent use of the questionnaire required 1- 2 min for most subjects. Explaining the distinction between the intensity and unpleasantness of a sensation including examples, should only take 1 or 2 minutes.

Focus period

It is important for the subject or patient to focus on a particular time or episode in responding to the questions (described on the first page of MDP instructions). (e.g. "the last minute of the experiment you just completed", or "when you walked up a flight of stairs yesterday". We have found it necessary to periodically remind the subject that they should report and rate only the sensations they experienced during the focus period.

Coaching and answering questions

The temptation to coach subjects or provide additional explanation for items can lead to an imposition of the investigators point of view and expectations about what the best response should be. In answering subject's questions about sensations they are asked to rate a non-directive approach is best emphasizing that there are no "right" answers and that it is the subject's own sensations and interpretations that are of interest.

Debriefing

Subjects' volunteered comments about their sensations can give important insights into experience of dyspnea. If comments are volunteered during the administration of the MDP they should be noted but not discussed; such discussions should follow completion of the instrument.

Other measures

Other dyspnea questionnaires or rating scales administered before the MDP have the potential to alter responses to the MDP. This may be unavoidable but should be noted in the discussion of results.

Feedback

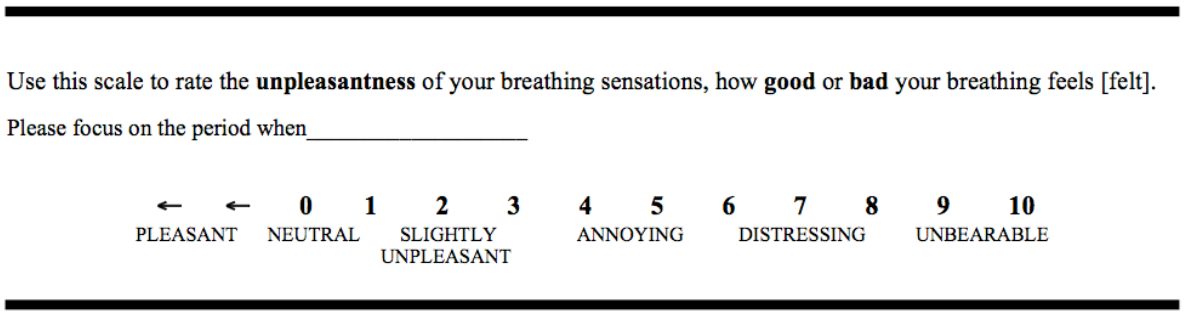
Reports of common problems or suggestions for improvement are welcomed by the authors.

A.3 Multidimensional Dyspnea Profile v2-1-beta

Script for first time use:
"On the following pages we will ask you to rate various aspects of your breathing sensations during _____[focus period]. Some ratings pertain to intensity and some pertain to unpleasantness. We will ask you to separately rate the intensity and the unpleasantness of your breathing sensations. The intensity or strength of the sensation is how much breathing sensation you feel; the unpleasantness of the sensation is how bad it feels. The distinction between these two aspects of breathing sensation might be made clearer if you think of listening to a sound, such as a radio. As the volume and content of the sound changes, I can ask you how loud it sounds or how unpleasant it is to hear it. For example, music that you hate can be unpleasant even when the volume is low, and will become more unpleasant as the volume increases; music that you like will not be unpleasant, even when the volume increases. The intensity of breathing sensation is like sound volume; the unpleasantness of breathing sensation depends not only on intensity but also on how good or bad the sensation is."

Use this scale to rate the **unpleasantness** of your breathing sensations, how **good** or **bad** your breathing feels [felt].

Please focus on the period when_____



Use these scales to rate the intensity of the breathing sensations you felt (like the loudness of sound, regardless of whether the sensation was pleasant or unpleasant). Each scale is defined by a group of phrases. ***If none of the phrases in a particular group apply*** to your breathing sensations, circle **0**. ***If one or more phrases in a group do apply***, rate the **intensity** on the scale provided**.** After completing the scales, please mark the group that *best* describes what you experienced in box on left.

Please focus on the period when _____

0= NONE
10= AS INTENSE AS I CAN IMAGINE

☐	My breathing requires muscle work or effort	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
☐	I am not getting enough air, I feel hunger for air, or, I am smothering	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
☐	My breathing requires mental effort or concentration	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
☐	My chest and lungs feel tight or constricted	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
☐	I am breathing a lot (breathing rapidly , deeply or heavily)	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

If you want to, you can add additional descriptions of your breathing sensations.

☐		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

When your breathing doesn't feel normal, you may experience emotions or 'feelings'. Using the scales below, please tell us about how your breathing sensations made you feel – rate zero for any emotion you did not feel.

Please focus on feelings during the period when _____.

	NONE										THE MOST I CAN IMAGINE
1. Depressed	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
2. Contented	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
3. Anxious	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
4. Frustrated	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
5. Angry	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
6. Happy	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
7. Afraid	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Other?	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Appendix B: Informed Consent

B.1 Informed Consent

a place of mind

THE UNIVERSITY OF BRITISH COLUMBIA

Title of Project: The effect of different interventions on the sensory and affective dimensions of dyspnea in patients with COPD during exercise

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INTRODUCTION

You are being invited to take part in this Master's research study funded by the University of British Columbia (Okanagan) because you have a lung disorder and likely notice that you become short of breath when you exert yourself physically. There are many possible factors that cause your shortness of breath and we are trying to

understand what causes these sensations and how you perceive them. We are also trying to investigate the extent to which certain interventions can decrease your shortness of breath and make exercise more tolerable for you.

YOUR PARTICIPATION IS VOLUNTARY

Your participation is entirely voluntary. 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. If you wish to participate, you will be asked to sign this form. Please take time to read the following information carefully and to discuss it with your family, friends, and doctor before you decide.

BACKGROUND

The reasons responsible for why you may feel short of breath during exercise have been the attention of much study. Due to your lung condition, as you exercise you trap extra air in your lungs, and this is partly responsible for your shortness of breath. Studies have recently shown that the way different patients describe their shortness of breath can vary, and that some sensations of shortness of breath can be more unpleasant than others. There are a number of therapies that have the ability to reduce your shortness of breath. Breathing oxygen gas, breathing a helium-oxygen gas (which is less dense than room air), or receiving some breathing assistance from a machine specifically designed to reduce the effort needed to breathe are all methods that are currently being used to meet this goal. This study is a pilot study, which means that it is a small-scale preliminary study, in our case with 20 participants, designed to study which specific sensations of shortness of breath can be affected by each therapy as you exercise.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to determine the extent to which three different therapies used to reduce shortness of breath (oxygen gas, helium-oxygen gas, or a machine to help you breathe) can change the intensity and the unpleasantness of your shortness of breath during exercise. This will help us understand the mechanisms and the contributing factors behind shortness of breath in patients with lung conditions like yours and will allow for more optimal exercise prescriptions and therapies to be designed to help patients with your condition.

WHO SHOULD NOT PARTICIPATE IN THE STUDY?

If you have had an increase in your sputum production and a worsening of shortness of breath, or have been admitted to hospital in the last six weeks you should not participate in the study until you have returned to your previous condition for at least six weeks. If you have a heart condition that limits your ability to exercise safely or you suffer from pains in your muscles and joints that regularly stop you from exercising, you will also not be able to participate in this study. Additionally, if you have a large reduction in oxygen levels in your blood during exercise, you will not be able to participate. Finally, if your body weight is a lot greater than normal you may not be able to participate because body fat can change the way you breathe.

WHAT DOES THE STUDY INVOLVE?

Visit 1: A breathing test (pulmonary function test) and an incremental cycling exercise test will be performed. During this visit we will also assess the amount of shortness of breath you are experiencing by using a questionnaire. Finally, once you feel rested from your first exercise test, we will ask you to briefly practice exercising while receiving assistance from a machine specifically designed to reduce the effort needed to breathe, so that we can optimize the settings for your next visit.

Visit 2: Two constant-load cycling exercise tests at a moderate intensity will be performed on the same day, separated by at least an hour of rest. During this visit, you will perform the tests using two of four possible interventions: breathing room air, breathing oxygen gas, breathing a helium-oxygen gas mixture, or breathing with a machine that helps you breathe. Although the machine that helps you breathe is an intervention that will likely be beneficial for most patients, others may experience discomfort. If you do experience discomfort please let us know and we will alter the setting.

Visit 3: Two constant-load cycling exercise tests at a moderate intensity will be performed on the same day, separated by at least an hour of rest. During this visit, you will perform the exercise tests using the remaining two interventions.

*All tests and associated time commitments are described in full below. Testing will likely occur in the afternoons, evenings, or weekends.

** This study is randomized cross-over design, which means that all interventions will be given in a random order. It also means that both you and research assistant will be unaware which gas is being used during the exercise tests. This is necessary so that neither you or the researcher will be able to anticipate certain results and cause a bias within the data collected. However, if there is any sort of medical emergency during the test we will immediately reveal which gas mixture was being given.

(1) Pulmonary Function Test

What is this? This test is similar to those you have performed on a regular basis to monitor your condition. A registered respiratory therapist will run and supervise this test. You will sit in a comfortable chair in a large clear chamber and breathe through a mouthpiece while wearing a nose clip. You will be asked to breathe normally and sometimes you will inhale all the way and exhale all the way as fast as you can. After the initial test is performed you will be given a bronchodilator medication (**bronchodilators are given by inhalation [with a puffer] to open or relax the breathing tubes or airways**) to be sure that your airways are fully open and the breathing test will be repeated. The bronchodilator we will be giving you is called Ventolin, and you will take 2 puffs of it (200mcg). In the unlikely event of an emergency, a physician nearby in the hospital will be contacted immediately.

Time commitment: 45 minutes

Location: Kelowna General Hospital

Why is this important? The breathing test (spirometry) will be done to measure your lung function (how strong the lungs are).

(2) Incremental Exercise Test

What is this test? This test is an exercise test that starts easy and slowly gets harder until you feel like you cannot keep exercising. This test will be done on a stationary bicycle and you will breathe through a mouthpiece while wearing a nose clip to collect your expired air. A physician will supervise this test, and the physician will screen you for cardiovascular disease. Small stickers (electrodes) will also be stuck to your chest so that we can monitor your heart during the test. Furthermore, your blood pressure will be monitored every two minutes.

Time commitment: 45 minutes (only exercising for 10-12 minutes)

Location: Kelowna General Hospital

3) Constant Load Exercise Test

What is this test? This test is an exercise test that remains at a constant workload until you get too tired or too short of breath to keep exercising. This test will be done on a stationary bicycle and you will breathe through a mouthpiece while wearing a nose clip to collect your expired air. When using the machine that reduces the effort needed to breathe, you will not be wearing a noseclip. Either air, oxygen gas, helium-oxygen gas, or a machine to help you breathe in air will be delivered to you during this test.

Time commitment: 45 minutes (only exercising for 5-15 minutes) for each test. You will be performing two of these tests per visit, with an hour of rest in between. Therefore you will be in the laboratory for 2-2.5 hours total on each visit.

Location: Kelowna General Hospital

MEASUREMENTS TO BE MADE DURING THE CONSTANT-LOAD TESTS

(1) Multidimensional Dyspnea Profile (Shortness of breath questionnaire)
What is this? This is a questionnaire that will ask you to describe and rate the intensity of your shortness of breath by pointing to a list of descriptors and a scale that rates the intensity of the sensation from 1-10. You do not have to answer any questions that you are uncomfortable with.
Time commitment: These tests will be done before, during, and after your exercise sessions, and will only take a couple of minutes to administer.

WHAT ARE THE RISKS?

The exercise that you will be performing is regarded as safe. All testing will be performed under appropriate supervision and appropriate resuscitation equipment will be available. Stress test data from other investigations, suggest that the likelihood of dying from sudden cardiac death is 5 per 100,000 tests. This usually only occurs in people who already have some form of heart disease. Following all of the exercise sessions you may experience muscle soreness, which will disappear within a few days. There are no known risks of breathing helium-oxygen or oxygen gas mixtures or using a machine to help inspire air (BiPAP). Our group has used oxygen and helium-oxygen gas on many occasions with healthy individuals and patients with your condition. BiPAP machines are used as a routine therapy for many sleep-related disorders. Should it be determined during testing that you require emergency medical care, you will be taken to the Emergency Department at the Kelowna General Hospital where you may be admitted.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

If you agree to participate in this study there may not be a direct medical benefit to you. However, you will get an up to date pulmonary function assessment, your current fitness level will be evaluated, and you will be told how your lungs are functioning at rest and during exercise. We will explain in detail any of your test results, if you wish. The information we get from this study may help us to provide better treatments in the future for patients with COPD as it will allow us to better understand the mechanisms of shortness of breath and how they influence exercise tolerance.

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

Participation in this study is entirely voluntary. You may refuse to participate or you may withdraw from the study at any time without prejudice and without providing any reasons. If you decide to withdraw from the study, there will be no penalty or loss of benefits to which you are otherwise entitled, and your future medical care will not be affected. You do not waive any of your rights by signing this consent form. **If you**

withdraw from the study, we will not use any of your data or information for the study without your consent.

The study investigators/doctor may decide to discontinue the study at any time, or withdraw you from the study at any time, if they feel that it is in your best interests.

WHAT WILL THE STUDY COST ME?
You will be reimbursed for any parking expenses that you incur while participating in the study. You should keep your parking receipts.

COMPENSATION AND INJURY:

In the event that you suffer injury as a result of participating in this research, the University of British Columbia, or the researchers will not voluntarily provide compensation to you. You still have all your legal rights. Nothing said in this consent form alters your right to seek damages against the sponsor, investigators, or anyone else.

CONFIDENTIALITY:
Your confidentiality will be respected. No information that discloses your identity will be released or published without your specific consent to the disclosure. However, research records and medical records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of Health Canada, the UBC Research Ethics Board, or the Interior Health Ethics Board for the purpose of monitoring the research. However, no records which identify you by name or initials will be allowed to leave the Investigators' offices.

All information collected during the study will be kept confidential. Individual data will be assigned a code designation so that personal identification is not possible. The data will be stored in a secure location accessible only to the researchers. If you withdraw from the investigation, your information will be removed from the study on request. Any report published as a result of the study will not identify you by name or initials since all findings will be reported as group averages. Nothing will be published without your consent.

WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY DURING MY PARTICIPATION?

A researcher will be available on every occasion to explain the procedure and answer any questions. If you have any other questions or desire further information about this study before or during participation, you can contact Ms. Sarah Perry at (250) 807 9122.

WHO DO I CONTACT IF I HAVE ANY QUESTIONS OR CONCERNS ABOUT MY RIGHTS AS A SUBJECT DURING THE STUDY?

Please note that you may ask questions at any time. We will be glad to discuss your results with you when they have become available and we welcome your comments and suggestions. If you have any concerns about your rights as a research subject and/or your experiences while participating in this study, contact the Research Subject Information Line in the University of British Columbia Office of Research Services' at 604-822-8598 or by email at RSIL@ors.ubc.ca or you may contact the Chair of the Interior Health Research Ethics Board through the Research Office at 250 870-4649.

SUBJECT CONSENT TO PARTICIPATE

In signing this form you are consenting to participate in this research project. Furthermore, signing this consent form in no way limits your legal rights against the sponsor, investigators, or anyone else.

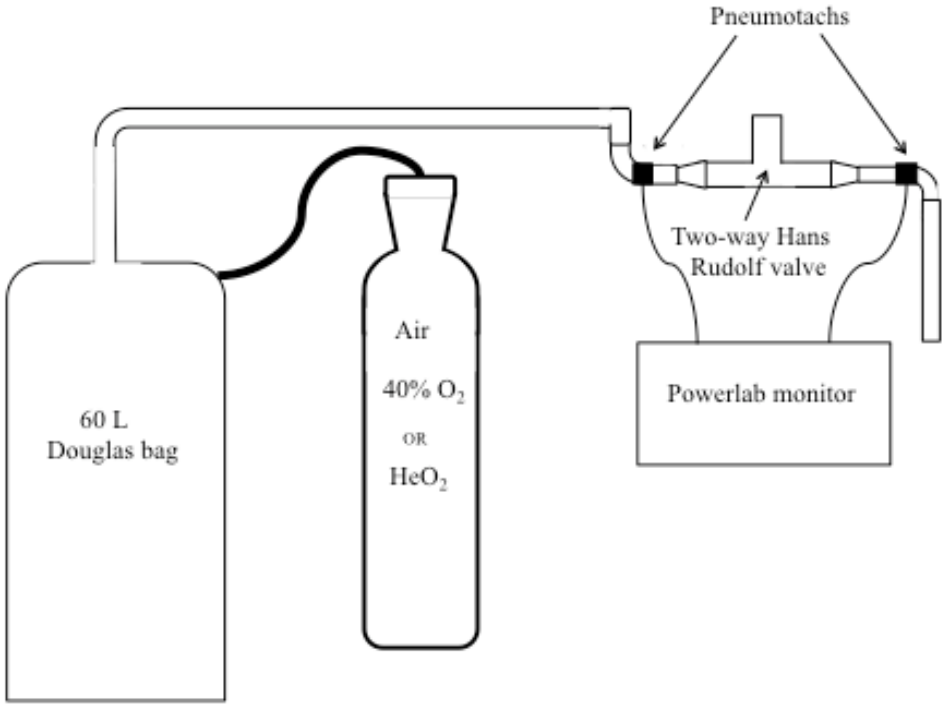
- *I have read and understood the subject information and consent form.*
- *I have had sufficient time to consider the information provided and to ask for advice if necessary.*
- *I have had the opportunity to ask questions and have had satisfactory responses to my questions.*
- *I understand that all of the information collected will be kept confidential and that the result 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 without changing in any way the quality of care that I receive.*
- *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 have read this form and I freely consent to participate in this study.*
- *I have been told that I will receive a dated and signed copy of this form.*

SIGNATURES

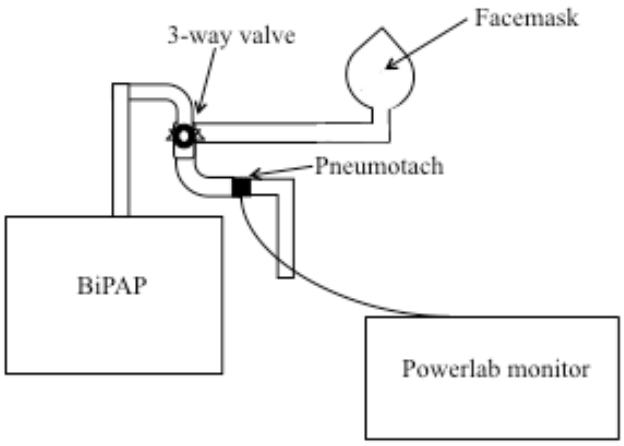
Printed name of subject	Signature	Date
Printed name of principal investigator/ designated representative	Signature	Date

Appendix C: Experimental Setup

C.1 Experimental setup during the air, hyperoxia, and heliox trials



C.2 Experimental setup during the BiPAP trial



Appendix D: Individual Responses

D.1 Individual Responses to Exercise

Table D.1: Individual S_I and A_1 Dyspnea Responses at Isotime

	Air	Hyperoxia	Heliox	BiPAP
Borg Dyspnea (S_I)				
Participant 1	7.0	3.0	0.0	1.5
Participant 2	3.0	2.0	2.0	4.0
Participant 3	3.5	1.0	2.0	2.5
Participant 4	7.0	6.0	8.0	7.0
Participant 5	3.0	3.0	4.0	4.0
Participant 6	6.0	3.5	3.0	5.0
Participant 7	5.0	2.0	3.0	3.0
Participant 8	4.0	4.0	1.0	3.0
Participant 9	4.0	2.0	2.0	4.0
Participant 10	3.0	3.0	2.0	3.0
Unpleasantness (A_1)				
Participant 1	4.0	2.0	0.0	1.5
Participant 2	3.0	2.0	2.0	4.0
Participant 3	3.0	0.0	2.0	2.5
Participant 4	6.0	6.0	8.0	7.0
Participant 5	3.0	2.0	4.0	4.0
Participant 6	7.5	4.0	3.0	5.0
Participant 7	3.0	2.0	3.0	3.0
Participant 8	4.0	4.0	1.0	3.0
Participant 9	5.0	2.0	2.0	4.0
Participant 10	2.0	2.0	2.0	3.0

Table D.2: Individual Qualities of Dyspnea at Isotime

	Air	Hyperoxia	Heliox	BiPAP
Muscle Work				
Participant 1	0.0	0.0	0.0	0.0
Participant 2	4.0	2.0	3.0	5.0
Participant 3	2.0	0.0	1.0	1.0
Participant 4	6.0	6.0	8.0	7.0
Participant 5	4.0	3.0	5.0	5.0
Participant 6	3.5	1.0	2.0	2.0
Participant 7	3.0	3.0	2.0	1.0
Participant 8	6.0	6.0	0.0	2.0
Participant 9	5.0	2.0	2.0	4.0
Participant 10	3.0	3.0	3.0	2.0
Air Hunger				
Participant 1	4.0	4.0	0.0	4.0
Participant 2	4.0	0.0	4.0	5.5
Participant 3	1.0	0.0	1.0	1.0
Participant 4	6.0	6.0	8.0	8.0
Participant 5	4.0	3.0	4.0	5.0
Participant 6	5.5	5.0	3.0	7.5
Participant 7	6.0	3.0	8.0	4.0
Participant 8	6.0	7.0	2.0	0.0
Participant 9	5.0	2.0	2.0	4.0
Participant 10	2.0	2.0	2.0	2.0

	Air	Hyperoxia	Heliox	BiPAP
Mental Effort				
Participant 1	3.5	0.0	0.0	0.0
Participant 2	3.0	2.0	3.0	4.5
Participant 3	1.0	0.0	1.0	1.0
Participant 4	5.0	6.0	8.0	8.0
Participant 5	4.0	3.0	5.0	5.0
Participant 6	1.0	0.0	1.0	0.0
Participant 7	6.0	3.0	7.0	5.0
Participant 8	7.0	7.0	2.0	1.0
Participant 9	5.0	2.0	1.0	3.0
Participant 10	4.0	4.0	2.0	4.0
Chest Tightness				
Participant 1	0.0	0.0	0.0	0.0
Participant 2	4.0	1.0	3.0	2.0
Participant 3	1.0	1.0	1.0	1.0
Participant 4	5.0	6.0	7.0	7.0
Participant 5	4.0	3.0	4.0	4.0
Participant 6	6.5	3.0	4.0	5.0
Participant 7	2.0	1.0	3.0	3.0
Participant 8	8.5	8.0	1.0	0.0
Participant 9	5.0	3.0	1.0	3.0
Participant 10	2.0	2.0	3.0	3.0

	Air	Hyperoxia	Heliox	BiPAP
Breathing a lot				
Participant 1	6.0	4.0	2.5	4.0
Participant 2	5.0	2.0	4.0	6.5
Participant 3	3.0	1.5	1.0	2.0
Participant 4	6.0	6.0	7.0	7.0
Participant 5	5.0	4.0	7.0	5.0
Participant 6	7.5	6.0	5.0	7.5
Participant 7	5.0	2.0	4.0	5.0
Participant 8	8.0	8.0	2.0	2.0
Participant 9	5.0	3.0	2.0	4.0
Participant 10	4.0	4.0	2.0	5.0
Leg Fatigue				
Participant 1	6.5	3.5	3.0	4.5
Participant 2	3.0	1.0	3.0	4.0
Participant 3	3.5	3.0	2.0	5.0
Participant 4	8.0	7.0	8.0	8.0
Participant 5	3.0	3.0	5.0	4.0
Participant 6	2.0	1.0	1.0	3.0
Participant 7	3.0	0.0	2.0	2.0
Participant 8	4.0	4.0	3.0	3.0
Participant 9	5.0	3.0	3.0	4.0
Participant 10	7.0	7.0	7.0	7.0

Table D.3: Individual S_I and A_1 Dyspnea Responses at End Exercise

	Air	Hyperoxia	Heliox	BiPAP
Borg Dyspnea (S_I)				
Participant 1	7.0	4.0	0.5	2.0
Participant 2	5.0	4.0	5.0	4.0
Participant 3	3.5	2.5	3.5	2.5
Participant 4	7.0	9.0	8.0	7.0
Participant 5	5.0	4.0	4.0	5.0
Participant 6	6.0	5.0	5.0	5.0
Participant 7	5.0	4.0	3.0	3.0
Participant 8	4.0	4.0	8.0	7.0
Participant 9	4.0	4.0	4.0	4.0
Participant 10	3.0	3.0	3.0	3.0
Unpleasantness (A_1)				
Participant 1	4.0	3.0	0.0	1.5
Participant 2	5.0	4.0	6.0	4.0
Participant 3	2.0	1.0	3.0	2.0
Participant 4	6.0	9.0	8.0	7.0
Participant 5	4.0	4.0	4.0	6.0
Participant 6	7.5	5.0	4.5	7.0
Participant 7	3.0	4.0	3.0	4.0
Participant 8	4.0	4.0	7.0	6.0
Participant 9	5.0	3.0	4.0	3.0
Participant 10	2.0	2.0	2.0	3.0

Table D.4: Individual Qualities of Dyspnea at End Exercise

	Air	Hyperoxia	Heliox	BiPAP
Muscle Work				
Participant 1	0.0	0.0	0.0	0.0
Participant 2	6.0	3.0	6.0	5.0
Participant 3	0.0	1.0	3.0	1.0
Participant 4	6.0	8.5	8.0	7.0
Participant 5	6.0	4.0	5.0	6.0
Participant 6	3.4	2.0	1.0	2.0
Participant 7	3.0	3.0	2.0	2.0
Participant 8	6.0	6.0	8.0	7.0
Participant 9	5.0	4.0	4.0	4.0
Participant 10	3.0	3.0	3.0	2.0
Air Hunger				
Participant 1	4.0	6.0	0.0	3.5
Participant 2	6.0	2.0	6.0	5.5
Participant 3	0.5	1.0	3.0	1.0
Participant 4	6.0	9.0	8.0	8.0
Participant 5	6.0	4.0	4.0	7.0
Participant 6	5.5	6.0	5.5	7.5
Participant 7	6.0	3.0	8.0	5.0
Participant 8	6.0	7.0	8.0	6.0
Participant 9	5.0	4.0	4.5	4.0
Participant 10	2.0	3.0	2.0	2.0

	Air	Hyperoxia	Heliox	BiPAP
Mental Effort				
Participant 1	3.5	0.0	0.0	0.0
Participant 2	6.0	2.0	5.0	4.5
Participant 3	1.5	1.0	2.5	1.0
Participant 4	5.0	9.0	8.0	8.0
Participant 5	6.0	4.0	5.0	7.0
Participant 6	1.0	1.0	1.0	0.0
Participant 7	6.0	3.0	7.0	7.5
Participant 8	7.0	7.0	7.0	7.0
Participant 9	5.0	1.0	4.0	3.0
Participant 10	4.0	4.0	2.0	4.0
Chest Tightness				
Participant 1	0.0	0.0	0.0	0.0
Participant 2	7.0	1.0	6.0	2.0
Participant 3	1.0	1.0	3.0	1.0
Participant 4	5.0	9.0	7.0	7.0
Participant 5	6.0	3.0	4.0	5.0
Participant 6	6.5	5.5	4.5	5.0
Participant 7	2.0	2.0	3.0	3.0
Participant 8	8.5	8.0	7.0	7.0
Participant 9	5.0	2.0	4.0	3.0
Participant 10	2.0	4.0	2.0	3.0

	Air	Hyperoxia	Heliox	BiPAP
Breathing a lot				
Participant 1	6.0	5.0	3.5	4.5
Participant 2	8.0	4.0	6.5	6.5
Participant 3	3.0	1.5	2.5	2.0
Participant 4	6.0	9.0	7.0	7.0
Participant 5	7.0	6.0	7.0	7.0
Participant 6	7.5	6.5	7.0	7.5
Participant 7	5.0	5.0	4.0	7.0
Participant 8	8.0	8.0	9.0	7.0
Participant 9	5.0	3.0	5.0	4.0
Participant 10	4.0	5.0	3.0	5.0
Leg Fatigue				
Participant 1	6.5	5.0	3.5	4.5
Participant 2	4.0	6.0	5.0	4.0
Participant 3	3.5	4.0	4.0	5.0
Participant 4	8.0	9.0	8.0	8.0
Participant 5	5.0	5.0	5.0	7.0
Participant 6	2.0	1.0	1.0	3.0
Participant 7	3.0	0.0	2.0	3.0
Participant 8	4.0	4.0	8.0	8.0
Participant 9	5.0	4.0	4.0	4.0
Participant 10	7.0	7.0	7.0	7.0

Table D.5: Individual Ventilatory Parameters at Isotime

	Air	Hyperoxia	Heliox	BiPAP
V_E				
Participant 1	30.73	27.16	38.48	-
Participant 2	32.52	24.95	36.27	-
Participant 3	57.37	55.49	59.53	-
Participant 4	38.53	34.21	53.02	-
Participant 5	52.64	47.20	61.24	-
Participant 6	21.48	21.50	30.22	-
Participant 7	27.38	24.76	21.89	-
Participant 8	18.55	19.64	26.18	-
Participant 9	21.31	27.47	27.21	-
Participant 10	36.48	34.50	44.00	-
V_T				
Participant 1	1.03	0.95	1.26	-
Participant 2	1.20	1.26	1.38	-
Participant 3	1.42	1.60	1.57	-
Participant 4	1.03	1.00	1.34	-
Participant 5	1.74	1.78	1.82	-
Participant 6	0.82	0.88	1.24	-
Participant 7	0.80	0.78	0.62	-
Participant 8	0.83	0.80	1.06	-
Participant 9	0.52	0.76	0.78	-
Participant 10	1.24	1.12	1.36	-

	Air	Hyperoxia	Heliox	BiPAP
RR				
Participant 1	29.88	28.59	30.54	-
Participant 2	27.10	19.80	26.28	-
Participant 3	40.40	34.68	38.00	-
Participant 4	37.29	34.21	39.57	-
Participant 5	30.25	26.47	33.71	-
Participant 6	26.19	24.57	24.37	-
Participant 7	34.23	31.74	35.31	-
Participant 8	22.39	24.55	24.70	-
Participant 9	41.25	36.15	34.89	-
Participant 10	29.42	30.80	32.35	-
T_I				
Participant 1	0.75	0.77	0.67	-
Participant 2	0.85	1.23	0.95	-
Participant 3	0.61	0.77	0.64	-
Participant 4	0.64	0.60	0.65	-
Participant 5	0.90	1.05	0.88	-
Participant 6	0.88	0.97	0.90	-
Participant 7	0.61	0.70	0.57	-
Participant 8	0.62	0.61	0.63	-
Participant 9	0.53	0.56	0.64	-
Participant 10	0.75	0.71	0.70	-

	Air	Hyperoxia	Heliox	BiPAP
T_E				
Participant 1	1.42	1.36	1.27	-
Participant 2	1.34	1.84	1.38	-
Participant 3	0.78	0.98	0.85	-
Participant 4	0.98	1.02	1.07	-
Participant 5	1.00	1.18	0.91	-
Participant 6	1.41	1.50	1.75	-
Participant 7	1.19	1.22	1.12	-
Participant 8	2.01	1.82	1.71	-
Participant 9	0.89	1.10	0.82	-
Participant 10	0.99	1.13	1.22	-
T_I / T_{TOT}				
Participant 1	0.36	0.36	0.35	-
Participant 2	0.39	0.40	0.41	-
Participant 3	0.44	0.44	0.43	-
Participant 4	0.39	0.37	0.38	-
Participant 5	0.47	0.47	0.49	-
Participant 6	0.38	0.39	0.34	-
Participant 7	0.34	0.37	0.34	-
Participant 8	0.24	0.25	0.27	-
Participant 9	0.37	0.34	0.45	-
Participant 10	0.44	0.38	0.36	-

	Air	Hyperoxia	Heliox	BiPAP
V_T/T_E				
Participant 1	0.73	0.70	1.00	-
Participant 2	0.89	0.68	1.00	-
Participant 3	1.82	1.63	1.84	-
Participant 4	1.05	0.98	1.25	-
Participant 5	1.74	1.74	2.00	-
Participant 6	0.58	0.58	0.71	-
Participant 7	0.67	0.64	0.55	-
Participant 8	0.41	0.44	0.62	-
Participant 9	0.58	0.69	0.95	-
Participant 10	1.25	0.99	1.12	-
IC				
Participant 1	1.60	1.50	2.20	1.30
Participant 2	1.30	1.70	1.70	1.20
Participant 3	2.00	2.10	2.10	1.80
Participant 4	1.50	1.50	1.70	1.20
Participant 5	2.00	2.20	2.50	1.40
Participant 6	1.00	1.30	1.40	1.80
Participant 7	1.30	1.40	1.50	1.20
Participant 8	1.10	1.00	1.40	1.20
Participant 9	1.00	1.10	1.30	1.40
Participant 10	1.50	1.40	1.80	1.00

	Air	Hyperoxia	Heliox	BiPAP
EELV				
Participant 1	8.16	8.26	7.56	8.46
Participant 2	6.03	5.63	5.63	6.13
Participant 3	3.17	3.07	3.07	3.37
Participant 4	4.99	4.99	4.79	5.29
Participant 5	4.99	4.79	4.49	5.59
Participant 6	9.03	8.73	8.63	8.23
Participant 7	2.43	2.33	2.23	2.53
Participant 8	7.47	7.57	7.17	7.37
Participant 9	6.28	6.18	6.08	5.89
Participant 10	4.18	4.28	3.88	4.68

Table D.6: Individual Ventilatory Parameters at End-Exercise

	Air	Hyperoxia	Heliox	BiPAP
V_E				
Participant 1	30.73	24.48	25.03	-
Participant 2	32.88	30.71	37.21	-
Participant 3	55.57	56.73	55.75	-
Participant 4	37.64	37.01	37.02	-
Participant 5	44.83	49.86	61.24	-
Participant 6	21.49	22.39	29.25	-
Participant 7	27.38	26.67	22.55	-
Participant 8	18.55	18.94	29.25	-
Participant 9	21.31	22.52	28.56	-
Participant 10	36.48	38.93	47.99	-
V_T				
Participant 1	1.03	0.79	1.28	-
Participant 2	1.08	1.10	1.27	-
Participant 3	1.35	1.40	1.38	-
Participant 4	1.00	1.02	0.99	-
Participant 5	1.76	1.58	1.82	-
Participant 6	0.80	0.87	1.08	-
Participant 7	0.80	0.80	0.67	-
Participant 8	0.83	0.77	1.00	-
Participant 9	0.52	0.68	0.70	-
Participant 10	1.24	1.15	1.53	-

	Air	Hyperoxia	Heliox	BiPAP
RR				
Participant 1	29.88	31.08	19.50	-
Participant 2	30.35	27.92	29.38	-
Participant 3	41.16	40.52	40.30	-
Participant 4	37.64	36.40	37.43	-
Participant 5	25.47	31.49	33.71	-
Participant 6	26.87	25.84	27.00	-
Participant 7	34.23	33.34	33.83	-
Participant 8	22.39	24.55	29.25	-
Participant 9	41.25	32.96	40.80	-
Participant 10	29.42	33.85	31.30	-
T_I				
Participant 1	0.75	0.68	0.73	-
Participant 2	0.79	0.86	0.73	-
Participant 3	0.66	0.69	0.60	-
Participant 4	0.65	0.65	0.60	-
Participant 5	0.98	0.87	0.88	-
Participant 6	0.83	0.92	0.80	-
Participant 7	0.61	0.66	0.68	-
Participant 8	0.62	0.57	0.55	-
Participant 9	0.53	0.53	0.52	-
Participant 10	0.75	0.69	0.78	-

	Air	Hyperoxia	Heliox	BiPAP
T_E				
Participant 1	1.42	1.33	1.30	-
Participant 2	1.21	1.27	1.26	-
Participant 3	0.69	0.77	0.77	-
Participant 4	0.94	1.04	0.89	-
Participant 5	1.35	1.02	0.91	-
Participant 6	1.39	1.38	1.38	-
Participant 7	1.19	1.19	1.18	-
Participant 8	2.01	1.76	1.45	-
Participant 9	0.89	0.94	0.87	-
Participant 10	0.99	1.09	1.27	-
T_I / T_{TOT}				
Participant 1	0.36	0.34	0.36	-
Participant 2	0.39	0.40	0.37	-
Participant 3	0.49	0.47	0.44	-
Participant 4	0.41	0.38	0.42	-
Participant 5	0.43	0.46	0.49	-
Participant 6	0.37	0.40	0.37	-
Participant 7	0.34	0.36	0.37	-
Participant 8	0.24	0.25	0.28	-
Participant 9	0.37	0.36	0.38	-
Participant 10	0.44	0.39	0.38	-

	Air	Hyperoxia	Heliox	BiPAP
V_T/T_E				
Participant 1	0.73	0.59	0.99	-
Participant 2	0.90	0.87	1.01	-
Participant 3	1.95	1.82	1.80	-
Participant 4	1.06	0.98	1.12	-
Participant 5	1.31	1.55	2.00	-
Participant 6	0.58	0.63	0.79	-
Participant 7	0.67	0.67	0.57	-
Participant 8	0.41	0.44	0.69	-
Participant 9	0.58	0.73	0.81	-
Participant 10	1.25	1.06	1.21	-
IC				
Participant 1	1.60	1.80	2.20	1.30
Participant 2	1.30	1.60	1.50	1.20
Participant 3	2.00	2.10	2.30	1.80
Participant 4	1.50	1.40	1.70	1.20
Participant 5	2.10	2.10	2.50	1.30
Participant 6	1.00	1.30	1.40	1.80
Participant 7	1.30	1.40	1.50	1.40
Participant 8	1.10	1.00	1.30	1.00
Participant 9	1.00	1.00	1.10	1.40
Participant 10	1.50	1.40	1.80	1.00

	Air	Hyperoxia	Heliox	BiPAP
EELV				
Participant 1	8.16	7.96	7.56	8.46
Participant 2	6.03	5.73	5.83	6.13
Participant 3	3.17	3.07	2.87	3.37
Participant 4	4.99	5.09	4.79	5.29
Participant 5	4.89	4.89	4.49	5.69
Participant 6	9.03	8.73	8.63	8.23
Participant 7	2.43	2.33	2.23	2.33
Participant 8	7.47	7.57	7.27	7.57
Participant 9	6.28	6.28	6.18	5.89
Participant 10	4.18	4.28	3.88	4.68

Appendix E: Ethics Certificates

E.1 UBC Ethics Certificate

The University of British Columbia
Office of Research Services
Clinical Research Ethics Board – Room 210, 828 West 10th Avenue, Vancouver, BC V5Z 1L8

ETHICS CERTIFICATE OF FULL BOARD APPROVAL

PRINCIPAL INVESTIGATOR:	INSTITUTION / DEPARTMENT:	UBC CREB NUMBER:
Neil Eves	UBC/UBCO Health & Social Development/UBCO Human Kinetics	H10-03100

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
UBC	Okanagan

Other locations where the research will be conducted:
Kelowna General Hospital

CO-INVESTIGATOR(S):
Jeffrey Rolf

SPONSORING AGENCIES:
- UBCO Faculty of Health and Social Development - "Eves Start Up Funds"

PROJECT TITLE:
The effect of different interventions on the sensory and affective dimensions of dyspnea in patients with COPD during exercise

THE CURRENT UBC CREB APPROVAL FOR THIS STUDY EXPIRES: January 25, 2012

The full UBC Clinical Research Ethics Board has reviewed the above described research project, including associated documentation noted below, and finds the research project acceptable on ethical grounds for research involving human subjects and hereby grants approval.

This approval applies to research ethics issues only. The approval does not obligate an institution or any of its departments to proceed with activation of the study. The Principal Investigator for the study is responsible for identifying and ensuring that resource impacts from this study on any institution are properly negotiated, and that other institutional policies are followed. The REB assumes that investigators and the coordinating office of all trials continuously review new information for findings that indicate a change should be made to the protocol, consent documents or conduct of the trial and that such changes will be brought to the attention of the REB in a timely manner.

REB FULL BOARD MEETING REVIEW DATE:
January 25, 2011

DOCUMENTS INCLUDED IN THIS APPROVAL:

Document Name	Version	Date
Protocol:		
Research Proposal	2	February 2, 2011
Consent Forms:		
Consent Form	2	February 6, 2011
Advertisements:		
Recruitment poster	1	March 1, 2011
Questionnaire, Questionnaire Cover Letter, Tests:		
MDP Questionnaire	2	November 4, 2008
Other Documents:		
Cover Letter	1	December 22, 2010

DATE DOCUMENTS APPROVED:
March 4, 2011

CERTIFICATION:
In respect of clinical trials:
1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.
2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.
3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

The documentation included for the above-named project has been reviewed by the UBC CREB, and the research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved by the UBC CREB.

Approval of the Clinical Research Ethics Board by one of:

Dr. Peter Loewen, Chair
Dr. James McCormack, Associate Chair

E.2 Interior Health Ethics Certificate

Interior Health

Research Office
Research Ethics Board
Suite 104 - 1815 Kirschner Road
Kelowna, B.C.,V1Y 4N7

Certificate of Full Research Ethics Board Approval

Principal Investigator: Dr. Neil Eves	**Institution of Primary Association** UBC Okanagan	**IH Research File Identifier** 2011-007
Research Study Title: The effect of different interventions on the sensory and affective dimensions of dyspnea in patients with COPD during exercise.		
IH Administrative Contact Nancy Serwo	**Co-Investigators** Sarah Perry Dr. Douglass Rolf	
Sponsoring/Funding Agencies UBCO Faculty of Health and Social Development – "Eves Start Up Funds"	**IH Departments Involved in Research Study** KGH Pulmonary Function Laboratory	
Documents Covered by this Approval Research Proposal dated 02 Feb 2011 Informed Consent Form v:3 dated 16 May 2011 Multidimensional Dyspnea Profile dated 08 Apr 2011 Recruitment poster (undated)	**Certificate of Approval from Primary REB** UBC Full CREB Jan 25, 2011	
Certification The above named documents have been reviewed according to Interior Health Research Ethics Board policy and the procedures were found to be acceptable on ethical grounds for research involving human subjects. This Certificate of Approval is valid for the term specified below provided there are no changes in the study procedures. *The Interior Health Research Ethics Board is in compliance with the ethical principles presented in the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*		
Conditions for Approval It is the responsibility of the principal investigator to inform the IH Research Office if there are changes to consents or other materials used with human subjects – these must be submitted to the IH Research Office for review and approval prior to implementation. It is the responsibility of the Principal Investigator to inform the IH Research Office if human subjects experience serious or unexpected events.		
Approval Date May 19, 2011	**Approval Term** 1 year	
IH Authorized Signature B. Ann Ferguson B. Ann Ferguson, Chair, Interior Health Research Ethics Board	19 May 2011 Date	