EXERCISE LIMITATION IN MILD COPD: 
THE ROLE OF RESPIRATORY MECHANICAL FACTORS

By

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ABSTRACT

The majority of patients with chronic obstructive pulmonary disease (COPD) have milder airway obstruction and are not diagnosed in a timely fashion. Nevertheless, these patients are largely under-studied; this, despite new evidence of increased morbidity and mortality in this sub-population. Recent studies have highlighted the increased ventilatory requirements and abnormalities in respiratory mechanics as important features to explain the relatively reduced exercise tolerance and greater exertional dyspnea in these patients. However, it remains uncertain whether such abnormal mechanical factors actually limit exercise capacity in mild COPD. Accordingly, the objective of this study was to determine whether ventilatory constraints represent a primary factor in exercise limitation and increased dyspnea in this patient group. To determine the role of mechanical factors in exercise limitation in mild COPD, we selectively loaded the respiratory system by adding dead space (DS) to the breathing circuit. We compared ventilation, breathing pattern, operating lung volumes, and dyspnea intensity during incremental cycle exercise in 20 patients with GOLD stage I COPD (post-bronchodilator FEV$_1$/FVC=61±5%, and FEV$_1$=95±11% predicted; mean±SD) and 20 healthy age-, sex- and BMI-matched subjects under two conditions, in randomized order: unloaded control (CTRL) or ventilatory stimulation by 600mL of an added DS. Compared to the CTRL condition, both healthy and COPD participants had small decreases in peak work rate and no significant increase in peak ventilation with the added DS. At the highest equivalent work rate of 60 watts, DS caused a smaller increase in tidal volume (V$_T$) in COPD compared with healthy subjects (+0.26±0.29 vs. +0.56±0.22 L respectively, p<0.01) with a correspondingly greater increase in dyspnea intensity (+1.8±1.8 vs. +0.2±0.6 Borg units, respectively, p<0.0001). At peak exercise, COPD patients failed to significantly increase V$_T$, reflecting the fact that end-inspiratory lung volume (EILV) could not increase with DS vs. CTRL (5.25±0.91 vs. 5.16±0.84 L, respectively, p=0.41). This contrasts the
results in health where EILV increased with DS vs. CTRL (5.40±1.01 vs. 5.13±0.90 L, respectively, p<0.05). We conclude that the lower exercise performance in mild COPD, compared with health, is explained by critical respiratory mechanical constraints which limit further increases in ventilation to support a higher metabolic load.
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LIST OF ABBREVIATIONS

AT – anaerobic threshold
BDI – baseline dyspnea index
BMI – body mass index
COPD – chronic obstructive pulmonary disease
CHAMPS – Community Healthy Activities Model Program for Seniors Questionnaire
CO₂ – carbon dioxide
CTRL – control condition
DH – dynamic hyperinflation
DLCO – diffusing capacity of the lung for carbon monoxide
DS – Dead Space
EELV – end expiratory lung volume
EFL – expiratory flow limitation
EILV – end inspiratory lung volume
ERV – expiratory reserve volume
Fb – breathing frequency
FEF25–75% – forced expiratory flow between 25% and 75% of the FVC
FEF50% – forced expiratory flow after 50% of the FVC has been exhaled
FEV₁ – forced expiratory volume in 1 second
FRC – functional residual capacity
FVC – forced vital capacity
GOLD – Global Initiative for Chronic Obstructive Lung Disease
HEWR – highest equivalent work rate
HR – heart rate
IC – inspiratory capacity
IRV – inspiratory reserve volume
LLN – predicted lower limit of normal for the FEV₁/FVC ratio based on sex and age
MEP – maximal expiratory pressure
MFVL – maximal flow volume loop
MIP – maximal inspiratory pressure
MRC – modified medical research council dyspnea scale
MVC – maximal ventilatory capacity
MVV – maximal voluntary ventilation
O₂ – oxygen
PaCO₂ – arterial partial pressure of carbon dioxide
PaO₂ – arterial partial pressure of oxygen
PEF – peak expiratory flow rate
PETCO₂ – partial pressure of end-tidal CO₂
R5 – resistance at 5 Hz from impulse oscillometry
R20 – resistance at 20 Hz from impulse oscillometry
RV – residual volume
Spo₂ – arterial oxygen saturation
sRAW – specific airways resistance
TLC – total lung capacity
VA – alveolar ventilation
VC – vital capacity
$\dot{V}CO_2$ – carbon dioxide output
$V_D$ – physiological dead space
$V_E$ – minute ventilation
$V_E/\dot{V}CO_2$ – ventilatory equivalent for CO$_2$
$\dot{V}O_2$ – oxygen consumption
$\dot{V}O_2/HR$ – oxygen pulse
$V_T$ – tidal volume
$X5$ – reactance at 5 Hz from impulse oscillometry
CHAPTER 1: INTRODUCTION

Section 1.1 - Chronic Obstructive Pulmonary Disease

1.1.1. – Definition and Fundamental Pathophysiology

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder that is characterized by progressive, partially reversible airway obstruction (O’Donnell et al. 2008). The pathophysiological hallmark of COPD is expiratory flow-limitation, and this is caused by the dual factors of parenchyma destruction (emphysema) and small airways disease (obstructive bronchiolitis) (Rodriguez-Roisin & Vestbo, 2011). The root cause for the development of persistent airflow limitation is thought to be an abnormally aggravated inflammatory response of the lung parenchyma and airways to a chronic exposure of noxious particles or gases (Rodriguez-Roisin & Vestbo, 2011). The pathological consequence of this inflammatory response is lung parenchymal (tissue) destruction and small airways disease. The former leads to a partial or complete loss of alveolar attachments to the small airways and also reduces the natural lung elastic recoil pressure, which serves as the driving pressure for expiratory flow (O’Donnell & Laveneziana, 2006a). Inflammation and fibrosis of the small airways effectively decreases the airway diameter and thus increases airflow resistance (O’Donnell & Laveneziana, 2006a). This combination of a reduced lung elastic recoil pressure and narrowed, poorly supported airways contributes to the expiratory flow-limitation that is the hallmark of COPD (Figure 1). Overall, COPD is considered a heterogeneous disease. Indeed, the relative contributions of parenchymal destruction and small airways disease vary between individuals (Rodriguez-Roisin & Vestbo, 2011). The natural course of disease progression is also unpredictable and can be complicated by the development of non-pulmonary, systemic consequences such as cardiovascular disease, deconditioning, and muscle wasting (Decramer et al. 2008)
FIGURE 1: Schematic drawing of alveolar units in health and COPD (top panels) and illustration of expiratory flow limitation (EFL) in COPD (bottom panels). In health (A), the lung parenchyma maintains its elastic recoil pressure, the airway diameter is preserved, and the integrity of the alveolar attachments to the small airways is retained. Consequently, EFL is avoided (C). In COPD (B), the effects of parenchymal destruction reduces the elastic recoil pressure and damages the integrity of the alveolar attachments to the small airways, rendering them more collapsible. Additionally, small airways disease reduces the airway diameter. The combined effects of a diminished lung recoil pressure with increased airway resistance leads to EFL in COPD (D), which is indicated by the intersection or overlap between the tidal expiratory flow with the maximal curve. 

1.1.2. – Prevalence and Burden

COPD is currently the fourth leading cause of death worldwide (Rabe et al. 2007) and is the only chronic disease with increasing mortality (Jemal et al. 2005). The World Health Organization estimates that 80 million people have moderate- to- severe COPD (WHO 2011); corresponding prevalence rates range from 4% to 10% of the adult population (Lange, 1992; Anto et al. 2001). Despite being largely underdiagnosed and undertreated (Rabe et al. 2007), there has been an alarming trend of rising mortality due to COPD: it was the 6th leading global cause of death in 1990, 5th in 2002 (WHO 2011), and is projected to rank 3rd in 2020 (Murray & Lopez, 1997). In the United States, COPD is the second most cited reason (next to coronary heart disease) for Social Security disability payments (Ries et al. 2007) and the total economic cost in 2010 was estimated at $49.9 billion (Qaseem et al. 2011). The prevalence of COPD is twice as high in individuals older than 65 years compared to those between 45 and 65 years (Vestbo & Lange, 2003). The single most important contributor to COPD development is cigarette smoking. Indeed, the majority of patients with COPD have a minimum of 10 pack-year smoking history and the prevalence is 3 to 4 times higher in smokers compared with non-smokers (Lange, 1992; Anto et al. 2001). The prevalence and burden of COPD will continue to rise worldwide due to the increasing prevalence of cigarette smoking, especially in third world countries. As an example, 51% of men are current smokers in China (WHO, 2011).

The majority of patients with COPD have milder (GOLD I and II; GOLD: Global Initiative for Chronic Obstructive Lung Disease) airway obstruction as revealed by a 2007 international population-based prevalence study (Buist et al. 2007). Additionally, a study conducted from our own laboratory of a random population sample (n=532) in Kingston, Ontario, Canada indicated an overall prevalence of 9.6%; the majority (92%) of these people with COPD fit the GOLD I or II criteria (Raghavan et al. 2012).
Recent studies have also revealed that patients with mild airway obstruction have increased mortality, morbidity, exertional dyspnea, exercise intolerance and activity restriction (Stavem et al. 2006; Decramer et al. 2008; Bridevaux et al. 2008; Ofir et al. 2008). In spite of this, this patient population remains relatively understudied. **Accordingly, the main focus of my thesis is to better understand the mechanisms of increased activity-related dyspnea and exercise intolerance in this population.** First, we will consider the normal ventilatory and sensory responses to the physiological stress of exercise in health. We will also review current concepts on the origins of respiratory discomfort during activity in patients with more advanced COPD so as to set the stage for our investigations of patients with mild COPD. Finally, we will review the results of a series of experiments conducted in our laboratory which provides novel information about the nature of physiological impairment in mild COPD. These experiments form the basis for my MSc thesis.

**Section 1.2 - Respiratory Responses During Exercise in Healthy Humans**

1.2.1. – *Homeostasis of Blood Gases*

The primary purpose of the lungs is to maintain an efficient level of gas exchange so that the arterial partial pressures of oxygen (O$_2$) and carbon dioxide (CO$_2$) ($P_aO_2$ and $P_aCO_2$, respectively) are preserved within the normal resting levels (Lovering et al. 2005). During exercise in humans, the increased energy requirements for ATP by the active locomotor muscles places a considerable demand on the cardiorespiratory system’s capacity to increase oxygen uptake (\(\dot{V}O_2\)) and carbon dioxide output (\(\dot{V}CO_2\)) in order to maintain near-resting values for $P_aO_2$ and $P_aCO_2$ (Rodman et al. 2002). The fact that the cardiorespiratory system is able to accomplish this during mild-to-moderate intensity exercise (< 70% \(\dot{VO}_2\)max) indicates that alveolar ventilation (\(\dot{V}_A\)) is precisely matched with CO$_2$ production, as prescribed by the alveolar
ventilation equation: \( \dot{V}_A = \frac{(863 \times \dot{V}CO_2)}{(P_{CO_2})} \). The physiological mechanisms which ensure that this increase in \( \dot{V}_A \) (i.e. the hyperpneic response) rises in proportion to \( \dot{V}CO_2 \) include the combination of feed-forward and feed-back regulation (Rodman et al. 2002). The feed-forward mechanism, also known as “central locomotor command,” is responsible for the immediate ventilatory response at the onset of exercise and also plays a central role during exercise. This feed-forward response originates from higher cortical centers of the central nervous system and provides the necessary stimulus for locomotor muscle activity. This, in turn, provides a parallel stimulus to the medullary respiratory control center of the brainstem which drives the respiratory pattern generator and ultimately causes phrenic, intercostal, and lumbar neuronal activity for the necessary ventilatory output (Eldridge, 1994; Kaufman & Forster, 1996). The feed-back mechanism that drives ventilation of increasing exercise intensity has two components. The first component consists of the type III mechanoreceptors and the type IV metaboreceptors. These reside within the locomotor muscles and send afferent feed-back signals to the respiratory control center in the medulla (Rodman et al. 2002; Kaufman & Forster, 1996). The second component consists of the peripheral and central chemoreceptors (Rodman et al. 2002). The former reside within the aortic arch and the carotid bodies, while the latter is located in the brainstem. These send additional afferent feed-back signals to the respiratory control center on arterial levels of \( O_2 \), \( CO_2 \), and pH during heavier levels of exercise intensity (> 70% \( VO_2max \)).

1.2.2. – Minimizing the Elastic and Resistive Work of Breathing

The maintenance of \( P_{O_2} \) and \( P_{CO_2} \) at near resting values during the increased metabolic demands of exercise can cause the healthy respiratory system to increase ventilation by as much as 20-fold (Lovering et al. 2005). Given this increased ventilatory demand, several important adaptations occur that minimize the metabolic cost of breathing. This is accomplished by reducing both the elastic and the resistive work of breathing. Minimizing the elastic work of
breathing during exercise (due to a progressively increased tidal volume ($V_T$) expansion), occurs especially during light to moderate intensities (Henke et al. 1988). Normally, this increase in $V_T$ occurs by eroding both the inspiratory reserve volume (IRV) and the expiratory reserve volume (ERV) (Henke et al. 1988). Expansion of $V_T$ into the ERV (reducing the end-expiratory lung volume; EELV) is due to the recruitment of the expiratory muscles (Henke et al. 1988). This decrease in EELV effectively allows the $V_T$ to remain on the linear, most compliant portion of the respiratory system’s pressure-volume relationship, thus minimizing the elastic work of breathing (Hey et al, 1966). Expiratory muscle recruitment also has two other advantageous effects that contribute to reducing the work of breathing. First, it lengthens the inspiratory muscles to a position that allows greater force generation during the subsequent inspiration (Lovering et al. 2005). Second, a sufficiently large expiration results in the storage of energy in the chest wall; this energy is released during the subsequent inspiration as the chest wall recoils outwards and thereby passively facilitates the subsequent inspiration. Expansion of $V_T$ also reduces the dead space to tidal volume ratio ($V_D/V_T$) and thus decreases the “wasted” portion of each inspiration (Rodman et al. 2002); a corollary of this is the maximization of ventilation-perfusion ($V/Q$) efficiency (O’Donnell et al. 2000).

As exercise progresses beyond moderate intensities, $V_T$ eventually reaches a plateau; this occurs when the $V_T$ is ~ 50% of the vital capacity (VC) (Hey et al. 1966; Cotes, 1970; Younes & Kivinen, 1984). Thereafter, further increases in ventilation are achieved by increases in breathing frequency ($F_b$) (Hey et al. 1966). As a result, both the inspiratory and expiratory times ($T_I$ and $T_E$) begin to shorten and large increases in air flow result. Despite this, the flow resistance is not significantly altered and therefore the resistive work of breathing remains fairly constant (Warren et al. 1984). Mechanisms for this include reducing the upper airways resistance by utilizing oro-nasal breathing instead of solely nasal breathing. Additionally, recruitment of inspiratory muscles
of the larynx (laryngeal abductors) (England & Bartlett 1982), tongue (Williams et al. 2000) and nasal passages (Williams et al. 2000) prevents negative inspiratory pressures from narrowing the airways (Rodman et al. 2002). Finally, exercise-induced reduction of parasympathetic activity decreases small airways resistance (Warren et al., 1984).

These remarkable adaptations that allow healthy humans to achieve high ventilation levels during activity and to maintain arterial blood gas homeostasis while minimizing the work of breathing (and accompanying breathing discomfort) become eroded with advancing age and to an even greater extent in smokers who have peripheral (small) airways dysfunction. In the results and discussion section, I will demonstrate how respiratory system performance is undermined in patients with mild COPD. The most clinically significant outcome of this is the distressing symptom of dyspnea.

Section 1.3 – Dyspnea

1.3.1. – General Concepts

The American Thoracic Society defines dyspnea as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. It derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioural responses (Parshall et al. 2012).” It is evident from this description that dyspnea is an inherently complex symptom. Although the precise mechanism of dyspnea perception is unclear, there are many possible sensory afferent sources that contribute to this sensation (O’Donnell & Webb, 2005). Some of these include: the peripheral and central chemoreceptors, mechanoreceptors of the lung and airways (i.e. the slowly and rapidly adapting pulmonary stretch receptors, and airway C-fibers), and mechanoreceptors of the respiratory pump muscles (i.e. muscle spindles and tendon organs) (Parshall et al. 2012). The
chemoreceptors can contribute to the genesis of dyspnea by stimulating ventilation in response to acute changes in the acid-base status. This is often the case in moderate-to-severe COPD, as many patients experience hypoxemia and an early onset of lactic acidosis during exercise (Casaburi, 2007). On the other hand, mechanoreceptors of the lung, airways, and respiratory muscle pump can contribute to the genesis of dyspnea by detecting inadequate inflation or thoracic displacement; this is often the case in COPD due to the effects of dynamic hyperinflation (more below) and the fact that the inspiratory muscles are maximally shortened and weakened at the end of exercise (O’Donnell, 2007a). Additionally, altered vagal afferent activity from diseased lungs may directly lead to unpleasant respiratory sensation but this has been difficult to quantify.

The complexity of dyspnea, which is synonymous with the terms “breathing discomfort”, “breathlessness”, or “respiratory difficulty”, also stems from the fact that it is not a simple unidimensional sensation. In fact, there are three major qualities of dyspnea that humans can distinguish: work/effort, air hunger/unsatisfied inspiration, and chest tightness (Parshall et al. 2012). The work/effort sensation of dyspnea is often described as “my breathing requires more work or effort” (Ora et al. 2010) or “my breathing takes a lot of work” (Banzett, 2007). This perception is thought to reflect the increased cortical (voluntary) descending respiratory motor output to the ventilatory muscles which simultaneously sends an ascending copy (of their descending motor command) to the somato-sensory cortex where the increased work/effort sensation can be consciously perceived (Chen et al. 1992; Gandevia, 1982). This efferent copy to the somato-sensory cortex has been termed “central corollary discharge.” Respiratory muscle afferents are probably also involved in the sensation of increased work/effort of breathing. The concept of “neuro-mechanical dissociation” (or “neuro-mechanical uncoupling”) has been hypothesized to be a fundamental source for the origin of air hunger/unsatisfied inspiration (i.e.
“I can’t get enough air in”) that is often described by COPD patients at the limits of exercise tolerance (O’Donnell et al. 2001a). This will be discussed in greater detail in Section 1.4.

Banzett (2007) has postulated that chest tightness predominantly arises in asthma and is related to the stimulation of pulmonary afferents of the airways during bronchoconstriction. However, many patients with COPD also experience chest tightness.

1.3.2. – Exertional Dyspnea in Health

The ventilatory adaptations observed in healthy individuals (Section 1.2) in response to the high metabolic demands of exercise not only minimize the work of breathing, but it also curtails significant respiratory discomfort as ventilation increases during exercise. Indeed, compared to patients with COPD, healthy individuals experience significantly less dyspnea (Borg Scale) at any given work rate, ventilation, or time (O’Donnell & Webb, 1993; O’Donnell et al. 1997, 1998). Additionally, exercise studies indicate that leg discomfort (and not intolerable dyspnea) is the primary exercise-limiting symptom at the peak of exhaustive exercise, especially in younger (< 30 years) healthy individuals (Killian et al. 1992; O’Donnell et al. 2000). Qualitatively, healthy individuals commonly describe their dyspnea at the symptom-limited peak of exercise only as sensations of increased work or effort (Simon et al. 1989; O’Donnell et al. 2000). Although the ventilatory demand approaches maximal near the peak of exercise, the healthy respiratory system has the capacity to satisfy this demand. Thus, even as the central neural respiratory drive is approaching maximal levels (as sensed via corollary discharge), afferent feedback indicates that the mechanical/muscular response of the respiratory system is proportionally increased and, therefore, appropriate. A state of balance exists between the increased drive to breathe and the capacity of the respiratory system to respond, and “neuro-mechanical coupling” is said to occur. The increased sense of work or effort in breathing may therefore not be perceived as unpleasant
(Jensen et al. 2009; Scano et al. 2010) and thus dyspnea is not reported as the predominant exercise-limiting symptom in healthy individuals.

1.3.3. – Exertional Dyspnea in COPD

Patients with COPD demonstrate the following symptoms: chronic cough, sputum production, and/or dyspnea that is progressive, persistent, and worse with physical exertion (Rabe et al. 2007). Among these, dyspnea remains the most distressing and represents the primary symptom that limits exercise in the majority of COPD patients (O’Donnell, 1997). Persistent activity-related dyspnea often deters patients from participating in physical activity and a reduced exercise tolerance and deconditioning often results (Marciniuk et al. 2010). Patients subsequently experience greater levels of dyspnea even during tasks of daily living. This downward spiral of activity limitation and breathlessness ultimately leads to a poor health-related quality of life and premature death. In fact, activity-related dyspnea contributes importantly to morbidity in COPD and is also an independent marker for premature death (Rabe et al. 2007; Nishimura et al. 2002). Given this disabling symptom, effective management of dyspnea remains the primary objective when treating patients with COPD. In the last two decades, there have been significant advances in our knowledge of the pathophysiological mechanisms of dyspnea during exercise, almost exclusively in moderate-to-severe COPD. Current knowledge of exertional dyspnea emphasizes the roles of increased ventilatory demand and contractile respiratory muscle effort along with abnormal dynamic ventilatory mechanics (O’Donnell et al. 1997, 1998, 2001b, 2006b). The phenomenon of dynamic hyperinflation (DH) is fundamental in relating the physiological and clinical consequences of COPD: expiratory flow limitation, dyspnea, and a diminished exercise tolerance.
Section 1.4 – Abnormal Dynamic Respiratory Mechanics and Current Concepts of Dyspnea in Advanced Disease

1.4.1. – Abnormal Dynamic Respiratory Mechanics

The equilibrium relaxation volume (also referred to as “functional residual capacity”; FRC) of the respiratory system is set by the natural inward and outward recoil pressures of the lung and chest wall, respectively, (Pride & Macklem, 1986). Given this, any changes in these two components would reset this equilibrium volume. In COPD, the increased compliance of the lungs with the reduced expiratory recoil pressure (due to the effects of parenchymal destruction) leads to an upward shift in the equilibrium lung volume; the volume the lungs return to after a tidal expiration (called the end-expiratory lung volume; EELV) is increased above the predicted normal, age-matched value (O’Donnell, 2009a). This phenomenon has been termed static lung hyperinflation (O’Donnell & Laveneziana, 2006a). On the other hand, dynamic hyperinflation (DH) is defined as “a temporary and variable increase in EELV above its baseline value” (O’Donnell & Laveneziana, 2006a). In flow-limited COPD patients, both airway resistance and lung compliance are increased and thus the overall mechanical time-constant for lung emptying (product of resistance and compliance) is increased (i.e. delayed) (O’Donnell, 2007a). With the presence of expiratory flow-limitation (EFL), the increase in ventilatory demand and respiratory frequency ($F_b$) during exercise means insufficient time is available for EELV to decline to its equilibrium value. Inspiration is initiated before expiration is complete and progressive air trapping – dynamic hyperinflation – becomes inevitable (Figure 2) (O’Donnell, 2009a). Several studies have documented the presence of DH in the majority of COPD patients (O’Donnell et al. 2001b; Maltais et al. 2005; O’Donnell et al. 2004a, b) and the adverse physiological consequences have been well characterized (Figure 3).
Given that the dynamic IC determines the operating limits for \( V_T \) expansion during exercise (Laveneziana et al. 2007), as DH worsens in flow-limited patients, there reaches a point when further \( V_T \) expansion becomes impossible. This mechanical boundary has been termed the critical “minimal” inspiratory reserve volume (IRV; Figure 2) (O’Donnell et al. 2001b); this volume occurs at an IRV of 0.5 ± 0.1 L (O’Donnell et al. 2006b) or 0.42 ± 0.33 L below TLC (O’Donnell et al. 2001b). In healthy age-matched individuals at a \( \dot{V}_E \) similar to that at peak exercise in COPD, the IRV is considerably greater at 1.75 ± 1.16 L. Thus, in healthy subjects there is less constraint on \( V_T \) expansion. In COPD, the mechanical constraint on \( V_T \) expansion (secondary to DH) necessitates that further increases in ventilation are achieved by tachypnea (O’Donnell et al. 2007b). This characteristic response of COPD, however, is associated with reduced dynamic lung compliance and increased velocity of shortening of the respiratory muscles (O’Donnell et al. 2009b).
FIGURE 2: Changes in operational lung volumes with exercise in a healthy subject (left panel) and an individual with COPD (right panel). As DH worsens in COPD – shown as progressive increases in EELV (arrow) or progressive decreases in IC – there reaches a point when $V_T$ expansion becomes impossible. This mechanical boundary is called the “minimal” inspiratory reserve volume (IRV). Comparing both panels, it is obvious that the $V_T$ approaches the minimal IRV much earlier during exercise in the COPD patient. Abbreviations: EELV = end-expiratory lung volume; EILV = end-inspiratory lung volume; IC = inspiratory capacity; IRV = inspiratory reserve volume; $V_T$ = tidal volume. Modified from O’Donnell et al. 2001b.
FIGURE 3: The respiratory system’s pressure-volume (PV) relationship for a healthy subject (left panel) and an individual with COPD (right panel). In health, during rest and exercise at the end-expiratory lung volume (EELV), the chest wall recoils outwards and the lung inwards. In contrast, in COPD during rest and exercise at the EELV, both the chest wall and the lungs recoil inwards. As a result of static and dynamic hyperinflation in COPD (characterized by the further increased EELV), the $V_T$ shifts to the non-compliant, upper portion of the PV relation. This results in elastic loading on the inspiratory muscles as there is relatively less volume response for any given pressure generation. In addition, there is also an abnormally high inspiratory threshold load (ITL) on the inspiratory muscles; since the recoil directions for both the chest wall and the lungs are inwardly directed (i.e. to expiration) at end-expiration in hyperinflated COPD individuals, they must generate greater inspiratory pressures at end-expiration just to initiate the next inspiration (Laveneziana et al. 2007; O’Donnell, 2007a). Abbreviations: $P =$ pressure; $RV =$ residual volume; $TLC =$ total lung capacity; $V =$ volume. Modified from O’Donnell & Laveneziana (2006c).
1.4.2. – Dyspnea and Increased Effort

As alluded to in section 1.2., the ventilatory adjustments during exercise in healthy individuals optimize pulmonary gas exchange efficiency and dynamic ventilatory mechanics. At high levels of ventilation during exercise, the increased sensation of inspiratory effort reflects the increased cortical (voluntary) motor output to the ventilatory muscles thought to be perceived by increased central corollary discharge to the sensory cortex (Gandevia 1988; O’Donnell et al. 2007a). The sensation of inspiratory effort occurs in both health and COPD; however, it is present with greater magnitude and becomes noticeable at lower levels of exercise in COPD (O’Donnell & Webb, 1993). In health, the ventilatory mechanical adaptations during exercise allow a concomitant increase in their mechanical output. Thus, although the sensation of inspiratory effort becomes “severe” at the peak of exercise (Simon et al., 1989; O’Donnell et al., 2000; Ofir et al., 2007), it may not be perceived as unpleasant. Consequently, dyspnea is often not the primary exercise-limiting symptom in healthy subjects (Killian et al., 1992; Jones & Killian, 2000; O’Donnell et al., 2000)

1.4.3. – Dyspnea and Neuromechanical Dissociation

The underlying abnormal respiratory mechanics that lead to DH clearly prevents COPD patients from mounting the appropriate ventilatory adaptations as those observed in healthy subjects. Furthermore, in contrast to healthy subjects, COPD patients have an increased ventilatory demand (i.e. greater breathing) during exercise due to several factors. The primary stimulus for the increased ventilation in COPD is a high physiological dead space; unlike in healthy subjects, worsening ventilation-perfusion (VA/Q) abnormalities prevent the physiological dead space to tidal volume ratio (VD/VT) from declining by approximately 30% from the resting value during exercise (Barbera et al. 1991; Dankzker & D’Alonzo, 1986; O’Donnell et al. 2001b). Secondary factors include an early metabolic (lactate) acidosis in deconditioned COPD
patients (Sinderby et al. 2001) and critical hypoxemia (Laveneziana et al. 2007). All of these variables in combination causes the increased submaximal ventilation seen in COPD patients (i.e. they have a higher $\dot{V}_E$ than healthy individuals at the same work rate) (Lewis et al. 1994; Nery et al. 1982). Concomitant to this increased ventilatory requirement, the abnormal respiratory mechanics (and subsequent constraint of the $V_T$ response) in COPD patients reduces their ventilatory capacity. Thus, as the neural drive to breathe reaches maximum at end exercise, the respiratory system is unable to mount an appropriate mechanical/muscular response due to the effects of both resting and dynamic lung hyperinflation. This mismatch between the respiratory drive to breathe and the mechanical ventilatory response has been termed “neuromechanical dissociation” and is hypothesized to be fundamental for the origin of dyspnea in COPD (O’Donnell 2007a; O’Donnell et al. 2000). Qualitatively, and like healthy subjects, COPD patients also describe their dyspnea as “increased work or effort” at the end of exercise. However, only COPD patients consistently select dyspnea descriptors alluding to “unsatisfied inspiration” (O’Donnell 2007a). These qualitative descriptors that are unique to COPD and which are inherently distressing, are thought to arise when the neural respiratory drive from the brainstem (which is communicated to the somato-sensory cortex as corollary discharge), is not matched by an appropriate ventilatory response (Banzett et al. 1989; Chen et al. 1992). The unpleasant qualitative aspect of dyspnea is important because, unlike in healthy subjects, patients with moderate-to-severe COPD have consistently chosen breathing discomfort as the primary exercise-limiting symptom (O’Donnell et al. 2001b O’Donnell et al. 2004a; Maltais et al. 2005; Puente-Maestu et al. 2005).

Several studies by O’Donnell et al. (1997, 2000, 2006b) have quantitatively measured neuro-mechanical dissociation (albeit crudely) by the measurement of contractile respiratory muscle effort [expressed as tidal esophageal pressure (Pes) relative to maximum inspiratory
pressure (PImax)] and volume displacement [expressed as the tidal volume (V_T) as a percentage of predicted vital capacity (VC)]. Therefore, neuro-mechanical dissociation is crudely reflected as the ratio of contractile respiratory muscle effort to volume displacement (Pes/PImax : V_T expressed as % predicted VC). In healthy subjects, this effort-displacement ratio remains relatively constant, which indicates that V_T expansion occurs within the compliant, linear portion of the respiratory system’s PV relation (O’Donnell et al. 2006 a, b); harmonious neuromechanical coupling is said to occur. In COPD, a diminished resting IC and IRV along with DH during exercise causes V_T expansion to reach the minimal critical IRV (~ 0.3-0.5 L below TLC) at a lower V_E than in healthy subjects. There is an increase in the effort-displacement ratio as exercise continues beyond this minimal IRV, and this indicates that V_T expansion is positioned within the non-compliant, upper portion of the PV relation. Neuromechanical uncoupling (or dissociation) occurs when a disparity arises between the contractile respiratory muscle effort (index of central respiratory neural drive) and the mechanical/volume displacement response [i.e. the effort-displacement ratio (Pes/PImax:V_T/VC) is augmented] (O’Donnell et al. 2006 a, b; 2007a). The relevance of these mechanical factors to the origins of dyspnea in mild COPD is unclear and represents the focus of the current project.

Section 1.5 – Mild COPD

1.5.1. – Epidemiology, Controversy, and Consequences

According to the GOLD criteria, the presence of airway obstruction is defined as a FEV_1/FVC ratio < 0.7 (FEV_1: forced expiratory volume in 1 second; FVC: forced expiratory vital capacity). Further classification of disease severity is based on the % predicted FEV_1 (based on age, height, and gender). Those with a post-bronchodilator (BD) FEV_1 ≥ 80% predicted have “mild airflow limitation” and are categorized as having “Stage 1 Mild COPD” (Rabe et al. 2007).
The prevalence of early COPD among all patients with COPD is high. The 2007 Burden of Obstructive Lung Disease (BOLD) Initiative estimated an 8.5% global average prevalence rate for GOLD stage I, with significant variation between countries: 1% in Manila, Philippines to 11% in Vancouver, Canada, to 16% in Salzburg, Austria (Buist et al. 2007). Other national studies estimate that among confirmed cases of COPD, 57% have mild disease in Greece (Tzanakis et al. 2004), 42% in England (Shahab et al. 2006), 56% in Spain (Miravitllles et al. 2009), 25% in Norway (Hvidsten et al. 2010), and 56% in Japan (Fukuchi et al. 2004). Studies such as these confirm that early stages of COPD are largely underdiagnosed.

There is controversy among the respiratory community concerning the diagnosis and therefore the existence of Stage 1 mild COPD. The debate derives from a lack of consensus regarding the GOLD criteria for airway obstruction (Raghavan et al. 2010). Many interpret a low FEV₁/FVC ratio with a FEV₁ ≥ 80% predicted not as mild obstruction but simply a “normal physiological variant” (Enright, 2006). It is argued that defining irreversible airflow obstruction as a post BD FEV₁/FVC ratio < 0.7 leads to: 1) underdiagnosis in younger adults and overdiagnosis in the elderly (Enright 2006, 2009; Pellegrino et al. 2005) and 2) potential negative psychological effects as a result of labelling someone with a ‘chronic disease’ (Miller 2007; Petsonk et al. 2007). The FEV₁/FVC ratio does decline with age (Mannino & Buist, 2007) and the possibility for misclassifying the elderly with COPD exists. However, the predominant issue has always been the under-diagnosis of COPD (Rabe et al. 2007); thus this should be the central focus. An associated concern with overdiagnosis is the subsequent use of inhaled bronchodilators and corticosteroids. This is legitimate, as there is insufficient evidence on the long-term safety and efficacy of these treatments in patients with milder airway obstruction (Ofir et al. 2008). The psychological effects of a COPD diagnosis need not be harmful. On the contrary, diagnosis seems to motivate people to quit smoking: smokers who were diagnosed with mild COPD were
more likely to quit than those with normal spirometry (Bednarek et al. 2006). Those diagnosed with moderate or severe COPD had even higher cessation rates. Despite the association between mild COPD and increased morbidity and mortality, there continues to be a persistent concern for overdiagnosis and misclassification of mild airway obstruction. In light of this, the supplemental use of the lower limit of normal (LLN) values for the FEV$_1$/FVC ratio derived from predictive equations has been suggested (Miller et al. 2005). The LLN is based on the normal distribution of the healthy population and classifies the bottom 5% as abnormal. It is hoped that this will provide a more accurate method for the diagnosis of airway obstruction and minimize potential misclassifications.

Patients with mild COPD have near normal spirometry (i.e. a relatively preserved FEV$_1$) that may obscure inflammatory injury to the peripheral airways, lung parenchyma, and pulmonary vasculature. Indeed, Hogg et al. (2004) and Barbera et al. (1990, 1994) have demonstrated active small-airway inflammation and significant V$_A$/Q abnormalities, respectively, in patients with GOLD stage I COPD. Recently, MacDonough et al. (2011) confirmed that patients with mild COPD have a significant loss of small conducting airways relative to healthy controls, a loss that likely contributes to the increased peripheral resistance.

The negative outcomes associated with these pathological abnormalities have been established. First, it is associated with increased mortality: men aged 40-59 with GOLD 1 (and 2) COPD have greater risks of earlier death compared to the normal healthy population (Stavem et al. 2006). Second, it is associated with functional decline: compared to healthy subjects, patients with GOLD 1 (and 2) have reduced walking times and increased inactivity times (Decramer et al. 2008); this becomes more pronounced as the disease progresses from GOLD 1 to 4. Although it is not known to what extent selected respiratory symptoms contribute to functional decline, the presence of the symptoms themselves is of paramount importance with respect to progression and
outcomes in mild COPD. Indeed, GOLD 1 symptomatic patients (chronic cough, phlegm, or dyspnea on exertion) have a greater rate of decline in FEV₁ and increased healthcare utilization compared to the reference population (Bridevaux et al. 2008). In contrast, asymptomatic GOLD 1 patients maintained the same rate of decline as the reference population (Bridevaux et al. 2008). These poor outcomes of the symptomatic patients are further reflected in lower quality of life scores compared with asymptomatic patients and healthy controls (Bridevaux et al. 2008). Both quality of life scores and levels of physical activity are important predictors of survival in COPD (Domingo-Salvany et al. 2002; Garcia-Aymerich et al. 2006). The results from these population studies cannot be clearer: there is an association between GOLD 1 COPD and increased morbidity and mortality.

1.5.2. – *Mechanisms of Dyspnea in Mild COPD*

Given the evidence of pathological impairment and the presence of dyspnea, activity limitation, and poor health status in mild COPD, it is crucial to focus on this group if the ultimate goal is to develop effective interventional strategies at the early stages of this disease. However, studies have been scarce. Ofir et al. (2008) were the first to study the mechanisms of dyspnea and activity limitation during cycle exercise in symptomatic patients with GOLD I COPD; it is one of only three published studies of its kind. Compared with healthy aged-matched controls, symptomatic mild GOLD I COPD had significantly reduced exercise capacity and greater dyspnea intensity. The former was indicated by a lower peak work rate (116 vs. 144 watts) and lower peak \( \dot{V}O_2 \) (reduced by 22% of the predicted normal value). The latter was indicated as a greater dyspnea intensity for any given work rate and ventilation. Ofir et al. (2008) proposed that the combination of increased ventilatory demand and abnormal dynamic respiratory mechanics were important contributors to the exercise intolerance and greater dyspnea intensity levels in mild COPD. Given that the ventilatory equivalents for CO₂ (\( \dot{V}E/\dot{V}CO_2 \)) and O₂ (\( \dot{V}E/\dot{V}O_2 \)) were
elevated during exercise in mild COPD, they postulated that the increased ventilatory demand reflects greater \( \dot{V}/Q \) abnormalities and a higher than normal \( V_D \) (Ofir et al. 2008). The higher ventilatory demand ultimately reflects an increased central drive to breathe and increased respiratory muscle effort (Ofir et al. 2008). Abnormal dynamic ventilatory mechanics was demonstrated as an average increase in the EELV by 0.54 L from rest to peak exercise (DH occurred); in health it increased by an average of 0.06 L. Mechanical abnormalities meant that further increases in \( \dot{V}_E \) beyond the \( V_T \) inflection point was achieved mainly by increasing \( F_b \); in healthy subjects there was still a small increase in \( V_T \) expansion beyond the inflection point compared to that in patients with mild COPD, who had little or no expansion after the inflection point. Finally, in individuals with mild COPD, as dyspnea intensity increased, dynamic IRV decreased (\( r = -0.51, P < 0.05 \)), which reinforces the notion that lung hyperinflation contributed to exertional dyspnea (Ofir et al. 2008).

Following the above study, O’Donnell et al. (2009c) tested the impact of bronchodilator (BD) therapy and thus the hypothesis that DH contributes to dyspnea in GOLD I symptomatic patients. Administration of a short-acting anticholinergic BD (ipratropium bromide) and a constant work-rate cycle exercise test were conducted. The BD was associated with improvements in DH, as both the dynamic IC and \( V_T \) increased significantly (\( P < 0.05 \)) during exercise. This was associated with improved (lowered) dyspnea intensity, but only at high levels of \( \dot{V}_E \); the lower dyspnea intensity correlated with reductions in the dynamic EELV. Modest improvements in EFL, pulmonary resistance, and work of breathing also occurred after BD. However, the cycle exercise endurance time did not increase significantly after administration of the BD compared to placebo. This study therefore demonstrated that abnormal mechanical factors contribute to exertional dyspnea, but not necessarily to exercise limitation, in selected patients with symptomatic milder COPD.
Section 1.6 – Study Rationale

1.6.1. – Research Question

The current knowledge from the few exercise studies on symptomatic patients with mild COPD have established that, compared with healthy age-matched subjects, these patients have a reduced exercise tolerance and peak ventilation, and experience greater exertional dyspnea at any given sub-maximal work rate. Ofir et al. (2008) proposed that the increased ventilatory demand (for a given metabolic load) and the increased dynamic air-trapping were contributory factors for these observed results. However, uncertainty remains: do such abnormal mechanical factors actually limit exercise capacity in mild COPD? It is possible that these abnormal ventilatory mechanical factors may have no physiological significance, as most of these patients appear to have adequate ventilatory reserve, as estimated by the maximal ventilatory capacity (MVC) minus the peak ventilation at the limits of exercise tolerance. Additionally, although administration of an anti-muscarinic bronchodilator (ipratropium bromide) favourably altered these mechanical abnormalities during rest and exercise (i.e. reduced hyperinflation), this was not associated with improved exercise endurance or reduced exertional dyspnea throughout exercise (O’Donnell et al. (2009c).

Based on these results, we felt it was important to build on these studies by examining in greater detail the role and importance of impaired ventilatory function in limiting exercise performance in patients with mild COPD. To accomplish this, it was necessary to selectively manipulate the function of the respiratory system. The most stringent method of evaluating whether mechanical factors limit exercise is to selectively stress the respiratory system to determine its true reserve (Brown et al. 1984; McParland et al. 1991; Syabbalo et al. 1993; Marciniuk et al. 1994; O’Donnell et al. 2000). In other words, failure to increase peak ventilation in the setting of increased ventilatory stimulation (i.e. the added stress) signals a true mechanical
limit to exercise capacity. An accepted method used by past investigators to selectively increase
the stress on the respiratory system has been the approach of adding an external dead space (DS)
(i.e. an external plastic tube) to the breathing circuit during rest and exercise (Brown et al. 1984;
McParland et al. 1991; Syabbalo et al. 1993; Marciniuk et al. 1994; O’Donnell et al. 2000). This
technique has also been termed “dead space loading.”

The added stress (load) of the external dead space has previously been studied only in
young healthy subjects during exercise; the added DS resulted in significant increases in their
peak ventilation with preservation of exercise capacity (Brown et al. 1984; McParland et al.
1991; Syabbalo et al. 1993). By utilizing the same approach of dead space loading in the current
study, we wished to determine if abnormal mechanical respiratory factors are responsible for
limiting exercise capacity in mild COPD.

1.6.2. – Objectives

1. To compare daily physical activity levels, chronic dyspnea ratings, and tests of airway
   function in mild COPD and in healthy subjects.

2. To compare ventilatory (operating lung volumes and breathing pattern), gas exchange,
   and sensory responses during incremental work-rate cycle exercise in mild COPD and
   healthy subjects to elucidate the pathophysiological mechanisms of dyspnea and activity-
   limitation in mild COPD.

3. To compare the ventilatory and sensory responses under selective respiratory stress by an
   added external dead space (DS) during cycle exercise in mild COPD and in healthy
   subjects who have no airway obstruction.
1.6.3. – Hypotheses

1. Patients with mild COPD, are compared to healthy subjects, unable to further increase $\dot{V}_E$, $V_T$, and EILV in response to the increased ventilatory requirements of an added DS. This indicates a true ventilatory limitation to exercise.

2. Such mechanical ventilatory constraints in the face of progressively increasing DS-induced central respiratory drive leads to an earlier onset of intolerable dyspnea in patients with mild COPD compared to healthy subjects.
CHAPTER 2: METHODS

Section 2.1 - Subjects

We studied 20 patients with GOLD stage I COPD (post-bronchodilator FEV$_1$/FVC < 0.70 and FEV$_1$ ≥ 80% predicted) (Rabe et al. 2007) and 20 healthy age-, height-, mass-, and gender-matched subjects with normal spirometry. Subjects were excluded if they had medical conditions (i.e. metabolic, cardiovascular, or any other respiratory disease) that could have contributed to dyspnea or if they had contraindications to exercise testing, such as neuromuscular or musculoskeletal conditions. Potential COPD subjects were recruited from physician referrals or from advertisements in the local senior’s magazine and hospital boards. All healthy subjects were recruited from advertisements or by telephone contact from the Respiratory Investigation Unit’s subject registry.

Section 2.2 - Study Design

This was a controlled, randomized, cross-sectional study that received ethics approval from the Queen’s University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (Appendix A). The study was conducted over 3 visits. On visit 1, informed consent, medical history screening, and anthropometric measurements were obtained. Subjects completed two chronic activity-related dyspnea questionnaires: the Medical Research Council dyspnea scale (Appendix B) (Fletcher et al. 1959) and the Baseline Dyspnea Index (Appendix C) (Mahler et al. 1984). The Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire was completed to estimate weekly caloric expenditure (Appendix D) (Stewart et al. 2001). Pre- and 30 min post-bronchodilator (400 mg salbutamol) pulmonary function testing and a symptom-limited incremental cycle exercise test were performed for screening and familiarization purposes. On visits 2 and 3, subjects completed pulmonary function testing followed by an incremental cycle exercise test under control (CTRL) or added external dead space (DS)
conditions. If randomized to the CTRL condition on visit 2 then subjects performed the DS condition on visit 3 and vice-versa. Subjects with mild COPD were asked to temporarily stop any short- and long-acting bronchodilators for between 8 and 72 hours, respectively, prior to each visit. Subjects avoided alcohol, caffeine, and heavy meals for 4 hours and avoided strenuous physical activity for at least 24 hours prior to each visit. Visits 2 and 3 were separated by ≥ 24 hours and all visits were conducted at the same time of day for each subject.

Section 2.3 - Pulmonary Function Tests

Spirometry, constant-volume body plethysmography, single-breath diffusing capacity for carbon monoxide (DLCO), maximal inspiratory and expiratory mouth pressures (MIPs and MEPs measured at FRC and TLC, respectively), maximal voluntary ventilation (MVV), and impulse oscillometry (Appendix E) were performed according to recommended techniques (Miller et al. 2005; Wanger et al. 2005; MacIntyre et al. 2005; American Thoracic Society, 2002; American Thoracic Society/European Respiratory Society, 2005; Oostveen et al. 2003) using an automated testing system (Vmax229d with Autobox 6200DL; SensorMedics, Yorba Linda, CA and Masterscreen IOS). The single-breath nitrogen washout test (Appendix F) was used to assess the alveolar plateau (N2 slope) (Buist & Ross, 1973). All measurements were expressed as percentages of predicted normal values (Morris et al. 1988; Crapo et al. 1982; Burrows et al. 1961; Briscoe & Dubois, 1958; Black & Hyatt, 1969; Hamilton et al. 1995). Predicted normal values for inspiratory capacity (IC) were calculated as predicted total lung capacity (TLC) minus predicted functional residual capacity (FRC).

Section 2.4 - Cardiopulmonary Exercise Testing

Symptom-limited incremental exercise tests were performed on an electronically braked cycle ergometer (Ergometrics 800S; SensorMedics, Yorba Linda, CA) with use of a calibrated SensorMedics Vmax229d cardiopulmonary exercise testing system according to ATS guidelines.
(American Thoracic Society, 2003). With nasal passages occluded by a noseclip, subjects underwent the exercise protocol which consisted of a steady-state resting period and a 1-min warm-up (0 watts), followed by incremental increases in work rate by 20 watts every 2 minutes until symptom limitation. Subjects maintained their cycling cadence between 50 and 70 revolutions/min.

**Section 2.5 - Symptom Evaluation**

Before exercise testing, subjects were familiarized with the modified Borg scale (Appendix G) (Borg, 1982), and its end points were anchored such that ‘0’ represented “no breathing/leg discomfort” and 10 represented “the most severe breathing/leg discomfort ever experienced or imagined experiencing.” Subjects rated the intensity of their perceived breathing and leg discomfort at rest, at every stage of exercise, and at peak exercise. Upon exercise cessation, subjects were asked to verbalize their main reason(s) for stopping exercise (i.e. breathing discomfort, leg discomfort, combination of breathing and legs, or some other reason) and to select qualitative descriptors of breathlessness (Appendix H) using a questionnaire previously modified by O'Donnell et al. (1997) from Simon et al. (1990). For this questionnaire, subjects were asked to “circle all phrases that described your breathing discomfort at the end of exercise when you had to stop.”

**Section 2.6 - Exercise Testing Measurements**

Subjects breathed through a mouthpiece and a low resistance flow transducer. Ventilatory, breathing pattern, and metabolic responses were measured on a breath-by-breath basis at rest and throughout exercise. The Vmax229d computer software calculated $V_E$, $V_T$, $F_b$, $\dot{V}O_2$, $\dot{V}CO_2$, and the end-tidal carbon dioxide partial pressure ($P_{ETCO_2}$). Accurate and reliable measurements of $\dot{V}O_2$ and $\dot{V}CO_2$ are only reported during the control condition since the metabolic cart used in this study does not allow corrections for DS volumes greater than 250 mL. Breath-by-breath variables
were averaged and analyzed at rest and during the first 30 seconds of the second minute of each exercise stage and at peak exercise; peak exercise values were defined as the mean over the last 30 seconds of exercise. Arterial oxygen saturation (SpO₂) and heart rate (HR) were measured by pulse oximetry and electrocardiography, respectively, at rest and throughout exercise. Exercise parameters were compared with the predicted normal values of Jones et al. (1985) and Fairbarn et al. (1994), which accounts for age, height, weight, and gender. All subjects performed IC maneuvers at rest, at every stage of exercise, and at peak exercise to determine operating lung volumes. Subjects were prompted to initiate the IC maneuver (i.e. “at the end of a normal breath out, take a deep breath all the way in until you are completely full”), and then verbal encouragement was given during the maneuver for subjects to make a maximal effort (i.e. “in in in...”). Assuming that TLC does not change significantly during exercise (Stubbing et al. 1980; Younes & Kivinen, 1984), changes in IC reflect changes in EELV (= TLC-IC), and changes in IRV (= IC-VT) reflect changes in EILV (= TLC-IRV).

We employed a rigorous process to accurately determine the anaerobic threshold (AT), which is an indicator of the onset of metabolic acidosis caused by lactic acid accumulation during exercise. The first method used for the non-invasive determination of the AT was the V-slope method (Wasserman et al. 1999). Here, the intersection of a change in the slope of two linear segments on the plot of the VCO₂-VO₂ relationship (the Slope1-Slope2 breakpoint) indicated the onset of additional CO₂ released due to the buffering of H⁺ ions associated with lactate ion accumulation (Beaver et al. 1986 a, b). We also employed the ventilatory equivalents method. Here, the AT was identified when the ventilatory equivalent for oxygen (Ve/VO₂) and the end-tidal O₂ tension (PETO₂) were at their lowest points before increasing, while simultaneously, the ventilatory equivalent for carbon dioxide (Ve/VCO₂) and the PETCO₂ remained unchanged (Wasserman et al. 1999). This method is based on the notion that ventilation normally occurs
during exercise to rid the CO$_2$ load at the lungs (Whipp & Ward, 1991). As recommended by Weisman & Zeballos (2002), both the V-slope and the ventilatory equivalents methods were used in conjunction. Furthermore, three different people from our laboratory independently verified the identification of the AT.

**Section 2.7 - Tidal Flow-Volume Loops**

Flow and integrated volume were continuously recorded during rest and exercise. Tidal flow volume curves at rest, at iso-work rates, and at peak exercise were placed within their respective maximal flow-volume loops according to coinciding IC measurements. The degree of expiratory flow limitation was estimated as the percentage of $V_T$ that encroached on the maximal flow-volume envelope obtained at rest (Johnson et al. 1999).

**Section 2.8 - Dead Space**

An externally added DS (i.e. large plastic tubing) with an internal diameter of 35 mm and a volume of 600 mL was inserted between the mouthpiece and a low-resistance, two-way non-rebreathing Hans Rudolph valve. This breathing circuit setup was similar to that of a previous study from our laboratory (O’Donnell et al. 2000). Although the DS arrangement was not concealed, subjects were naïve to the purpose of the DS and no subjects gave any indication of being aware of the added DS throughout the experiment.

**Section 2.9 – Statistical Analysis**

A sample size of 20 was used to provide the statistical power (80%) needed to detect a 1 Borg unit difference in dyspnea intensity between-groups (COPD vs. Health) at a standardized work rate (iso-work) during incremental cycle exercise, based on a SD of 1 Borg unit, $\alpha=0.05$ and a 2-tailed test of significance. First, descriptive characteristics and pulmonary function test results were compared between groups (health vs. mild COPD) with unpaired $t$-tests. Second, preplanned comparisons were used for within group (health or COPD) analysis to examine the
effects of the CTRL vs. DS condition for measured parameters at rest, at standardized sub-maximal work rates during exercise, at the highest equivalent work rate (HEWR) of 60 watts that all subjects completed, and at peak exercise using paired \( t \)-tests. Third, preplanned comparisons were used for between-group comparisons (health vs. COPD) to examine the effects of the CTRL vs. DS condition for measured parameters at rest, at standardized sub-maximal work rates during exercise, at the HEWR, and at peak exercise using unpaired \( t \)-tests. Fourth, reasons for stopping exercise and qualitative descriptors of breathlessness were analyzed as frequency statistics and compared using the Fisher’s exact test. Results were reported as means ± SD unless otherwise specified. Statistical significance for all analyses was set at \( P<0.05 \).
CHAPTER 3: RESULTS

Section 3.1 - Subject Characterization

3.1.1. - General Description

General descriptions of anthropometric measurements, cigarette smoking history, baseline activity-related dyspnea, and estimates of weekly physical activity levels for all subjects in this study are summarized in Table 1. Subjects in both groups were well matched for age, sex, height, weight, and body mass index (BMI). Compared to the healthy group, patients with COPD had a significant smoking history (42.6 ± 21.6 pack-years; range: 10–108 pack-years); 15 of these patients were ex-smokers and 5 remained current smokers. No current smokers were part of the healthy group; 2 healthy subjects had a prior smoking history of only 2 and 2.5 pack years and had stopped smoking for more than 20 years.

The COPD group had significantly greater chronic activity-related dyspnea as assessed by the BDI (Mahler et al. 1984) and MRC (Fletcher et al. 1959) dyspnea scales. For the MRC scale (range: 1-5), the majority of COPD patients (15/20) had a rating of ≥ 2 while only 3/20 healthy subjects rated this same score. For the BDI focal score (range: 0-12), almost half of all COPD patients (9/20) had a score of ≤ 8, with scores ranging between 5 and 12; the range was between 9 and 12 for the healthy subjects. A BDI score of ≤ 8 indicates the presence of clinically significant activity-related dyspnea.

Weekly habitual physical activity levels, as estimated by the CHAMPS questionnaire for older adults (Stewart et al. 2001), indicated that our COPD group was already more sedentary compared with health.
**TABLE 1: Subject characteristics in health and in patients with GOLD Stage I MILD COPD**

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>Mild COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Subjects</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Male : Female</td>
<td>11 : 9</td>
<td>11 : 9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 ± 8</td>
<td>68 ± 6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167 ± 9</td>
<td>166 ± 9</td>
</tr>
<tr>
<td>Mass (kg)</td>
<td>75.8 ± 12.6</td>
<td>75.8 ± 18.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.9 ± 2.8</td>
<td>27.4 ± 6.3</td>
</tr>
<tr>
<td>Cigarette smoking (pack-years)</td>
<td>0.2 ± 0.7</td>
<td>42.6 ± 21.6*</td>
</tr>
<tr>
<td>BDI focal score (0-12)</td>
<td>11.4 ± 0.9</td>
<td>8.7 ± 2.0*</td>
</tr>
<tr>
<td>MRC dyspnea scale (1-5)</td>
<td>1.3 ± 0.7</td>
<td>2.0 ± 0.7*</td>
</tr>
<tr>
<td>CHAMPS (kcal/week) consumed for all activities</td>
<td>5966 ± 2975</td>
<td>2535 ± 2392*</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: BDI = modified Baseline Dyspnea Index; MRC = Medical Research Council; CHAMPS = Community Healthy Activities Model Program for Seniors. Values are means ± SD. (*) denotes significant difference (P < 0.05) between the healthy and COPD groups.*
Thirteen of the 20 COPD subjects had a previous diagnosis of GOLD Stage I COPD; 9 out of the 13 had received the diagnosis within the previous 5 years. Among the subjects with COPD: 8 did not use any respiratory medications, 2 used a short-acting β2-agonist bronchodilator on an ‘‘as needed’’ basis, and 10 used an inhaler on a regular basis. Of these latter 10 subjects: 4 used short-acting β2-agonists, 2 used a short-acting anticholinergic bronchodilator, 7 used a long-acting anticholinergic bronchodilator, 6 used an inhaled corticosteroid/long-acting β2-agonist combination, and 2 used an inhaled corticosteroid only.

Co-morbidities in the COPD group included well-controlled hypertension (n=12). Among these 12 subjects, 5 had well-controlled type 2 diabetes mellitus and another 3 had hypercholesterolemia. Two of the subjects with hypertension also reported having arthritis; however, their ability to cycle was not hindered because of this. One subject reported only having sleep apnea for the past 5 years. Co-morbidities in the healthy group included well-controlled hypertension (n=4). Among these 4 subjects, one had arthritis and another had hypercholesterolemia and diabetes. Finally, three subjects in the healthy group reported only having arthritis; this was not a concern during all exercise tests.
TABLE 2: Pulmonary Function Test (PFT) results in healthy subjects and in patients with GOLD Stage I MILD COPD

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>Mild COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absolute Units</td>
<td>% predicted</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>74 ± 6</td>
<td>105 ± 9</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>2.96 ± 0.72</td>
<td>117 ± 13</td>
</tr>
<tr>
<td>Post-BD FEV₁/FVC (%)</td>
<td>77 ± 5</td>
<td>-</td>
</tr>
<tr>
<td>Post-BD FEV₁ (L)</td>
<td>3.12 ± 0.67</td>
<td>122 ± 11</td>
</tr>
<tr>
<td>FEV₁/FVC (predicted LLN)</td>
<td>65 ± 2</td>
<td>-</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.99 ± 0.90</td>
<td>111 ± 12</td>
</tr>
<tr>
<td>TLC (L)</td>
<td>5.93 ± 0.97</td>
<td>102 ± 13</td>
</tr>
<tr>
<td>FRC (L)</td>
<td>2.92 ± 0.63</td>
<td>93 ± 23</td>
</tr>
<tr>
<td>RV (L)</td>
<td>1.76 ± 0.44</td>
<td>83 ± 21</td>
</tr>
<tr>
<td>IC (L)</td>
<td>3.01 ± 0.82</td>
<td>111 ± 18</td>
</tr>
<tr>
<td>PEF (L/s)</td>
<td>8.61 ± 2.58</td>
<td>125 ± 24</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅% (L/s)</td>
<td>2.35 ± 1.04</td>
<td>89 ± 31</td>
</tr>
<tr>
<td>FEF₅₀% (L/s)</td>
<td>3.62 ± 1.64</td>
<td>92 ± 42</td>
</tr>
<tr>
<td>MVV (L/min)</td>
<td>127.9 ± 30.7</td>
<td>-</td>
</tr>
<tr>
<td>DLCO (mLCO/min/mmHg)</td>
<td>21.5 ± 5.5</td>
<td>104 ± 17</td>
</tr>
<tr>
<td>N₂ slope: (%/L)</td>
<td>2.84 ± 1.09</td>
<td>-</td>
</tr>
<tr>
<td>sRaw (cmH₂O•s)</td>
<td>5.4 ± 2.2</td>
<td>129 ± 57</td>
</tr>
<tr>
<td>MIP (cmH₂O)</td>
<td>90 ± 26</td>
<td>115 ± 24</td>
</tr>
<tr>
<td>MEP (cmH₂O)</td>
<td>154 ± 47</td>
<td>90 ± 20</td>
</tr>
<tr>
<td>R₅-R₂₀ (cmH₂O/L/s)</td>
<td>12.4 ± 7.2</td>
<td>-</td>
</tr>
<tr>
<td>X₅ (cmH₂O/L/s)</td>
<td>-1.1 ± 0.5</td>
<td>-</td>
</tr>
</tbody>
</table>

Pulmonary function parameters are pre-bronchodilator unless otherwise noted. Definition of abbreviations: BD = bronchodilator; FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity; LLN = lower limit of normal calculated from Hankinson et al. (1999) based on sex and age; TLC = total lung capacity; FRC = functional residual capacity; RV = residual volume; IC = inspiratory capacity; PEF = peak expiratory flow; FEF₂₅₋₇₅% = force expiratory flow between 25 and 75% of FVC; FEF₅₀% = forced expired flow at 50% of vital capacity; MVV = Maximal Voluntary Ventilation; DLCO = diffusing capacity of the lung for carbon monoxide; sRaw = specific airways resistance; MIP = maximal inspiratory pressure; MEP = maximal expiratory pressure; R₅ = resistance at 5 Hz; R₂₀ = resistance at 20 Hz; X₅ = reactance at 5 Hz.

(*) p< 0.05 denotes significant difference between the healthy and COPD groups, expressed in absolute values.

(#) p< 0.05 denotes significant difference between the healthy and COPD groups, expressed as a % of predicted.

Values are means ± SD.
3.1.2. - Pulmonary Function Tests

Pulmonary function test results for both groups are summarized in table 2. Compared with the healthy group, spirometry confirmed that the COPD group had significant expiratory airflow limitation (based on the FEV₁/FVC ratio and the FEV₁, %predicted) that satisfied the GOLD stage I criteria. In addition, every subject in the healthy group had a post-bronchodilator FEV₁/FVC ratio that was greater than their predicted lower-limit of normal (LLN) value. For the COPD group, 17 subjects were below their predicted LLN; the rest (n=3) were above by only 1 ± 0%. Although our COPD population had significantly higher lung volumes (FRC and RV, % predicted) compared to the healthy subjects, these values were not greater than 120% predicted (the arbitrary “cut-off” that may potentially be clinically important) (O’Donnell & Laveneziana, 2006c). As such, our COPD group could not be characterized as having clinically relevant static lung hyperinflation. Compared to healthy subjects, the COPD group had significant reductions in the following: IC (% predicted), DLCO, expiratory flows, and ventilatory capacity as measured by the MVV breathing maneuver. In contrast, the COPD group had significant increases in the: N₂ slope, specific airways resistance (sRaw), and differential change in the resistance of the airways at 5 and 20 Hz (R5 - R20) as measured by impulse oscillometry. Collectively, these results suggest an increase in peripheral (distal) airway resistance in mild COPD.

3.1.3. – Symptom-limited Incremental Cycle Exercise

Given the controversy surrounding the classification and existence of mild COPD, it was important to demonstrate, in addition to the pulmonary function tests of section 3.1.2, the presence of substantial differences in cardio-respiratory, metabolic, and sensory responses that occurred during physical exertion in those with mild COPD compared to healthy subjects. To illustrate these differences, comparisons between the healthy and mild COPD group during cycle exercise under the CTRL condition (i.e. no added DS) will be examined first in this section.
Significant differences in exercise measurements between the two test groups at the peak of cycle exercise and at a standardized work rate of 60 watts (the highest equivalent work rate; HEWR) are shown in Tables 3 and 4, respectively. Compared to health, the mild COPD group had significantly reduced exercise capacity: the peak work rate and \( \dot{V}O_2 \) [both in absolute units (L/min) and normalized for body mass (mL/kg/min)] were all significantly lower in COPD.
TABLE 3: Measurements at the peak of symptom-limited incremental cycle exercise for the healthy and COPD groups under control (CTRL) conditions

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>Mild COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work Rate (W)</td>
<td>162 ± 55</td>
<td>92 ± 26*</td>
</tr>
<tr>
<td>(% predicted)</td>
<td>(122 ± 31)</td>
<td>(77 ± 23)*</td>
</tr>
<tr>
<td>VO₂ (L/min)</td>
<td>2.45 ± 0.84</td>
<td>1.58 ± 0.45*</td>
</tr>
<tr>
<td>(% predicted)</td>
<td>(103 ± 22)</td>
<td>(71 ± 14)*</td>
</tr>
<tr>
<td>VO₂ (mL/kg/min)</td>
<td>32.0 ± 8.8</td>
<td>21.2 ± 5.5*</td>
</tr>
<tr>
<td>VE (L/min)</td>
<td>95.0 ± 30.9</td>
<td>55.6 ± 16.0*</td>
</tr>
<tr>
<td>(% of MVV)</td>
<td>(73 ± 13)</td>
<td>(69 ± 17)</td>
</tr>
<tr>
<td>VT (L)</td>
<td>2.26 ± 0.65</td>
<td>1.62 ± 0.41*</td>
</tr>
<tr>
<td>(% predicted VC)</td>
<td>(62 ± 10)</td>
<td>(47 ± 8)*</td>
</tr>
<tr>
<td>VT/IC (%)</td>
<td>76 ± 13</td>
<td>68 ± 11*</td>
</tr>
<tr>
<td>Fe (breaths/min)</td>
<td>42 ± 9</td>
<td>35 ± 9</td>
</tr>
<tr>
<td>IC (L)</td>
<td>3.01 ± 0.86</td>
<td>2.40 ± 0.51*</td>
</tr>
<tr>
<td>(% predicted)</td>
<td>(111 ± 18)</td>
<td>(92 ± 17)*</td>
</tr>
<tr>
<td>Δ IC from rest (L)</td>
<td>0.09 ± 0.52</td>
<td>-0.30 ± 0.43*</td>
</tr>
<tr>
<td>IRV (L)</td>
<td>0.74 ± 0.43</td>
<td>0.78 ± 0.32</td>
</tr>
<tr>
<td>(% predicted TLC)</td>
<td>(12 ± 7)</td>
<td>(14 ± 6)</td>
</tr>
<tr>
<td>EILV (% predicted TLC)</td>
<td>88 ± 14</td>
<td>90 ± 7</td>
</tr>
<tr>
<td>EELV (% predicted TLC)</td>
<td>50 ± 13</td>
<td>62 ± 8*</td>
</tr>
<tr>
<td>EFL (% of VT overlapping maximal flow-volume curve)</td>
<td>49 ± 24</td>
<td>65 ± 25†</td>
</tr>
<tr>
<td>PETCO₂ (mm Hg)</td>
<td>32.2 ± 4.8</td>
<td>33.6 ± 4.5</td>
</tr>
<tr>
<td>VE/VCO₂</td>
<td>34.7 ± 5.8</td>
<td>33.9 ± 4.7</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>158 ± 16</td>
<td>136 ± 19*</td>
</tr>
<tr>
<td>(% predicted)</td>
<td>(93 ± 10)</td>
<td>(82 ± 11)*</td>
</tr>
<tr>
<td>VO₂/HR (mL/beat)</td>
<td>15.9 ± 5.4</td>
<td>11.8 ± 3.8*</td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>94 ± 4</td>
<td>94 ± 3</td>
</tr>
<tr>
<td>Dyspnea (Borg)</td>
<td>6.1 ± 3.2</td>
<td>5.4 ± 2.0</td>
</tr>
<tr>
<td>Leg Discomfort (Borg)</td>
<td>6.8 ± 3.2</td>
<td>6.2 ± 2.1</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: VO₂ = oxygen uptake; AT = anaerobic threshold; VE = minute ventilation; MVV = maximal voluntary ventilation; VT = tidal volume; VC = vital capacity; Fe = breathing frequency; IC = inspiratory capacity; IRV = inspiratory reserve volume; TLC = total lung capacity; EILV = end-inspiratory lung volume; EELV = end-expiratory lung volume; EFL = expiratory flow limitation; PETCO₂ = end-tidal CO₂; VE/VCO₂ = ventilatory equivalent for CO₂; HR = heart rate; VO₂/HR = oxygen pulse; SpO₂ = arterial O₂ saturation.

(*) p< 0.05 denotes significant difference.
(†) p=0.05 healthy vs. COPD
Values are means ± SD.
TABLE 4: Measurements at the highest equivalent work rate (HEWR) of 60 watts during symptom-limited incremental cycle exercise for the healthy and COPD groups under control (CTRL) conditions

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>Mild COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\dot{V}O_2$ (L/min)</td>
<td>1.12 ± 0.12</td>
<td>1.15 ± 0.19</td>
</tr>
<tr>
<td>$\dot{V}O_2$ (mL/kg/min)</td>
<td>14.9 ± 2.0</td>
<td>15.6 ± 3.1</td>
</tr>
<tr>
<td>$V_E$ (L/min)</td>
<td>29.4 ± 7.4</td>
<td>35.5 ± 8.1</td>
</tr>
<tr>
<td>(% of MVV)</td>
<td>(24 ± 7)</td>
<td>(46 ± 15)</td>
</tr>
<tr>
<td>$V_T$ (L)</td>
<td>1.31 ± 0.25</td>
<td>1.41 ± 0.24</td>
</tr>
<tr>
<td>(%predicted VC)</td>
<td>(37 ± 8)</td>
<td>(42 ± 8)</td>
</tr>
<tr>
<td>$V_T$/IC (%)</td>
<td>45 ± 13</td>
<td>55 ± 11*</td>
</tr>
<tr>
<td>$F_b$ (breaths/min)</td>
<td>24 ± 10</td>
<td>26 ± 8</td>
</tr>
<tr>
<td>IC (L)</td>
<td>3.13 ± 0.91</td>
<td>2.64 ± 0.58†</td>
</tr>
<tr>
<td>(%predicted)</td>
<td>(116 ± 25)</td>
<td>(101 ± 21)†</td>
</tr>
<tr>
<td>Δ IC from rest (L)</td>
<td>0.22 ± 0.36</td>
<td>-0.06 ± 0.35*</td>
</tr>
<tr>
<td>IRV (L)</td>
<td>1.83 ± 0.88</td>
<td>1.23 ± 0.51†</td>
</tr>
<tr>
<td>(%predicted TLC)</td>
<td>(30 ± 12)</td>
<td>(21 ± 8)*</td>
</tr>
<tr>
<td>EILV (% predicted TLC)</td>
<td>70 ± 15</td>
<td>82 ± 11*</td>
</tr>
<tr>
<td>EELV (% predicted TLC)</td>
<td>47 ± 15</td>
<td>58 ± 11*</td>
</tr>
<tr>
<td>EFL (% of $V_T$ overlapping maximal flow-volume curve)</td>
<td>26 ± 26</td>
<td>60 ± 26*</td>
</tr>
<tr>
<td>$P_{ET}CO_2$ (mm Hg)</td>
<td>38.7 ± 4.2</td>
<td>35.8 ± 4.9†</td>
</tr>
<tr>
<td>$\dot{V}E$/VCO₂</td>
<td>30.0 ± 3.6</td>
<td>33.2 ± 4.6*</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>104 ± 17</td>
<td>115 ± 17†</td>
</tr>
<tr>
<td>(%predicted)</td>
<td>(62 ± 11)</td>
<td>(71 ± 9)*</td>
</tr>
<tr>
<td>$\dot{V}O_2$/HR (mL/beat)</td>
<td>11.2 ± 2.5</td>
<td>10.1 ± 2.5</td>
</tr>
<tr>
<td>$SpO_2$ (%)</td>
<td>97 ± 1</td>
<td>96 ± 2</td>
</tr>
<tr>
<td>Dyspnea (Borg)</td>
<td>0.6 ± 0.6</td>
<td>1.7 ± 1.6*</td>
</tr>
<tr>
<td>Leg Discomfort (Borg)</td>
<td>0.7 ± 0.7</td>
<td>2.3 ± 1.8*</td>
</tr>
</tbody>
</table>

* Definition of abbreviations: $\dot{V}O_2$ = oxygen uptake; $\dot{V}E$ = minute ventilation; MVV = maximal voluntary ventilation; $V_T$ = tidal volume; VC = vital capacity; $F_b$ = breathing frequency; IC = inspiratory capacity; IRV = inspiratory reserve volume; TLC = total lung capacity; EILV = end-inspiratory lung volume; EELV = end-expiratory lung volume; EFL = expiratory flow limitation; $P_{ET}CO_2$ = end-tidal CO$_2$; $\dot{V}E$/VCO$_2$ = ventilatory equivalent for CO$_2$; HR = heart rate; $\dot{V}O_2$/HR = oxygen pulse; $SpO_2$ = arterial O$_2$ saturation.

(*) p< 0.05 denotes significant difference.
(+†) p = 0.05 healthy vs. COPD
Values are means ± SD.
3.1.4. – Ventilatory Responses and Pulmonary Gas Exchange

Compared with health, the ventilatory demand ($\dot{V}_E$) was higher at rest and at all sub-maximal work rates in the COPD group; this reached significance at the HEWR of 60 watts at which the mean difference between the 2 groups was $6.1 \pm 0.8$ L/min (Figure 4A). At the peak of exercise, the healthy group was able to achieve a significantly greater $\dot{V}_E$ compared to COPD (95 vs. 56 L/min, $p<0.00005$). However, the ventilatory reserve [(\dot{V}_{Epeak}/MVV)*100] at peak exercise was not significantly different between the healthy (73%) and COPD (69%) groups.

The $\dot{V}_E/\dot{V}CO_2$ for both the healthy and COPD groups are illustrated in Figure 4B. For both groups, the $\dot{V}_E/\dot{V}CO_2$ decreased hyperbolically as the work rate increased. However, compared with health, the ventilatory equivalent for CO$_2$ was greater at rest and at all sub-maximal work rates in COPD during exercise; the corresponding p-value at 20 watts was 0.05. No significant differences were observed at the peak of exercise between the two groups.

Compared to the healthy group, the end-tidal CO$_2$ ($P_{ET}CO_2$) was lower in the COPD group at rest ($34.9 \pm 2.5$ vs. $32.0 \pm 3.6$ mm Hg, respectively) and at all sub-maximal work rates (Figure 4C); it was lower by 2.9 mmHg, 2.9 mmHg, 2.5 mmHg, and 3.0 mmHg at rest, 20 watts, 40 watts, and 60 watts, respectively.

The anaerobic threshold (AT) occurred at a significantly lower $\dot{VO}_2$, both in absolute and relative terms, in mild COPD compared to health. In COPD, the $\dot{VO}_2$ at the AT was $0.94 \pm 0.21$ L/min compared to $1.29 \pm 0.51$ L/min in health ($p<0.05$), a 31% difference. When expressed in relative terms, the COPD group reached their AT at 40 ± 11% of their predicted $\dot{VO}_2$ max; in health it was significantly higher ($p<0.05$): 55 ± 19% of predicted $\dot{VO}_2$ max.
FIGURE 4: Ventilation (panel A), ventilatory equivalent for CO\textsubscript{2} (panel B), and the end-tidal PCO\textsubscript{2} (panel C) response with increasing work rate in health and mild COPD. **Panel A:** The ventilatory demand was higher at rest and throughout all sub-maximal work rates in mild COPD compared to health. The ventilation was significantly lower at the peak of exercise in mild COPD. **Panel B:** Compared to health, the ventilatory equivalent for CO\textsubscript{2} was significantly greater at rest and at the sub-maximal work rates of 40 and 60W. **Panel C:** P\textsubbox{ET}CO\textsubscript{2} was lower at rest and throughout all sub-maximal work rates in mild COPD compared to health. Significant differences were observed at rest and 20W; the corresponding p values at 40W and 60W were 0.07 and 0.05, respectively. (*) p< 0.05 denotes statistical significance. Values are means ± SE.
3.1.5. – Mechanics

Compared to health, the IC was on a lower trend at rest and throughout exercise (Figure 5A) in COPD. The IC was lower in COPD by 0.22 L at rest and 0.50 L at 60 watts; these differences, however did not reach statistical significance. In the COPD group, the change in the IC at the peak of exercise from rest (ΔIC = ICpeak - ICrest = -0.30 ± 0.43 L) was significantly greater than that in health (ΔIC = +0.09 ± 0.52 L, p< 0.05). Although hyperinflation (represented by a - ΔIC) occurred in both groups, it was much more prevalent in the COPD group: 17 (85%) of the COPD patients hyperinflated at the peak of exercise while only 9 (45%) of the healthy subjects did so.

The operating lung volumes are illustrated in Figure 5B. Complimentary to the reduced IC throughout exercise in the COPD group, the EELV (%predicted TLC) was elevated at rest and throughout exercise in the COPD group compared to health. The EILV (%predicted TLC) was also elevated in COPD, reaching significance at all sub-maximal work rates. Compared to health, the upward shift in the operating lung volumes in the COPD group indicated that they were breathing closer to their TLC. Indeed, at the peak of exercise, the EELV (% of predicted TLC) was significantly greater in the COPD group (62 ± 8%) than in health (50 ± 13%).

All healthy subjects and 19/20 COPD subjects had a noticeable inflection in their tidal volume (VT) response during exercise (Figure 6). This VT inflection occurred at a lower VE (COPD: 36.8 ± 10.0 L/min vs. health: 46.3 ± 21.5 L/min; p=0.08), VO₂ (COPD: 1.21 ± 0.32 L/min vs. health: 1.58 ± 0.46 L/min; p<0.0001), and work rate (COPD: 64 ± 25 W vs. health: 103 ± 32 W; p<0.0005) in COPD compared with health.
FIGURE 5: Changes in inspiratory capacity (IC) (panel A) and the end-expiratory lung volume (EELV) and end-inspiratory lung volume (EILV, both expressed as % of predicted TLC) (panel B) with increasing work rate in health and mild COPD. **Panel A:** In health, IC increased at the start of exercise and then progressively returned to its initial level. In COPD, IC progressively decreased throughout exercise. The corresponding p values at 40 and 60W were 0.06 and 0.05, respectively. **Panel B:** There is an upward shift in the operating lung volumes in the COPD group (shaded); at any given work rate, the EELV and EILV were greater in the mild COPD group compared to those in healthy subjects. *Abbreviations:* $V_T =$ tidal volume; IRV = inspiratory reserve volume; TLC = total lung capacity. (*) p< 0.05 denotes statistical significance. Values are means ± SE.
FIGURE 6: Individual example for the determination of the V_T inflection point as a function of ventilation in a healthy (left) and mild COPD (right) subject. In both there is a noticeable mechanical ceiling during exercise as represented by the V_T inflection point (arrows). This V_T inflection, however, occurs at a substantially lower V_E in COPD than in health.
The resting and exercise tidal flow-volume (FV) loops are shown in relation to the resting maximal flow volume loop (MFVL) in three types of individuals: the healthy young, the healthy older individual, and an individual with mild COPD (Figure 7). Note the relatively greater “scooping” of the MFVL in the healthy older individual compared to the healthy young subject. Likewise, there was an even greater degree of “scooping” in the MFVL for the individual with mild COPD compared to the healthy older individual. Due to the greater decline in the expiratory flow in COPD, there was a greater degree of expiratory flow limitation (EFL) than in the healthy older individual; the degree of EFL is estimated as the percent of the exercise FV loop that overlaps the MFVL. Similarly, the degree of EFL was greater in the healthy older subject compared with the young.

Note that the FV loops for the healthy young individual were constructed from data from O’Donnell et al. (2000, with permission). It is shown here in relation to the healthy older and mild COPD individual as it becomes essential for our later discussions.
FIGURE 7: Maximal and tidal flow-volume loops are shown at rest and during incremental cycle exercise in (A) a healthy 30 year-old individual, (B) a healthy 69 year-old individual and (C) a 68 year-old individual with mild COPD. The tidal flow-volume loops are positioned within the resting maximal flow volume loop (MFVL) according to end-expiratory lung volume (EELV). Tidal flow-volume loops are provided at rest (dotted line), at a submaximal work rate of 60 W (dashed line), and at peak exercise (solid line). Expiratory flow limitation (EFL) is present when the tidal expiratory flow intersects or overlaps the MFVL. The flow-volume loop of the healthy young subject is constructed from data from O’Donnell et al. 2000, with permission.
3.1.6. – Respiratory Symptoms

Dyspnea intensity was greater in the COPD group throughout exercise, reaching significant differences (p< 0.01) at the HEWR of 60 watts when the group mean difference was greater than 1 Borg unit (Figure 8A); the corresponding p values at 20 and 40W were 0.08 and 0.06, respectively. Leg discomfort ratings were also greater in the COPD group throughout exercise (Figure 8B). While significant differences were observed at all sub-maximal work rates, the group mean difference became greater than 1 Borg unit only at the HEWR of 60 watts. Ries (2005) has postulated that a change in 1 Borg unit represents a clinically relevant change. Dyspnea and leg discomfort Borg ratings were not different between the two groups at the peak of exercise (Table 3).

Reasons for stopping exercise are illustrated in Figure 9. Although none of the options reached significance, it is interesting to note that half of the COPD group (10, or 50%) stopped exercise because of severe breathing discomfort, either alone or in combination with leg discomfort. In contrast, most healthy subjects (13, or 65%) stopped exercise primarily because of leg discomfort. The rest of the COPD group (40%) stopped only because of leg discomfort while the minority (10%) stopped because of some “other reason” such as general fatigue. Qualitative descriptors pertaining to each subject’s breathing discomfort at the end of exercise are shown in Figure 10.
FIGURE 8: Dyspnea intensity (panel A) and leg discomfort ratings (panel B) with increasing work rate in health and mild COPD. A significant difference in dyspnea intensity between the 2 groups was observed at the HEWR of 60 watts; the corresponding p values at 20W and 40W were 0.08 and 0.06, respectively. Significant increases in leg discomfort ratings occurred at all sub-maximal work rates in COPD compared to health. (*) p< 0.05 denotes statistical significance. Values are means ± SE.
FIGURE 9: The selection frequency for the reason for stopping exercise in the healthy and mild COPD group. No significant differences were observed for any given reason between the 2 groups.

FIGURE 10: The selection frequency for 3 of the qualitative descriptors of breathlessness experienced at the end of exercise in the healthy and mild COPD group. While the descriptors “my breathing requires more work” and “my breathing is heavy” were selected with similar frequencies in both groups, the descriptor “breathing in requires effort” was much more common in COPD (14, or 70% of the group) compared to health (6, or 30% of the group). (*) p< 0.05 denotes statistical significance.
Section 3.2 – Effects of Added Dead Space: Within and Between Group Comparisons in Health and Mild COPD

3.2.1. – Exercise Tolerance

In the healthy group, exercise tolerance was diminished by added DS (Table 5): the peak work rate fell by 4 watts (p=0.02), a 2.5 % difference. In 13 healthy subjects, DS decreased peak work rate by an average of 9 watts, DS had no effect in four subjects and in 3 subjects, DS increased peak work rate by 9 watts. Other exercise measurements at the peak of exercise and at the HEWR of 60W in health are summarized in Tables 5 and 6, respectively.

In the mild COPD group, DS decreased exercise tolerance (Table 7): the peak work rate fell by 9 watts (p=0.001), a 10.3% difference. In 11 COPD subjects, DS decreased peak work rate by an average 17 W; DS had no effects in 8 subjects, and DS increased peak work rate (by only 1 watt) in 1 subject. Other exercise measurements at the peak of exercise and at the HEWR of 60W in COPD are summarized in Tables 7 and 8, respectively.

Comparisons between the two groups (healthy vs. mild COPD) for the magnitude of changes in selected variables in going from the CTRL to the DS condition (i.e. $\Delta = DS_{\text{measurement}} - CTRL_{\text{measurement}}$) at the peak of exercise are summarized in Table 9. The reduced peak work rate caused by DS in both groups (-4 ± 8 and -9 ± 11 W) did not differ significantly.
TABLE 5: Measurements at the peak of symptom-limited incremental cycle exercise in the healthy group during control (CTRL) and dead space (DS) conditions

<table>
<thead>
<tr>
<th></th>
<th>CTRL</th>
<th>DS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work rate (W)</td>
<td>162 ± 55</td>
<td>158 ± 57*</td>
</tr>
<tr>
<td>( \dot{V}_E ) (L/min) (%) of MVV</td>
<td>95.0 ± 30.9 (73 ± 13)</td>
<td>95.8 ± 29.7 (74 ± 10)</td>
</tr>
<tr>
<td>( P_{ETCO_2} ) (mm Hg)</td>
<td>32.2 ± 4.8</td>
<td>40.5 ± 6.3*</td>
</tr>
<tr>
<td>HR (beats/min) (%) of predicted</td>
<td>158 ± 16 (93 ± 10)</td>
<td>157 ± 13 (93 ± 8)</td>
</tr>
<tr>
<td>( \text{SpO}_2 ) (%)</td>
<td>94 ± 4</td>
<td>93 ± 5</td>
</tr>
<tr>
<td>Dyspnea, Borg scale</td>
<td>6.1 ± 3.2</td>
<td>5.9 ± 3.3</td>
</tr>
<tr>
<td>Leg discomfort, Borg scale</td>
<td>6.8 ± 3.2</td>
<td>6.4 ± 3.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for stopping exercise</th>
<th>10 %</th>
<th>25 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>65 %</td>
<td>50 %</td>
</tr>
<tr>
<td>Leg Discomfort</td>
<td>20 %</td>
<td>25 %</td>
</tr>
<tr>
<td>Dyspnea + legs</td>
<td>5 %</td>
<td>0 %</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Breathing Pattern and Operational Lung Volumes

<table>
<thead>
<tr>
<th></th>
<th>CTRL</th>
<th>DS</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_T ) (L)</td>
<td>2.26 ± 0.65</td>
<td>2.47 ± 0.76*</td>
</tr>
<tr>
<td>( V_T / IC ) (%)</td>
<td>76 ± 13</td>
<td>84 ± 11*</td>
</tr>
<tr>
<td>( V_T / \text{predicted VC} ) (%)</td>
<td>62 ± 10</td>
<td>68 ± 10*</td>
</tr>
<tr>
<td>( F_b ) (breaths/min)</td>
<td>42 ± 9</td>
<td>39 ± 7*</td>
</tr>
<tr>
<td>IC (L)</td>
<td>3.01 ± 0.86</td>
<td>2.92 ± 0.72</td>
</tr>
<tr>
<td>IRV (L) (%) of predicted TLC</td>
<td>0.74 ± 0.43 (12 ± 7)</td>
<td>0.45 ± 0.33* (8 ± 5) *</td>
</tr>
<tr>
<td>EILV (L) (%) of predicted TLC</td>
<td>5.13 ± 0.90 (88 ± 14)</td>
<td>5.40 ± 1.01* (92 ± 12) *</td>
</tr>
<tr>
<td>EELV (L) (%) of predicted TLC</td>
<td>2.87 ± 0.61 (50 ± 13)</td>
<td>2.93 ± 0.54 (51 ± 1)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: W = watts; \( \dot{V}_E \) = minute ventilation; MVV = maximal voluntary ventilation; \( P_{ETCO_2} \) = end-tidal \( CO_2 \); HR = heart rate; \( \text{SpO}_2 \) = arterial \( O_2 \) saturation; \( V_T \) = tidal volume; IC = inspiratory capacity; VC = vital capacity; \( F_b \) = breathing frequency; IRV = inspiratory reserve volume; EILV = end-inspiratory lung volume; EELV = end-expiratory lung volume.

(*) denotes significant difference (p < 0.05) between the CTRL and DS conditions. Values are means ± SD.
### TABLE 6: Measurements at the highest equivalent work rate (HEWR) of 60 watts in the healthy group during control (CTRL) and dead space (DS) conditions

<table>
<thead>
<tr>
<th></th>
<th>CTRL</th>
<th>DS</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_\dot{E}$ (L/min)</td>
<td>29.4 ± 7.4</td>
<td>40.7 ± 8.1*</td>
</tr>
<tr>
<td>$P_{ET}CO_2$ (mm Hg)</td>
<td>38.7 ± 4.2</td>
<td>42.4 ± 4.5*</td>
</tr>
<tr>
<td>SpO2 (%)</td>
<td>97 ± 1</td>
<td>96 ± 1</td>
</tr>
<tr>
<td>Dyspnea, Borg scale</td>
<td>0.6 ± 0.6</td>
<td>0.9 ± 0.7</td>
</tr>
<tr>
<td>Leg discomfort, Borg scale</td>
<td>0.7 ± 0.7</td>
<td>1.1 ± 1.0*</td>
</tr>
</tbody>
</table>

**Breathing Pattern and Operational Lung Volumes**

<table>
<thead>
<tr>
<th></th>
<th>CTRL</th>
<th>DS</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_T$ (L)</td>
<td>1.31 ± 0.25</td>
<td>1.86 ± 0.31*</td>
</tr>
<tr>
<td>$V_T$/IC (%)</td>
<td>45 ± 13</td>
<td>61 ± 9*</td>
</tr>
<tr>
<td>$V_T$/ predicted VC (%)</td>
<td>37 ± 8</td>
<td>53 ± 8*</td>
</tr>
<tr>
<td>$F_b$ (breaths/min)</td>
<td>24 ± 10</td>
<td>23 ± 6</td>
</tr>
<tr>
<td>IC (L)</td>
<td>3.13 ± 0.91</td>
<td>3.10 ± 0.67</td>
</tr>
<tr>
<td>IRV (L) (% predicted TLC)</td>
<td>1.83 ± 0.88</td>
<td>1.24 ± 0.50*</td>
</tr>
<tr>
<td>EILV (L) (% predicted TLC)</td>
<td>4.05 ± 0.78</td>
<td>4.61 ± 0.68*</td>
</tr>
<tr>
<td>EELV (L) (% predicted TLC)</td>
<td>2.74 ± 0.73</td>
<td>2.74 ± 0.60</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: $V_\dot{E}$ = minute ventilation; $P_{ET}CO_2$ = end-tidal CO$_2$; SpO2 = arterial O$_2$ saturation; $V_T$ = tidal volume; IC = inspiratory capacity; VC = vital capacity; $F_b$ = breathing frequency; IRV = inspiratory reserve volume; EILV = end-inspiratory lung volume; EELV = end-expiratory lung volume

(*) denotes significant difference (p< 0.05) between the CTRL and DS conditions. Values are means ± SD.
**TABLE 7: Measurements at the peak of symptom-limited incremental cycle exercise in the mild COPD group during control (CTRL) and dead space (DS) conditions**

<table>
<thead>
<tr>
<th></th>
<th>CTRL</th>
<th>DS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Work rate (W)</strong></td>
<td>92 ± 26</td>
<td>83 ± 28*</td>
</tr>
<tr>
<td><strong>( \dot{V}_E ) (L/min)</strong> (% of MVV)</td>
<td>55.6 ± 16.0 (69 ± 17)</td>
<td>57.5 ± 17.1 (71 ± 20)</td>
</tr>
<tr>
<td><strong>P_{ET}CO_2 (mm Hg)</strong></td>
<td>33.6 ± 4.5</td>
<td>41.4 ± 5.3*</td>
</tr>
<tr>
<td><strong>HR (beats/min)</strong> (%) predicted</td>
<td>136 ± 19 (82 ± 11)</td>
<td>133 ± 20 (81 ± 12)</td>
</tr>
<tr>
<td><strong>SpO_2 (%)</strong></td>
<td>94 ± 3</td>
<td>93 ± 4</td>
</tr>
<tr>
<td><strong>Dyspnea, Borg scale</strong></td>
<td>5.4 ± 2.0</td>
<td>6.0 ± 2.4†</td>
</tr>
<tr>
<td><strong>Leg discomfort, Borg scale</strong></td>
<td>6.2 ± 2.1</td>
<td>5.8 ± 2.3</td>
</tr>
<tr>
<td><strong>Reason for stopping exercise</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5 %</td>
<td>40 %*</td>
</tr>
<tr>
<td>Leg Discomfort</td>
<td>40 %</td>
<td>10 %</td>
</tr>
<tr>
<td>Dyspnea + legs</td>
<td>45 %</td>
<td>45 %</td>
</tr>
<tr>
<td>Other</td>
<td>10 %</td>
<td>5 %</td>
</tr>
</tbody>
</table>

**Breathing Pattern and Operational Lung Volumes**

<table>
<thead>
<tr>
<th></th>
<th>CTRL</th>
<th>DS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>( V_T ) (L)</strong></td>
<td>1.62 ± 0.41</td>
<td>1.72 ± 0.52</td>
</tr>
<tr>
<td><strong>( V_T / IC ) (%)</strong></td>
<td>68 ± 11</td>
<td>71 ± 14</td>
</tr>
<tr>
<td><strong>( V_T / \text{predicted VC} ) (%)</strong></td>
<td>47 ± 8</td>
<td>50 ± 10</td>
</tr>
<tr>
<td><strong>( F_b ) (breaths/min)</strong></td>
<td>35 ± 9</td>
<td>34 ± 7</td>
</tr>
<tr>
<td><strong>IC (L)</strong></td>
<td>2.40 ± 0.51</td>
<td>2.42 ± 0.56</td>
</tr>
<tr>
<td><strong>IRV (L)</strong> (% predicted TLC)</td>
<td>0.78 ± 0.32 (14 ± 6)</td>
<td>0.71 ± 0.41 (12 ± 8)</td>
</tr>
<tr>
<td><strong>EILV (L)</strong> (% predicted TLC)</td>
<td>5.16 ± 0.84 (90 ± 7)</td>
<td>5.25 ± 0.91 (91 ± 8)</td>
</tr>
<tr>
<td><strong>EELV (L)</strong> (% predicted TLC)</td>
<td>3.54 ± 0.64 (62 ± 8)</td>
<td>3.53 ± 0.63 (62 ± 8)</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** W = watts; \( \dot{V}_E \) = minute ventilation; MVV = maximal voluntary ventilation; P_{ET}CO_2 = end-tidal CO₂; HR = heart rate; SpO₂ = arterial O₂ saturation; \( V_T \) = tidal volume; IC = inspiratory capacity; VC = vital capacity; \( F_b \) = breathing frequency; IRV = inspiratory reserve volume; EILV = end-inspiratory lung volume; EELV = end-expiratory lung volume

(*) denotes significant difference (p< 0.05) between the CTRL and DS conditions. Values are means ± SD.

(†) p=0.05 CTRL vs. DS
TABLE 8: Measurements at the highest equivalent work rate (HEWR) of 60 watts in the mild COPD group during control (CTRL) and dead space (DS) conditions

<table>
<thead>
<tr>
<th>Table 8</th>
<th>CTRL</th>
<th>DS</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V\dot{E}$ (L/min)</td>
<td>$35.5 \pm 8.1$</td>
<td>$43.3 \pm 10.8^*$</td>
</tr>
<tr>
<td>$P_{ETCO_2}$ (mm Hg)</td>
<td>$35.8 \pm 4.9$</td>
<td>$41.4 \pm 5.0^*$</td>
</tr>
<tr>
<td>$SpO_2$ (%)</td>
<td>$96 \pm 2$</td>
<td>$95 \pm 2^*$</td>
</tr>
<tr>
<td>Dyspnea, Borg scale</td>
<td>$1.7 \pm 1.6$</td>
<td>$3.2 \pm 2.3^*$</td>
</tr>
<tr>
<td>Leg discomfort, Borg scale</td>
<td>$2.3 \pm 1.8$</td>
<td>$3.2 \pm 1.7^*$</td>
</tr>
</tbody>
</table>

**Breathing Pattern and Operational Lung Volumes**

<table>
<thead>
<tr>
<th>Table 8</th>
<th>CTRL</th>
<th>DS</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_T$ (L)</td>
<td>$1.41 \pm 0.24$</td>
<td>$1.65 \pm 0.41^*$</td>
</tr>
<tr>
<td>$V_T$/IC (%)</td>
<td>$55 \pm 11$</td>
<td>$66 \pm 15^*$</td>
</tr>
<tr>
<td>$V_T$/predicted VC (%)</td>
<td>$42 \pm 8$</td>
<td>$47 \pm 8^*$</td>
</tr>
<tr>
<td>$F_b$ (breaths/min)</td>
<td>$26 \pm 8$</td>
<td>$27 \pm 7$</td>
</tr>
<tr>
<td>IC (L)</td>
<td>$2.64 \pm 0.58$</td>
<td>$2.58 \pm 0.68$</td>
</tr>
<tr>
<td>IRV (L)</td>
<td>$1.23 \pm 0.51$</td>
<td>$0.94 \pm 0.50^*$</td>
</tr>
<tr>
<td>(% predicted TLC)</td>
<td>$(21 \pm 8)$</td>
<td>$(16 \pm 9)^*$</td>
</tr>
<tr>
<td>EILV (L)</td>
<td>$4.71 \pm 0.83$</td>
<td>$5.03 \pm 0.84^*$</td>
</tr>
<tr>
<td>(% predicted TLC)</td>
<td>$(82 \pm 11)$</td>
<td>$(88 \pm 9)^*$</td>
</tr>
<tr>
<td>EELV (L)</td>
<td>$3.31 \pm 0.75$</td>
<td>$3.38 \pm 0.64$</td>
</tr>
<tr>
<td>(% predicted TLC)</td>
<td>$(58 \pm 11)$</td>
<td>$(59 \pm 9)$</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** $V\dot{E}$ = minute ventilation; $P_{ETCO_2}$ = end-tidal CO$_2$; $SpO_2$ = arterial O$_2$ saturation; $V_T$ = tidal volume; IC = inspiratory capacity; VC = vital capacity; $F_b$ = breathing frequency; IRV = inspiratory reserve volume; EILV = end-inspiratory lung volume; EELV = end-expiratory lung volume

(*) denotes significant difference ($p< 0.05$) between the CTRL and DS conditions. Values are means ± SD.

*There are only n=18 COPD subjects with 60W data during the DS condition.*
TABLE 9: Measurements at the peak of symptom-limited incremental cycle exercise comparing the magnitude of change between the CTRL and DS conditions for the healthy and mild COPD group

<table>
<thead>
<tr>
<th></th>
<th>∆ Healthy (DS – CTRL)</th>
<th>∆ COPD (DS – CTRL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work rate (W)</td>
<td>-4 ± 8</td>
<td>-9 ± 11</td>
</tr>
<tr>
<td>$V_e$ (L/min)</td>
<td>0.82 ± 12.13</td>
<td>1.88 ± 8.81</td>
</tr>
<tr>
<td>$P_{ETCO_2}$ (mm Hg)</td>
<td>8.3 ± 3.3</td>
<td>7.8 ± 3.7</td>
</tr>
<tr>
<td>$SpO_2$ (%)</td>
<td>-1 ± 3</td>
<td>-1 ± 5</td>
</tr>
<tr>
<td>Dyspnea, Borg scale</td>
<td>-0.2 ± 1.3</td>
<td>0.9 ± 1.7*</td>
</tr>
<tr>
<td>Leg discomfort, Borg scale</td>
<td>-0.4 ± 1.2</td>
<td>-0.1 ± 1.6</td>
</tr>
</tbody>
</table>

Breathing Pattern and Operational Lung Volumes

<table>
<thead>
<tr>
<th></th>
<th>∆ Healthy (DS – CTRL)</th>
<th>∆ COPD (DS – CTRL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_T$ (L)</td>
<td>0.20 ± 0.21</td>
<td>0.10 ± 0.24</td>
</tr>
<tr>
<td>$V_T$/IC (%)</td>
<td>8 ± 14</td>
<td>3 ± 11</td>
</tr>
<tr>
<td>$V_T$/ predicted VC (%)</td>
<td>5 ± 5</td>
<td>2 ± 8</td>
</tr>
<tr>
<td>$F_b$ (breaths/min)</td>
<td>-3 ± 6</td>
<td>-1 ± 6</td>
</tr>
<tr>
<td>IC (L)</td>
<td>-0.09 ± 0.38</td>
<td>0.03 ± 0.28</td>
</tr>
<tr>
<td>IRV (L) (% predicted TLC)</td>
<td>-0.30 ± 0.47</td>
<td>-0.07 ± 0.33</td>
</tr>
<tr>
<td></td>
<td>(-5 ± 8)</td>
<td>(-1± 6)</td>
</tr>
<tr>
<td>EILV (L) (% predicted TLC)</td>
<td>0.27 ± 0.42</td>
<td>0.08 ± 0.44</td>
</tr>
<tr>
<td></td>
<td>(4 ± 7)</td>
<td>(1 ± 8)</td>
</tr>
<tr>
<td>EELV (L) (% predicted TLC)</td>
<td>0.06 ± 0.33</td>
<td>-0.02 ± 0.37</td>
</tr>
<tr>
<td></td>
<td>(1 ± 5)</td>
<td>(0 ± 7)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: $W =$ watts; $V_e =$ minute ventilation; $P_{ETCO_2} =$ end-tidal CO$_2$; $SpO_2 =$ arterial O$_2$ saturation; $V_T =$ tidal volume; IC = inspiratory capacity; VC = vital capacity; $F_b =$ breathing frequency; IRV = inspiratory reserve volume; EILV = end-inspiratory lung volume; EELV = end-expiratory lung volume (*) denotes significant difference (p< 0.05) for the magnitude of change between the CTRL and DS conditions for the healthy and mild COPD group. Values are means ± SD.
3.2.2. – Ventilation

In health, the added DS significantly increased $\dot{V}_E$ at rest and at all submaximal work rates; $\dot{V}_E$ was increased by 7.6 L/min ($p<0.0005$) at rest and by 10.5-11.3 L/min ($p<0.0005$) during exercise (Figure 11A). The ventilation at the peak of exercise, however, was not significantly different ($p=0.766$) from the CTRL condition (Table 5). There was some ventilatory reserve left at peak exercise under both conditions. Indeed, ventilation (expressed as a % of MVV) reached 73% and 74% during the CTRL and DS conditions, respectively. It is interesting to note that 35% of the healthy group (n=7) did actually increase peak ventilation with the added DS by an average of 14.5 L/min. The rest of the group (n=13) who did not increase peak ventilation had an average reduction of 6.5 L/min.

In COPD, the added DS also significantly increased ventilation at rest and at all submaximal work rates; ventilation was increased by 7.4 L/min ($p<0.0005$) at rest and by 9.3-10.5 L/min ($p<0.0005$) during exercise (Figure 11B). The ventilation at the peak of exercise was also not significantly different ($p=0.35$) from the CTRL condition (Table 7). There was also some ventilatory reserve at peak exercise in both conditions: ventilation (% of MVV) reached 69% and 71% during the CTRL and DS conditions, respectively. Similar to that in health, some subjects with COPD (n=7) actually increased peak ventilation with the added DS while others (n=13) did not. Those who increased their peak ventilation with the DS did so by an average of 11.8 L/min and those who did not had an average reduction of 2.4 L/min.
FIGURE 11: The effects of added dead space on ventilation in health (panel A) and mild COPD (panel B). (*) p< 0.05 denotes statistical significance. Values are means ± SE.
3.2.3. – Tidal Volume

In health, the added DS significantly increased $V_T$ at rest, throughout exercise, and at the peak of exercise (Figure 12A). Seventeen healthy subjects increased their peak $V_T$ by $+0.25 \pm 0.19$ L, while 3 subjects had a slight decrease of $-0.07 \pm 0.05$ L.

In COPD, the added DS significantly increased $V_T$ during rest and throughout exercise (Figure 12B); however, at the peak of exercise, $V_T$ did not increase significantly. Twelve COPD subjects increased their peak $V_T$ by $+0.25 \pm 0.11$ L, while 8 subjects decreased it by $-0.13 \pm 0.19$ L.

Between group comparisons (health vs. COPD) of the magnitude of increase in $V_T$ due to the added DS revealed significant differences (Figure 12C). Compared to COPD, the increase in $V_T$ was consistently larger at rest, throughout, and at the peak of exercise in the healthy group; significant increases were observed during all submaximal work rates ($p<0.01$). In health, the magnitude of the $V_T$ increase with the DS was 0.60 L, 0.59 L, and 0.56 L at 20, 40, and 60 watts, respectively. In contrast, in COPD, the magnitude of $V_T$ increase with the DS was 0.43 L, 0.35 L, and 0.26 L at 20, 40, and 60 watts, respectively. At the peak of exercise, the increase was $+0.20 \pm 0.21$ L in health vs. $+0.10 \pm 0.24$ L in COPD, although this difference did not reach significance ($p=0.15$).
FIGURE 12: The effects of added dead space on the tidal volume response in health (panel A) and mild COPD (panel B). Panel C compares the magnitude of change in the tidal volume with added DS between the two groups. The shaded area represents the magnitude of change in the COPD group. (*) p< 0.05 denotes statistical significance. Values are means ± SE.
3.2.4. – Breathing Frequency

In health, the breathing frequency ($F_b$) response with the added DS was similar at rest and at all submaximal work rates (Figure 13A). $F_b$ in the CTRL and DS conditions, respectively, were $22 \pm 12$ vs. $20 \pm 5$ at $20$ W, $23 \pm 10$ vs. $21 \pm 5$ at $40$ W, and $24 \pm 10$ vs. $23 \pm 6$ at $60$W; these differences were not statistically significant. However, $F_b$ at peak exercise with DS decreased significantly (Table 5): $39 \pm 7$ vs. $42 \pm 9$ breaths/min during DS and CTRL, respectively (p< 0.05).

In COPD, the $F_b$ response with DS was also similar to that during CTRL at rest and at all submaximal work rates (Figure 13B). In contrast to the healthy group at the peak of exercise, $F_b$ did not differ between the two conditions in COPD (DS: $34 \pm 7$ vs. CTRL: $35 \pm 9$ breaths/min; Table 7).

Between group comparisons (health vs. COPD) for the magnitude of change in $F_b$ with added DS showed that $F_b$ did not differ significantly at rest, during, and at the peak of exercise (Figure 13C and Table 9). Despite this, there was an evident upward shift in the $F_b$ in the COPD group, indicating that for any one condition (i.e. CTRL or DS), they were breathing faster than the healthy subjects.
The effects of added dead space on breathing frequency in health (panel A) and mild COPD (panel B). Panel C compares the magnitudes of changes in the breathing frequency with the added DS between the two groups. The shaded area represents the magnitude of change in the COPD group. (*) p<0.05 denotes statistical significance. Values are means ± SE.

**FIGURE 13:** The effects of added dead space on breathing frequency in health (panel A) and mild COPD (panel B). Panel C compares the magnitudes of changes in the breathing frequency with the added DS between the two groups. The shaded area represents the magnitude of change in the COPD group. (*) p<0.05 denotes statistical significance. Values are means ± SE.
3.2.5. – Operating Lung Volumes: End-Inspiratory Lung Volume (EILV) and End-Expiratory Lung Volume (EELV)

In health, the added DS had no significant effect on the EELV at rest, during, and at the peak of exercise (Figure 14A). Thus, at rest, the EELV were 51% and 53% (of predicted TLC) during the CTRL and DS conditions, respectively. This remained unchanged even at the peak of exercise, when the EELV were 50% and 51% (of predicted TLC) during CTRL and DS conditions, respectively. In contrast, the EILV increased significantly at rest and throughout exercise with the added DS (Figure 14A). Even at peak exercise, the healthy group still significantly increased their EILV from 5.13 L (88% predicted TLC) during the CTRL condition, to 5.40 L (92% predicted TLC; p<0.05) under the DS. This increase in EILV reflected the increased V_T induced by the added DS.

Similar to that in health, the added DS in COPD also had no significant effect on the response of the end-expiratory lung volume (EELV) at rest and throughout exercise (Figure 14B). EILV also significantly increased at rest and at all sub-maximal work rates with the added DS (Figure 14B), just as in the healthy group. However, the major difference in the COPD group was that the EILV failed to increase at the peak of exercise under the DS. Indeed, the EILV was almost identical during the CTRL (5.16 L, 90% predicted TLC) and DS conditions (5.25 L, 91% of predicted TLC; p=0.41).
FIGURE 14: The effects of added dead space on the operating lung volume responses in health (panel A) and mild COPD (panel B). The shaded area represents the shift in the operating lung volumes under DS in both groups. Similar responses of EELV were observed in the CTRL and DS conditions in both groups. The EILV could not be further increased with the added DS at the peak of exercise in the COPD group. Abbreviations: EILV = end-inspiratory lung volume; EELV = end-expiratory lung volume; IRV = inspiratory reserve volume; TLC = total lung capacity. (*) p< 0.05 denotes statistical significance. Values are means ± SE.
3.2.6. – Inspiratory Reserve Volume (IRV)

In health, the added DS caused the IRV (expressed as % predicted TLC) to continuously and significantly decline at rest, at all sub-maximal work rates, and at the peak of exercise (Figure 15A). Thus, at rest, the IRV were 37% and 27% (of predicted TLC) during the CTRL and DS conditions, respectively. At the HEWR of 60 watts, the IRV fell to 30% and 21% (of predicted TLC) during the CTRL and DS conditions, respectively. The IRV was further reduced at the peak of exercise to 12% and 8% (of predicted TLC) during the CTRL and DS conditions, respectively. Compared to CTRL, these significant reductions in the IRV during DS are consistent with the continued ability of the healthy subjects to significantly increase their V\textsubscript{T} by increasing EILV, as demonstrated in the previous section.

Analogous to the response in health, in COPD, the added DS also caused the IRV to continuously and significantly decrease at rest and at all sub-maximal work rates (Figure 15B). Thus, at rest, the IRV were 35% and 26% (of predicted TLC) during the CTRL and DS conditions, respectively. At the HEWR of 60 watts, the IRV fell to 21% and 16% (of predicted TLC) during the CTRL and DS conditions, respectively. However, the major difference in the COPD group was that the IRV failed to decrease at the peak of exercise under the DS condition. Therefore, the IRV was almost identical between the two conditions (CTRL: 14% of predicted TLC vs. DS: 12% of predicted TLC). Compared to CTRL, the inability to significantly diminish IRV under the DS condition at the peak of exercise is consistent with the inability of the COPD subjects to significantly increase their V\textsubscript{T} and EILV, as demonstrated in the previous section.

Between group comparisons (health vs. COPD) for the magnitude of decrease in the IRV revealed that compared to COPD, the magnitude of decrease was consistently greater in the healthy group at rest, throughout exercise, and at the peak of exercise (Figure 15C). The magnitude of decrease, however, reached significance (p< 0.05) only at 40 watts when the ΔIRV
(ΔIRV = IRV_{DS} − IRV_{CTRL}) was -12 ± 7% (of predicted TLC) in health and -7 ± 5% (of predicted TLC) in COPD. Altogether, this pattern of response in the IRV indicates that in health, there is greater “room” for the $V_T$ to expand by eroding into the IRV.
FIGURE 15: The effects of added dead space on the inspiratory reserve volume in health (panel A) and mild COPD (panel B). Panel C compares the magnitude of change in the inspiratory reserve volume with the added DS between the two groups. The shaded area represents the magnitude of change in the COPD group. (*) p< 0.05 denotes statistical significance. Values are means ± SE.
3.2.7. – Heart Rate (HR)

In health, DS had no significant effect on HR (beats/min) at rest (Figure 16A). Added DS resulted in a 3.4 beats/min increase at 20 watts (p<0.05). Although this difference of approximately 3 beats/min was maintained at standardized work rates thereafter, it did not reach statistical significance. The HR at peak exercise did not differ between the two conditions: 158 ± 16 beats/min (CTRL) vs. 157 ± 13 beats/min (DS).

In COPD, DS also increased the HR (Figure 16B). At the work rate of 20 watts, compared to CTRL, DS increased HR by an average of 4 beats/min (p= 0.05); this difference increased to 5 beats/min at 40 and 60 watts (p< 0.05). The HRs at peak exercise did not differ between the two conditions: 136 ± 19 beats/min (CTRL) vs. 133 ± 20 beats/min (DS).
**FIGURE 16:** The effects of added dead space on the heart rate response in health (panel A) and mild COPD (panel B). (*) p< 0.05 denotes statistical significance. Values are means ± SE.
3.2.8. – Sensory Consequences

Dyspnea

In health, the added DS had no influence on the dyspnea intensity at rest, at any given work rate, and at the peak of exercise: the dyspnea vs. work rate relations were similar (Figure 17A). The Borg dyspnea scores at the peak of exercise during the CTRL and DS conditions were 6.1 ± 3.2 and 5.9 ± 3.3, respectively.

In COPD, the added DS did not influence dyspnea intensity at rest and at 20 watts (Figure 17B). However, the added DS resulted in significant increases in dyspnea ratings at 40 watts (by 0.5 Borg units) and at 60 watts (p< 0.05); the Borg dyspnea scores at 60 watts during the CTRL and DS conditions were 1.7 ± 1.6 and 3.2 ± 2.3, respectively. Dyspnea ratings were also greater with the added DS at the peak of exercise (p= 0.05); the Borg scores were 6.0 ± 2.4 and 5.4 ± 2.0 for the DS and CTRL conditions, respectively.

Between group comparisons (health vs. COPD) for the magnitude of increase in dyspnea ratings with the added DS revealed significant differences at 60 watts and at the peak of exercise (Figure 17C). At 40 watts in the COPD group, the magnitude of increase in dyspnea intensity with the DS (+0.5 ± 0.9 Borg units) was greater than that in the healthy group (+0.1 ± 0.3 Borg units, p = 0.06). At 60 watts, the magnitude of increase for the COPD group (+1.8 ± 1.8) was also greater than that in health (+0.2 ± 0.6, p<0.0001). Finally, at the peak of exercise, the magnitude of increase with the DS for the COPD group was (+0.9 ± 1.7) compared to that in health (-0.2 ± 1.3, p<0.05). Thus, the added DS resulted in relatively greater dyspnea intensity levels for the mild COPD group compared to that in health.
FIGURE 17: The effects of added dead space on dyspnea ratings (Borg scale) in health (panel A) and mild COPD (panel B). Panel C compares the magnitude of change in the dyspnea ratings with the added DS between the two groups. The shaded area represents the magnitude of change in the COPD group. (*) p< 0.05 denotes statistical significance. Values are means ± SE.
Figure 18 illustrates dyspnea intensity as a function of $\dot{V}_E$. Compared to health, COPD subjects had higher dyspnea ratings at any given $\dot{V}_E$; this is more apparent at $\dot{V}_E$ above 40 L/min (Figure 18A). Stated differently, compared to health, dyspnea intensity increased disproportionately in COPD, as demonstrated by the steeper slope.

In health, the dyspnea/$\dot{V}_E$ relation with the added DS was similar to that of the CTRL condition (Figure 18B). At the HEWR comparison of 60 watts, the dyspnea intensities were almost identical.

In COPD, compared to the CTRL condition, dyspnea and $\dot{V}_E$ increased along the same slope with the added DS (Figure 18C). However, at the HEWR comparison of 60 watts, dyspnea intensity was significantly higher with the DS (3.2 Borg units) compared to the CTRL condition (1.7 Borg units).
FIGURE 18: Dyspnea intensity (Borg scale) vs. ventilation for the healthy and mild COPD group in the CTRL condition (panel A). Compared to health, the dyspnea/$V_E$ slope was visibly steeper in the COPD group. Panel B illustrates the dyspnea/$V_E$ relation in health for the CTRL and DS conditions; panel C also illustrates the dyspnea/$V_E$ relation in mild COPD for the two test conditions. At the HEWR of 60 W in the healthy group, the $V_E$ was 29.4 L/min during CTRL and 40.7 L/min during DS, with corresponding dyspnea ratings of 0.6 and 0.9 Borg units, respectively. At the HEWR in mild COPD, the $V_E$ was 35.5 L/min during CTRL and 44.3 L/min during DS, with corresponding dyspnea ratings of 1.7 and 3.2 Borg units, respectively. Values are means ± SE.
3.2.9. – Reasons for Stopping Exercise

Reasons for stopping exercise under CTRL and DS conditions in both groups are illustrated in Figure 19. In the healthy group (panel A), none of the 3 options in the reasons for stopping the exercise test were significantly different between the CTRL and DS conditions.

In the COPD group (panel B), key differences were observed in the reasons for stopping exercise between the 2 test conditions. Significantly more COPD subjects (8, or 40% of the group) chose breathing discomfort as the primary reason for stopping exercise during the DS condition, compared to only 1 (5%) of the group during the CTRL condition. In stark contrast, leg discomfort was the primary reason for stopping exercise in more COPD subjects (8, or 40% of the group) during the CTRL condition, compared to only 2 (10% of the group) during the DS condition. Thus, the DS caused significantly more people in the COPD group to select breathing discomfort as the primary reason for stopping exercise. In contrast, more people in the COPD group selected leg discomfort as the primary reason for stopping exercise when they were cycling under the CTRL condition compared to the added DS.
FIGURE 19: The selection frequency for the reasons for stopping cycle exercise in the healthy (panel A) and mild COPD group (panel B). No significant differences were observed for any given reason between the CTRL and DS conditions in the healthy group. In contrast, clear differences in the selection frequencies for breathing and leg discomfort were reported depending on the test conditions (CTRL or DS) in the mild COPD group.
CHAPTER 4: DISCUSSION

Section 4.1 – Original Findings

This is the first study to examine the role of mechanical respiratory factors in limiting exercise capacity in patients with milder forms of COPD. The main findings of this study were as follows: 1) we confirmed that patients with mild COPD had greater respiratory impairment (i.e. significantly lower expiratory flow rates and diffusing capacity for carbon monoxide, and peripheral airway dysfunction), exercise intolerance, lower peak ventilation, and greater dyspnea than age-matched healthy individuals; 2) on average, added DS was associated with small decreases in peak work rate and no significant increase in peak ventilation in both health and COPD; 3) critical mechanical constraints on tidal volume expansion was present only in COPD; in contrast to health, EILV and \( V_T \) failed to increase at the peak of exercise in COPD despite the increased ventilatory stimulation; and 4) while added DS had no effect on dyspnea in health, intensity ratings consistently increased at submaximal work rates in the mild COPD group.

Section 4.2 – Characterization of the Study Sample

Our sample of older healthy subjects provided a good representation of a generalized older healthy population. They had almost no smoking history and no chronic activity-related dyspnea. Their pulmonary function tests revealed no airflow obstruction (FEV\(_1\)/FVC >70\%) and all subjects were above their predicted FEV\(_1\)/FVC LLN. Our healthy sample also had a normal exercise capacity; their peak VO\(_2\) (L/min) was 103\% of predicted.

Our sample of COPD subjects was classified as having mild COPD according to the GOLD stage I criteria (Rabe \textit{et al.} 2007). Compared to health, they had a significantly greater smoking history, increased levels of chronic activity-related dyspnea, and almost all subjects (n=17) had a FEV\(_1\)/FVC ratio below their predicted LLN. Our COPD sample also had remarkably preserved
spirometry (FEV₁ of 95% predicted), although the presence of small airways dysfunction was already evident. Thirteen of the 20 COPD subjects had already seen a physician and were given a prior diagnosis of mild COPD; 12 of them were already using respiratory medications when they entered our study.

Section 4.3 – Cardiopulmonary Exercise Responses in Mild COPD

Section 4.3.1. – Exercise Capacity

Despite the fact that patients with mild COPD had relatively preserved spirometry (FEV₁ 95% of predicted), their exercise capacity as measured by the peak work rate and VO₂ were significantly reduced compared with the healthy subjects (Table 3). Indeed, peak power output and VO₂ (L/min) was substantially lower than health by 57% and 43%, respectively. When normalized with respect to body mass, the COPD group had a peak VO₂ of only 21.2 mL/min/kg compared with 32.0 mL/min/kg in health; these values are consistent with a recent study in symptomatic mild COPD (Ofir et al. 2008). This finding compliments the current understanding that resting pulmonary function tests cannot reliably predict functional capacity (ATS, 2003). The peak VO₂ represents the gold standard for the evaluation of cardio-respiratory fitness and the assessment of exercise capacity (Weisman & Zeballos, 2002). When expressed as a percent of predicted, the VO₂ peak (L/min) averaged 103% of predicted for the healthy group, compared to a significant reduction in COPD (71% of predicted). A low peak VO₂ has important clinical implications, as it can predict survival independent of age and the FEV₁ (Oga et al. 2003). Additionally, measures of health status correlate better with exercise capacity than any resting measurement (Oga et al. 2002). The relatively reduced peak VO₂ in the mild COPD group was expected because of their reduced habitual physical activity levels (Table 1; CHAMPS values). In fact, their reduced exercise capacity and dyspnea may have prevented or shortened the duration
of certain physical activities compared to their healthy counterparts who had greater cardiorespiratory fitness.

Section 4.3.2. – Ventilatory Demand

Compared to health, the ventilatory response to exercise was abnormal in mild COPD as it was consistently elevated at any given sub-maximal work rate; a significant increase of 6 L/min was observed at the standardized work rate of 60 watts (Figure 4A). The increased ventilation in our mild COPD group is consistent with findings in patients with moderate-to-severe (Jones et al. 1971; O’Donnell et al. 2001b) and symptomatic mild COPD (Ofir et al. 2008). The possible sources for the increased submaximal ventilation are shown in the following equation (Jones, 1997):

$$\dot{V}_E = \frac{[863 \times \dot{V}_{CO_2}]}{[P_{aCO_2} (1 - V_D/V_T)]}$$

where $\dot{V}_{CO_2}$ is the carbon dioxide output, $P_{aCO_2}$ is the regulated arterial partial pressure of carbon dioxide, and $V_D/V_T$ is the physiologic dead space-to-tidal volume ratio. The $V_D/V_T$ is referred to as “wasted ventilation” as it represents the fraction of each breath that is used to ventilate the anatomic dead space and the unperfused alveoli. A high physiological dead space ($V_D$) that does not decline (as normally occurs) during exercise represents the primary stimulus for the increased ventilatory demand (i.e. increased ventilation) in moderate-to-severe COPD (Dantzker & D’Alonzo, 1986; O’Donnell, 2001c). A high $V_D$ is the result of greater ventilation-perfusion [$\dot{V}/Q$] abnormalities in both severe and mild COPD (Barbera et al. 1994), and is believed to be a major contributory cause for the increased ventilatory demand (Figure 4A). Indeed, the finding that the $\dot{V}_E/\dot{V}_{CO_2}$ ratio was slightly but consistently elevated in COPD compared with health (Figure 4B) suggests reduced efficiency of CO$_2$ elimination due to the
higher $V_D$. Additionally, the lower diffusing capacity ($DL_{CO}$) in our COPD subjects (Table 2) reflects a reduced surface area for pulmonary gas exchange, secondary to emphysema, that can also contribute to a higher $V_D$. A higher $V_D$, however, is not the only possible source for the increased $V_E$ in mild COPD. The reduction in $P_{ET}CO_2$ compared with health (Figure 4C) suggests the possible presence of alveolar hyperventilation due to a lower set-point for arterial carbon dioxide ($P_{aCO_2}$) of the ventilatory control system.

Other factors contributing to the increased ventilation in COPD (in general) include a greater metabolic demand (i.e. increased $VCO_2$ for a given work load), and hypoxemia or hypercapnia (Dantzker & D’Alonzo, 1986; Barbera et al, 1991; O’Donnell, 2001; O’Donnell & Webb, 2003). However, an increased metabolic demand ($VCO_2$) near end exercise in our patients with COPD was certainly plausible. Compared to health, our COPD subjects had a significantly lower anaerobic threshold by 31% (section 3.1.4.), higher submaximal HR (Table 4), and greater leg discomfort throughout exercise (Figure 8B). Collectively, these results suggest that our COPD group, who had a more sedentary lifestyle, were more likely to be deconditioned. Therefore, it is possible that the higher ventilation at comparable work rates near end exercise may reflect additional stimulation from earlier lactic acidosis in some individuals with COPD. Importantly, there is now an increased recognition for the importance of deconditioning and the associated skeletal muscle dysfunction as a contributing factor in exercise limitation (which is potentially reversible) in patients with cardio-respiratory disease (ATS, 2003). The significantly earlier occurrence of the AT along with the higher submaximal HR may also indicate cardiac dysfunction even in patients with mild forms of COPD. A recent study by Malerba et al. (2011) concluded that sub-clinical left ventricular diastolic dysfunction was present in the majority (70.9 \%) of their sample of 55 COPD patients at the earlier stage of this disease.
There was no evidence to suggest that critical hypoxemia occurred as \( \text{SpO}_2 \) levels were normal throughout and at the peak of exercise. Although an impaired ventilatory efficiency (i.e. greater \( \dot{V}_E/\dot{V}\text{CO}_2 \) ratio) was present in COPD, this was not sufficiently compromised to result in significant reductions in their \( \text{SpO}_2 \) during exercise as a result of hypercapnia (Table 3, 4). Although it was not possible to accurately determine \( P_{a\text{CO}_2} \) levels by non-invasive methods (ATS, 2003), the consistently lower \( P_{ET\text{CO}_2} \) levels in the mild COPD group suggest a preserved compensatory hyperpnea at the end of exercise. Lastly, any alterations in the control of breathing in mild COPD were beyond the scope of this study; experiments utilizing the re-breathing technique would be ideal to address this question.

**Section 4.3.3. – Dynamic Mechanical Abnormalities**

Considerable dysfunction of the small airways was present in the mild COPD group. Indeed, compared to health, subjects with COPD had significantly reduced peak- and mid-expiratory flow rates, mal-distribution of ventilation (i.e. greater \( N_2 \) slope) as assessed by the \( N_2 \) washout test, and impulse oscillometry revealed a frequency-dependant increase in airway resistance (i.e. relatively greater \( R_{5-20} \) value) (Table 2). Given these indications of small airways dysfunction at rest, it is possible that negative mechanical and sensory consequences would be manifested during the increased ventilatory demand of exercise. Thus, DH (progressive air trapping) was observed in the COPD group but not in health: IC decreased by 0.30 L from rest to peak exercise in COPD compared to a slight increase of 0.06 L in health (Figure 5A). A previous study in patients with GOLD stage II COPD (Babb et al. 1991) showed that the IC decreased by 0.42 L; another study in patients with moderate-to-severe COPD showed a similar decrease in the IC by 0.37 L, but at considerably earlier time points during exercise when the ventilation and work rate were at much lower levels than in our patients. Not surprisingly, the reduction in dynamic IC in our COPD subjects was associated with restrictive constraints on
volume expansion during exercise, as the EELV and EILV were consistently elevated (Figure 5B), and the maximum $V_T$ achieved was significantly less in COPD compared to health (Table 3). In keeping with previous studies (O’Donnell et al. 2001b; Ofir et al. 2008), the majority (17 of 20, or 85%) of our mild COPD patients showed dynamic increases in EELV from rest to peak exercise. The corollary of this is that, on average, the $V_T/V_E$ inflection or plateau occurred at a substantially lower $V_E$ in COPD patients compared to health (37 L/min vs. 46 L/min, respectively; Figure 6). This plateau marks the point at which the dynamic IRV reaches its minimal value and the elastic work of breathing is increased as the $V_T$ becomes positioned close to TLC (Laveneziana et al. 2007). The greater ventilatory constraints experienced in our COPD group is consistent with the finding of a greater degree of expiratory flow limitation (EFL) at a relatively earlier stage of exercise compared to health, as crudely estimated by flow-volume loop analysis (Table 3).

The mechanical abnormalities in COPD were simultaneously associated with greater dyspnea during exercise (Figure 8A). This observation has been previously established in symptomatic mild COPD and in patients with more severe airflow obstruction (Ofir et al. 2008; O’Donnell et al. 1998, 2001b). In the former group, the $V_T/IC$ ratio (an index of the constraints on $V_T$ expansion) correlated best with dyspnea intensity during exercise (Ofir et al. 2008). Although the exact mechanisms by which dynamic hyperinflation leads to dyspnea are unknown, it is possible that the dyspnea sensation arises from the increased inspiratory muscular effort required to sustain ventilation in the face of continued volume constraints (i.e. mechanical loading). As such, although the qualitative descriptors “my breathing requires more work” and “my breathing is heavy” were selected with similar frequencies in both groups, the descriptor “breathing in requires more effort” was more common in COPD (Figure 10). In addition to mechanical abnormalities, increased ventilation in our COPD subjects may also have contributed
to the increased dyspnea. Although dyspnea ratings were not different at the limits of tolerance in both mild COPD and health, it must be appreciated that the similar peak dyspnea ratings (Borg unit of ~ 5-6; “strong” breathing discomfort) occurred at a substantially lower work rate in the COPD group (Figure 8A)

**Section 4.4 – DS Loading in the Healthy Elderly**

Previous studies that have examined the effects of DS loading have primarily been conducted on young (20-40 yrs) untrained healthy individuals (McParland et al. 1991; Syabbalo et al. 1993; O’Donnell et al. 2000). These studies have convincingly demonstrated the stimulatory effects of an added DS and have concluded that ventilatory limitation does not normally contribute to exercise limitation. Indeed, significant increases in ventilation occur at rest and during exercise during DS loading. Importantly, the peak $\dot{V}_E$ (and $V_T$) increased at end exercise while the peak work rate remained similar to that in the unloaded control condition. For example, McParland et al. (1991) found that healthy subjects increased their peak $\dot{V}_E$ from 134 L/min (under CTRL) to 147 L/min with the added DS; the exercise tolerance was slightly (but not significantly) less during DS loading compared to CTRL [peak $\dot{V}O_2$ of 3.57 L/min (106 % predicted) vs. 3.86 L/min (115 % predicted), respectively]. In another study, O’Donnell et al. (2000) found that healthy young subjects increased their peak $\dot{V}_E$ from 87 L/min (CTRL) to 96 L/min (DS) while the work rate fell by 4% (of predicted max work rate) with the added DS.

To our knowledge, this is the first study determining the effects of DS loading during exercise in older individuals, in whom responses may be more variable (Johnson et al. 1994; Johnson, 2002). The added DS provided noticeable stimulatory effects in our healthy older group, as significant increases in resting and sub-maximal $\dot{V}_E$ was observed (Figure 11A). Compared to the CTRL condition, although significant $V_T$ expansion occurred at rest, throughout, and at the
peak of exercise with the DS (Figure 12A), the $V_E$ at the peak of exercise remained similar in both conditions. This finding differs from studies whereby subjects were capable of increasing their peak $V_E$ at maximal exercise. It is important to realize that the average age of our healthy group was 65 years, considerably greater than the younger subjects studied previously where the ages ranged between 20-40 years (McParland et al. 1991; Syabbalo et al. 1993; O’Donnell et al. 2000). This discrepancy is likely due to the age-related impairment in respiratory function. Thus, the well described age-related impairment of respiratory mechanics and pulmonary gas exchange may result in a ventilatory limit to exercise performance in some older individuals, particularly in fitter individuals who are able to achieve higher work rates (Johnson et al. 1994; Johnson, 2002).

The aging lung displays two major structural changes. The first is a reduced elastic recoil pressure due to changes in the arrangement of the lungs’ elastin and collagen fibers (Lovering et al. 2005). The second is a decreased surface area of the lung for gas exchange due to loss of alveoli; the alveolar size actually increases with age (Thurlbeck, 1991). Together, the reduced elastic recoil with the attendant loss of supporting alveolar attachments to the small airways renders them more likely to close during forced expirations. The characteristic “scooping” of the maximal flow volume loop (MFVL) relative to the healthy young reflects these age-related changes (Whipp et al. 2007; Figure 7). During the high metabolic and ventilatory demands of exercise, these age-induced pulmonary changes predispose older healthy subjects to EFL, which is characterized by the intersection and/or overlap of a portion of the tidal FV loop with the expiratory boundary of the MFVL. An example of aging effects is provided in Figure 7 where flow limitation occurred in our healthy older subjects at the work rate of 60 watts. In contrast, the young untrained adult does not experience flow limitation at this same work rate. At the peak of exercise, the older adult becomes even more flow limited (i.e. a greater percentage of his $V_T$
overlaps with his or her MFVL). Again, the young adult still does not experience any flow limitation at his respective peak work rate.

As EFL is reached during exercise, EELV begins to increase in an attempt to utilize the remaining flow reserve to increase ventilation (Johnson et al. 1994; Johnson, 2002). Accordingly, 9/20 of our healthy subjects increased EELV from rest to peak exercise; the others were unable to substantially decrease EELV. Thus, given that the EELV did not progressively diminish in our healthy older subjects as normally occurs in young individuals (Henke et al. 1988), this provides further support for the normal aging effect as an explanation for why our healthy older group was unable to increase peak $V_E$ on average, under the imposition of an added DS. The evident reduction in the flow reserves of our healthy subjects also leads to a diminished maximal ventilatory capacity (MVC) of their respiratory system. Indeed, on average, our healthy group had MVVs (an index of the MVC) of 128 L/min, which is considerably less (about 30%) than previously reported in young healthy individuals (Johnson et al. 1994).

The preceding discussion attributes the normal aging effects of the respiratory system to account for our observations that on average, peak $V_E$ was not significantly increased by added DS despite consistent increases in $V_T$ and EILV at end exercise. It follows that peak $V_E$ was not preserved by a compensatory increase in $F_b$ (Figure 13A), probably because of its unfavourable effects on increasing the dead space ventilation and its potential to increase air trapping. It was apparent that in our healthy subjects at the peak of exercise (CTRL condition), there was already clear evidence of ventilatory constraints: EILV was 88% (predicted TLC), there was a 49% overlap between the $V_T$ and the MFVL (i.e. the degree of EFL was 49%), and the $V_T$/IC ratio was elevated at 76%. Concurrently, the estimated breathing reserve averaged 73% as assessed by the $V_E$/MVV ratio, indicating that the demand/capacity ratio of the respiratory system was close to the upper limit of normal in health (ATS, 2003). Despite the presence of these ventilatory mechanical
constraints, our healthy older group could still significantly increase $V_T$ even at peak exercise during DS loading. As illustrated in Figure 14A, this increase in $V_T$ was accommodated by the significant increase in EILV from 5.13 L (88% predicted TLC) to 5.40 L (92% predicted TLC). Reciprocal to this EILV response was a significant reduction in the IRV (Figure 15A) at the peak of exercise with the DS load.

Equally important to the ventilatory response is the recognition that at peak exercise, the healthy group approached or reached cardiovascular limits as the peak HR reached 93% of predicted during both the CTRL and DS conditions. By this assessment, our healthy subjects were also limited by the cardiovascular system and systemic $O_2$ delivery. As already mentioned, our healthy participants were unable to increase $\dot{V}_E$ at peak exercise under the DS which indicates that ventilatory factors likely contributed to their exercise termination. However, ventilatory limitation was not exclusive, as they also approached or reached their maximum HR (93% predicted max). Collectively, these results suggest that both the respiratory and cardiovascular system approached or actually reached their physiological limits: ventilatory and cardiac limitation occurred at the limits of tolerance in the healthy elderly. This corresponds to the well-established notion that, although the aging respiratory system may encroach on its pulmonary reserves to a greater extent, it is rarely the only system that limits exercise capacity in the healthy older individual (Johnson et al. 1994; Johnson, 2002).

Section 4.5 –DS Loading in Mild COPD

Given the aforementioned discussion, the question arises whether dynamic mechanical abnormalities resulted in actual ventilatory limitation to exercise in our mild COPD group. That is, was exercise terminated because they were not capable of increasing their ventilation more to support a higher metabolic demand? Certainly, a peak $\dot{V}_E/MVV$ of 69% (Table 3) suggests a
reduced breathing reserve to some extent (ATS, 2003). Additionally, the finding that the $V_T/IC$ ratio reached 68% and that the EILV reached 90% (of predicted TLC), at a peak $\dot{V}_E$ of only 56 L/min suggest that mechanical factors or the associated severe respiratory discomfort could have limited (or opposed) further increases in $\dot{V}_E$ at the peak of exercise. Therefore, we reasoned that failure to further increase peak $V_T$ and peak $\dot{V}_E$, in the face of increased ventilatory stimulation from the added DS, would confirm the presence of true mechanical limitation of ventilation.

The effect of DS loading in mild COPD was in the same direction as in health: average peak $\dot{V}_E$ was not significantly increased (Figure 11B) and peak power output was slightly but significantly reduced. However, ventilatory limitation occurred at a substantially lower power output and $\dot{V}_E$ in the mild COPD group. At the standardized work rate comparison of 60 watts, $V_T$ expansion was significantly limited during DS loading in COPD (the magnitude of increase was 0.26L), compared with healthy subjects who had a significantly larger increase of 0.56L (Figure 12C). Additionally, in contrast to health, at end exercise (when peak $\dot{V}_E$ was 58 L/min; Table 7), there was no further expansion of $V_T$ and EILV as a result of the added DS (Figure 12B and 14B, respectively). Given this and the apparent cardiac reserve (HR was 82% of predicted max) at end exercise in COPD, our results suggest that critical respiratory mechanical constraints contributed to exercise limitation (i.e. during the CTRL condition) in this patient group. Indeed, compared to older healthy participants, the greater “scooping” of the MFVL in mild COPD (Figure 7) suggests an even greater reduction in the elastic recoil pressure of the lung that minimizes the flow reserves and leads to a diminished ventilatory capacity during exercise. Collectively, these results suggest that in many such patients, respiratory mechanical impairment was the predominant factor that limited further increases in $\dot{V}_E$ required to support the increased metabolic demand of a higher work rate.
One study that also utilized DS loading (although in healthy subjects), but whose results reinforces our own conclusions in mild COPD, is that of McParland et al. (1991). In that study, the authors tested the hypothesis that the lack of a continual increase in $V_T$ at higher levels of exercise (i.e. near peak) in healthy humans is due to mechanical limitation of the MVC of their respiratory system. If so, then any increases in $V_T$ that occurs at low and moderate levels of exercise intensities and $V_E$, due to an added DS, would cease to exist at the high levels of $V_E$ near the end of exercise. In other words, added DS should no longer cause $V_T$ to increase near end exercise if mechanical limitation is present. Subsequent comparisons near the peak of exercise revealed that, compared to CTRL, added DS induced a significantly greater $V_T$ response (and significantly lowered $F_b$). Quantitatively, at a $V_E$ of 120 L/min, the $V_T$ and $F_b$ were $2.90 \pm 0.29$ L and $41.8 \pm 7.3$ breaths/min, respectively, in the CTRL condition; in contrast, the $V_T$ and $F_b$ became $3.31 \pm 0.33$ L and $36.7 \pm 6.7$ breaths/min during the DS condition. A similar pattern of response was also observed by Jones et al. (1971), Kelman & Watson (1972, 1973), and Syabbalo et al. (1993). Thus, the ability to mount an augmented $V_T$ response during heavy exercise, in the face of added DS, indicates that the gradual plateau in $V_T$ at high levels of exercise is not due to mechanical limitation of the respiratory system’s MVC in healthy young humans. With the same reasoning, the fact that our mild COPD subjects failed to significantly increase $V_T$ at peak exercise (Figure 12B) provides a strong indication that the relatively restricted $V_T$ response (Figure 12C) during exercise is in fact due to mechanical limitation of their MVC. Interestingly, Goode et al. (1969) and Cunningham et al. (1973) did not observe that added DS induced significant increases in $V_T$ at higher levels of ventilation. The fundamental difference, however, was that these studies were performed under hypoxic conditions which can induce a rapid shallow breathing pattern. It is possible that hypoxic stimulation may over-ride the effects of DS loading alone on the respiratory controller. Thus, this tachypneic response may
have prevented the usual increase in $V_T$ that would have otherwise occurred with DS loading in healthy subjects.

The question arises, then, why our mild COPD subjects were not capable of increasing $V_T$ at the peak of exercise during DS loading. As discussed previously, our results support the finding that the respiratory impairments in mild COPD caused a true mechanical ventilatory limitation to exercise. To further support this conclusion, previous studies in GOLD stage I COPD have shown that selective *unloading* of the respiratory system by inhaled bronchodilators result in higher peak $\dot{V}_E$ (O’Donnell *et al.* 2009c; O’Donnell & Webb, 2011). Associated with the increased $\dot{V}_E$ after BD treatment were improved respiratory mechanics, as both the IC and $V_T$ were subsequently increased at the peak of exercise. Thus, these studies bolster our current results which suggest that, compared to the response in healthy subjects, the reduced exercise tolerance in patients with mild COPD is indeed due to limitation of their impaired ventilatory capacity: ventilatory limitation is the predominant factor accounting for the reduced exercise tolerance in mild COPD.

In contrast to our subjects with mild COPD who were unable to significantly increase peak $\dot{V}_E$ with the DS, a previous study of patients with more severe chronic airflow obstruction (FEV$_1$ = 0.96 ± 0.41 L) surprisingly found the opposite result (Brown *et al.* 1984). In that study (the only other that has attempted to determine the effects of DS in COPD), the authors observed an increase in peak $\dot{V}_E$ of 12.5%, from 35.9 L/min (CTRL) to 40.4 L/min (DS). Despite this increase, exercise capacity was adversely affected, as the $\dot{VO}_2\text{max}$ and work load achieved were significantly reduced by the added DS (CTRL maximum work load = 52 W vs. DS maximum work load = 42 W; CTRL $\dot{VO}_2\text{max}$ = 0.92 L/min vs. DS $\dot{VO}_2\text{max}$ = 0.81 L/min). Based on the diminished exercise tolerance alone with the DS load, the authors concluded that patients with severe airflow obstruction were limited by their impaired ventilatory mechanics. Furthermore,
measurements of arterial blood gases revealed significant increases in the $P_aCO_2$ during DS. Thus, in the CTRL condition, $P_aCO_2$ increased from 39 (rest) to 42 mmHg (peak exercise); during DS the condition, $P_aCO_2$ increased from 43 (rest) to 48 mmHg (peak exercise). It is apparent that the increased peak $\dot{V}_E$ during DS did not prevent CO$_2$ retention, which suggests that adequate levels of alveolar ventilation could not be maintained. This, in conjunction with the reduced exercise capacity during DS, further supports the authors claim that impaired ventilatory mechanics was the factor responsible for exercise termination.

The differing results between the study of Brown et al. (1984) and our own in terms of the ability of subjects to increase peak $\dot{V}_E$ under a DS load, despite the fact that our COPD subjects had milder forms of airway obstruction, may be attributed to the different methodologies. First, the applied DS volume used in their study was not the same in all subjects. The more severe patients ($FEV_1 < 0.80$ L, $n = 10$) only received 250 mL of DS while the less severe patients ($FEV_1 > 0.80$ L, $n = 12$) received 500 mL. These DS volumes are both less than our DS (600 mL). Furthermore, the investigators in that study did not evaluate dyspnea intensity or operating lung volumes, which makes any comparisons, and therefore definitive conclusions, difficult.

Several studies in patients with moderate-to-severe COPD have established that the reduced exercise tolerance in these patients is limited mainly by their impaired ventilatory mechanics (Potter et al. 1971; Brown & Wasserman, 1981; Gallagher, 1994; O’Donnell, 2001c). Traditional estimates of ventilatory limitation have been based on the concept of the ventilatory reserve. In this regard, the $\dot{V}_E^{\text{max}}/\text{MVV}$ or $\dot{V}_E^{\text{max}}/\text{MVC}$ ratio (MVV is the maximal ventilatory capacity as determined from the Maximal Voluntary Ventilation breathing test and MVC is the estimated maximal ventilatory capacity as determined by $FEV_1 \times 35-40$) have conventionally been used to determine the proximity between the maximal achievable ventilation of exercise and the MVV (or MVC); the higher this ratio, the less the breathing reserve. Moderate and severe COPD
patients have consistently greater $\dot{V}_{\text{E}}$/MVV ratios compared with those of healthy subjects (Clark et al. 1969; Brown & Wasserman, 1981); i.e. they have less ventilatory reserve. In our mild COPD group, the $\dot{V}_{\text{E}}$/MVV ratio was 69% in CTRL and 71% in DS. Given the conservative estimates by the European Respiratory Society (2007) which states that ventilatory limitation to exercise is present when the $\dot{V}_{\text{E}}$/MVV exceeds 85%, it would seem that our COPD group do indeed have some breathing reserve at the end of exercise. Nevertheless, as our results have demonstrated, ventilation could not be further increased with an added DS at the peak of exercise in this group. Although the MVV (as obtained from the 12- to 15-s hyperventilation breathing test) is easily applied, it is essential to note that there are many downfalls that can render it an inaccurate estimate of the true maximal ventilatory capacity that can be achieved during exercise. For example, there are significant differences in the breathing pattern; voluntary hyperpnea of the MVV maneuver occurs at much higher lung volumes than during exercise (i.e. EELV and EILV becomes elevated). This causes a significant elastic load to breathing (Johnson et al. 1999) and subjects subsequently generate larger expiratory pressures early in expiration (Klas & Dempsey, 1989). Given this, it is not surprising that the work of breathing during the voluntary hyperpnea of the MVV is greater than that of the reflexly-driven hyperpnea of exercise (Klas & Dempsey, 1989). Furthermore, confirmation of the excessive work of breathing during the MVV maneuver comes from findings that have concluded that it cannot be sustained for > 15 to 30 seconds (ATS, 2003). Lastly, the MVV is highly motivation-dependent (ATS, 2003). In light of these concerns and taking our own results into consideration, we suggest that the traditional approach to assessing ventilatory reserve and limitation using the $\dot{V}_{\text{E}}$/MVV ratio may not be applicable in patients with mild COPD. Other methods, such as utilizing an added DS, may be more sensitive in evaluating the ventilatory reserve in these patients.
Section 4.6 – Sensory effects of DS loading during exercise

In health, compared to the CTRL condition, the increase in ventilation with the added DS did not affect dyspnea intensity, as the dyspnea vs. work rate relation was similar throughout and at the peak of exercise (Figure 17A). At the HEWR of 60 watts, dyspnea ratings remained low (~1 Borg unit) during both CTRL and DS. There was also no significant difference for the selection frequency in the reasons for stopping exercise (breathing discomfort, leg discomfort, or both) between the two conditions (Figure 19A). Therefore, we propose that the relatively greater ability for $V_T$ expansion and greater reserves of lung volume in the face of ventilatory stimulation prevented healthy older subjects from experiencing high levels of dyspnea. Consequently, breathing discomfort does not become a predominant exercise-limiting symptom despite the ventilatory stress imposed by the added DS. The avoidance of major breathing discomfort is likely due to the harmonious relationship between the increased levels of respiratory drive during exercise and the concomitant increase in thoracic volume displacement. Indeed, a previous study in young healthy subjects showed that the $P_{es}/V_T$ slopes (where $P_{es}$ and $V_T$ are indices for respiratory drive and volume displacement, respectively) remained superimposed during exercise in both the CTRL and DS conditions (O’Donnell et al. 2000). Those younger subjects who were able to accommodate an increased $V_T$ and $\dot{V}_E$ in response to an added DS during exercise also did not experience any increase in dyspnea intensity. Accordingly, the logical presumption is that in our healthy older subjects, the $P_{es}/V_T$ relation also remained similar in both the CTRL and DS conditions throughout exercise.

Unlike healthy subjects, patients with mild COPD experienced with the addition of DS. Indeed, the magnitude of change in dyspnea ratings with the DS was significantly greater at the HEWR of 60 watts and at the peak of exercise (Figure 17C). At 60 watts, the dyspnea score increased by +1.8 units in COPD while it remained almost the same in health (+0.2 units).
Additionally, at the peak of exercise, the dyspnea score increased by +0.9 units in COPD compared to a trivial drop of 0.2 units in health. We propose that the greater dyspnea intensity ratings in COPD are likely the result of the combination of higher ventilatory requirements and greater respiratory mechanical abnormalities which is associated with increased contractile respiratory muscle effort (Ofir et al. 2008). While the dominant qualitative descriptors at end exercise (“my breathing requires more work” and “my breathing is heavy”) were selected with similar frequencies in both groups, the descriptor “breathing in requires more effort” was much more common in COPD (Figure 10). The greater increase in dyspnea (by ~2 Borg units) at sub-maximal work rates in COPD compared to health, for a similar increase in $\dot{V}_E$ (by 9-11 L/min) with added DS, is partially explained by the steeper baseline dyspnea/$\dot{V}_E$ relation in the former (Figure 18A). This increased slope, in turn, reflects the greater mechanical derangements and an increased intrinsic mechanical loading of the respiratory muscles that is present in mild COPD (Ofir et al. 2008). The greater increase in dyspnea in COPD with the DS load can also be partially attributed to the increased ventilation levels. This is demonstrated in Figure 18C, where the dyspnea and $\dot{V}_E$ increased along the same slope with the added DS. However, at the HEWR comparison of 60 watts, it is clear that the DS had forced the COPD group to move “up the slope” such that the dyspnea rating was significantly higher (3.2 Borg units) compared to the CTRL condition (1.7 Borg units).

Following the same logic as that discussed for the healthy group, the relatively impaired ability for $V_T$ expansion with the added DS in mild COPD, along with inadequate volume reserves at the peak of exercise predisposed them to greater dyspnea intensities. A number of experimental studies in health have shown that perceived dyspnea (or “air hunger”) rises sharply if the normal $V_T$ response is restricted (either voluntarily or by external imposition) in the setting of an increased ventilatory drive to breathe (Schwartzstein et al. 1989; Harty et al. 1999;
O’Donnell et al. (2000, 2006b). For example, O’Donnell et al. (2000) have shown that, as is the case with our older healthy group in the current study, young healthy participants can accommodate an increased $V_T$ and $V_E$ in response to added DS during exercise, without any increase in dyspnea intensity. However, when the normal $V_T$ increase was restricted by chest wall strapping in these participants, imposition of the same DS resulted in earlier exercise termination, compared with the unrestricted condition, due to a steeper rise in dyspnea to intolerable levels (O’Donnell et al. 2000). We believe that similar mechanisms are at play in our mild COPD patients, who analogously have a restricted capacity for $V_T$ expansion concomitant with an increased ventilatory drive at higher exercise levels.

In accordance with this previous study (O’Donnell et al. (2000)), we suspect a disparity arose between the increased levels of respiratory drive and the thoracic volume displacement. We propose that this disparity, a phenomenon O’Donnell et al. (2009b) have termed neuro-mechanical uncoupling, represents one underlying mechanism of dyspnea amplification in COPD during DS loading. In contrast to health, $V_T$ expansion was significantly less in COPD for a similar degree of ventilatory stimulation at sub-maximal work rates. The inability to expand $V_T$ appropriately in COPD is explained by the restriction imposed by lung hyperinflation: the $V_T$ plateau occurred at a much lower work rate (COPD: 64 W vs. Health: 103 W) and $V_E$ (COPD: 36.8 L/min vs. Health: 46.3 L/min) in COPD than in health (section 3.1.5. and Figure 6). Thus, the widening disparity between increased central neural drive (sensed by increased central corollary discharge) and the limited volume displacement of the respiratory system (sensed by multiple mechanoreceptors), may form the basis for the increased respiratory discomfort during DS loading in COPD. In this regard, it is interesting to note that significantly more COPD subjects also attributed breathing discomfort as the dominant exercise-limiting symptom with the DS as compared to the CTRL condition (Figure 19B).
Section 4.7 – Limitations of the Study

Similar to more recent studies utilizing an external DS (O’Donnell et al. 2000, Zaton & Smolka, 2011), gas exchange measurements (VO$_2$ and VCO$_2$) could not be accurately obtained during exercise with the added DS. Past studies with DS loading that were capable of collecting these measurements all utilized an exercise testing system which had separate expiratory and inspiratory lines. The expiratory line was connected to a mixing chamber whereby the O$_2$ and CO$_2$ concentrations were subsequently determined by gas analyzers. This mode of gas collection allowed for the accurate determination of the fractional concentrations of O$_2$ and CO$_2$ in mixed expired gas (FE,O$_2$ and FE,CO$_2$, respectively). Finally, VO$_2$ and VCO$_2$ were calculated with standard formulas of Jones & Campbell (1982) or Jones (1988) to determine its measurements during exercise with the added DS. As in our study, Zaton & Smolka (2011) stated that, “measuring limitation of the apparatus” prevented gas exchange measurements to be obtained during the DS condition. Indeed, our Vmax229d computer software system does not allow corrections for DS volumes greater than 250 mL.

Our groups were not matched for activity levels at study entry as our healthy subjects were generally more active than the COPD group. Thus we cannot exclude the possibility that de-conditioning could have amplified respiratory impairment in some COPD volunteers. We did not, however, intentionally select healthy subjects who participated in athletic competitions. Indeed, half of our healthy participants were “walkers” – they liked to walk at a leisurely-to-moderate pace for most days of the week at ~30 min each time. The other half of the group participated in gym activities and/or sports for ~ 2-3 days/week (i.e. elliptical, biking). The fact that the healthy subjects preferred to remain relatively active, compared to COPD, suggests that avoidance of daily activities due to dyspnea is already present in patients with early stages of COPD.
We used a standardized DS of 0.6 L in all participants knowing that individual ventilatory responses will vary with lung size. However, each individual acted as his or her own control during the two test conditions and both groups were well matched for age, sex, and BMI. Moreover, $V_{E}$ increased during submaximal exercise to a similar extent (by 9-11 L/min) in both groups, indicating a comparable physiological stress with the same DS load.

Although the DS arrangement was not concealed to the participants, they were all naïve to the specific purpose of the experiments. Additionally, no subjects gave any indication of being aware of the added DS throughout the DS visits and for the duration of the study.

Respiratory mechanical pressure measurements (i.e. esophageal pressures) were not available. These measurements would enable a greater understanding of potential differences in the respiratory mechanical pressure changes that occur with added respiratory stress in both health and mild COPD.

Section 4.8 – Future Studies

The exact physiological reason for the documented increase in ventilatory requirement during physical activity is currently unknown in mild COPD. Future studies should clarify the nature and extent of pulmonary gas exchange abnormalities by obtaining arterial blood samples at rest and during exercise. Lactate measurements will also allow a better evaluation of deconditioning.

Measurements of ventilatory mechanics from esophageal (Pes) and gastric- derived pressures (Pga) are needed to cast further light on mechanical constraints in mild COPD. Furthermore, measurements of the electromyogram of the diaphragm (EMGdi) from a multipair electrode catheter should also be employed to assess neural respiratory drive in COPD patients (Luo & Moxham, 2005; Qin et al. 2010). Collectively, these additional studies will increase our
understanding of the pathophysiological abnormalities that is relevant to exertional dyspnea and activity-limitation in mild COPD.

We have shown that compared to health, there was a consistent reduction in the $P_{ET}CO_2$ in mild COPD subjects (Figure 4C). Although this suggests the presence of chronic alveolar hyperventilation, future studies should determine whether this is due to a lowered $CO_2$ set-point (i.e. a lowered ventilatory threshold for $CO_2$) of the ventilatory control system in mild COPD.

Section 4.9 – Conclusions and Implications

This study provides new insights into the mechanisms of dyspnea and exercise limitation that are increasingly reported in sub-populations with mild COPD. While older healthy individuals reached a peak $\dot{VO}_2$ that was at the predicted level, evidence of both ventilatory and cardiac limitation was present at the limits of tolerance. This is the first study to demonstrate that critical respiratory mechanical constraints are measurable in the healthy elderly as they reach predicted peak $\dot{VO}_2$. Traditional estimations of breathing reserve have therefore underestimated ventilatory limitation at peak exercise.

In contrast with healthy individuals, the respiratory system had reached or approached its physiological limit in the setting of a relatively preserved cardiac reserve and this occurred at a significantly lower peak power output in the mild COPD group. Thus, critical ventilatory constraints or limitation occurred at a much lower $\dot{V}_E$ in the COPD group. Furthermore, unique to the COPD group was the greater constraint on $V_T$ expansion throughout exercise and an earlier limitation of $V_T$ expansion during DS and the attendant increase in perceived breathing discomfort.

We propose that the troublesome chronic dyspnea and reduced daily activity levels reported by our COPD group are related, in part, to the higher ventilatory demand and
abnormal dynamic respiratory mechanics that are associated with physical tasks in this group. While the respiratory system in mild COPD may still be capable of supporting the metabolic needs of most normal daily activities without associated dyspnea, this may not be the case in situations where the ventilatory requirements are augmented (i.e. with co-existent deconditioning, during strenuous activity, or walking at altitude). Our results warrant further studies designed to evaluate the impact of interventions that improve respiratory mechanics (i.e. bronchodilators) and/or reduce ventilatory demand (i.e. exercise training) in selected patients with mild COPD who report persistent activity-related dyspnea.
REFERENCES


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APPENDIX A: RESEARCH ETHICS BOARD (REB) APPROVAL

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD

September 24, 2009

Dr. D.E. O'Donnell
Division of Respiratory and Critical Care Medicine
c/o Respiratory Investigation Unit
Connell 2
Kingston General Hospital

Dear Dr. O'Donnell,

Study Title: Pathophysiological Mechanisms of Dyspnea and Activity-Limitation in Mild COPD
Co-Investigators: Dr. Dennis Jensen

The members of the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board have examined the revised protocol (September 21, 2009), advertisement/recruitment notice, visit schedule, Borg's Modified 0-10 Category Ratio Scale, List of Descriptive Phases, List of Qualitative Descriptors, Baseline Dyspnea Index, MRC Dyspnea Scale, Oxygen Cost Diagram, Epworth Sleepiness Scale, State-Trait Anxiety Inventory, Hospital Anxiety and Depression Scale, CHAMPS physical activity questionnaire, St. George's Respiratory Questionnaire, Study Budget and the revised consent form (September 21, 2009) for your project (as stated above) and consider it to be ethically acceptable. This approval is valid for one year from the date of the Chair's signature below. Please attend carefully to the following list of ethics requirements you must fulfill over the course of your study:

- Reporting of Amendments: If there are any changes to your study (e.g., consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval. (see http://www.queensu.ca/vpr/teb.html).
- Reporting of Serious Adverse Events: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information.
- Reporting of Complaints: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. Note: All documents supplied to participants must have the contact information for the Research Ethics Board.
- Annual Renewal: Prior to the expiration of your approval (which is one year from the date of the Chair's signature below), you will be reminded to submit your renewal form along with any new changes or amendments you wish to make to your study. If there have been no major changes to your protocol, your approval may be renewed for another year.

Yours sincerely,

[Signature]
Chair, Research Ethics Board

Date: Sept 28, 2009

ORIGINAL TO INVESTIGATOR - COPY TO DEPARTMENT HEAD - COPY TO HOSPITAL(S) /FWT IF APPROPRIATE - FILE COPY

Study Code: DMED-1243-09

Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete

SHIPPED SEP 29 2009
The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards as defined by the Tri-Council Policy Statement; Part C Division 5 of the Food and Drug Regulations, OHRP, and U.S DHHS Code of Federal Regulations Title 45, Part 46 and carries out its functions in a manner consistent with Good Clinical Practices.

Federalwide Assurance Number: #FWA00004184
#IRB00091373

Current 2009 membership of the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board

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Dr. S. Wood  Director, Office of Research Services (Ex-Officio)
APPENDIX B: MEDICAL RESEARCH COUNCIL (MRC) DYSPNEA SCALE

GRADE

1 NOT TROUBLED WITH BREATHELESSNESS EXCEPT WITH STRENUOUS EXERCISE

2 TROUBLED BY SHORTNESS OF BREATH WHEN HURRYING ON THE LEVEL OR WALKING UP A SLIGHT HILL

3 WALKS SLOWER THAN PEOPLE OF THE SAME AGE ON THE LEVEL BECAUSE OF BREATHELESSNESS OR HAS TO STOP FOR BREATHE WHEN WALKING AT OWN PACE ON THE LEVEL

4 STOPS FOR BREATHE AFTER WALKING ABOUT 100 YARDS OR AFTER A FEW MINUTES ON THE LEVEL

5 TOO BREATHELESS TO LEAVE THE HOUSE OR BREATHELESS WHEN DRESSING OR UNDRESSING
APPENDIX C: MODIFIED BASELINE DYSPNEA INDEX (BDI)

MAGNITUDE OF TASK

GRADE 4: Extraordinary:  Becomes SOB* only with extraordinary activity, such as:
- carrying very heavy loads on the level
- carrying lighter loads upstairs
- running

GRADE 3: Major: Becomes SOB only with major activities, such as:
- walking up a steep hill
- climbing two flights of stairs or more
- carrying a heavy bag of groceries on the level

GRADE 2: Moderate: Becomes SOB with moderate or average tasks, such as:
- climbing up stairs up to two flights
- walking up a gradual hill
- walking briskly on the level
- carrying a light load on the level

GRADE 1: Light: Becomes SOB with light activities, such as:
- walking on the level with others of the same age
- walking to the bathroom in residence
- washing up
- dressing
- shaving

GRADE 0: No Task: Becomes SOB with no activity, such as:
- while sitting and/or lying down
- while standing motionless

W: Amount Uncertain

X: Unknown

Y: Impaired for Reasons Other than SOB

Please describe the nature of this other limiting condition(s):

*SOB = Shortness of Breath
MAGNITUDE OF EFFORT

For the most strenuous task the patient can perform (for at least five minutes):

GRADE 4: It is done briskly without pausing because of SOB or even slowing down to rest.

GRADE 3: It is done slowly but without pausing or stopping to catch breath.

GRADE 2: It is done slowly and still with rare pauses (one or two) to catch breath before completing the task or quitting altogether.

GRADE 1: It is done slowly and with many stops or pauses before the task is completed or abandoned.

GRADE 0: The patient is SOB at rest, or while sitting, or lying down.

W: Amount Uncertain

X: Unknown

Y: Impaired for Reasons Other than SOB.

Please describe the nature of this other limiting condition(s):
FUNCTIONAL IMPAIRMENT AT HOME

GRADE 4: No Impairment: The patient is able to carry out usual home activities without SOB; there is no curtailment of the number or type of home activities, and no reduction in the pace with which the activities are done.

GRADE 3: Slight Impairment: The patient recognizes that SOB has caused alteration in the usual home activities in any of the following ways:

(a) Although no usual activities have been completely abandoned as a result of SOB, up to several (but not all) activities are done more slowly.

(b) Although the patient continues all activities, at least one activity may be done less frequently as a result of SOB.

GRADE 2: Moderate Impairment: SOB has caused the patient to curtail activities in at least one of the following ways:

(a) Up to several (but not all) activities have been completely abandoned because of SOB.

(b) Most or all usual activities are done more slowly because of SOB.

GRADE 1: Severe Impairment: SOB has caused the patient to abandon most or all of the usual activities.

W: Amount Uncertain

X: Unknown

Y: Impaired for Reasons Other than SOB.

Please describe the nature of this other limiting condition(s):
CHAMPS Activities Questionnaire for Older Adults

CHAMPS: Community Healthy Activities Model Program for Seniors
Institute for Health & Aging, Center for Healthy and Active Aging
University of California San Francisco
Stanford Center for Research in Disease Prevention, Stanford University

CHAMPS PHYSICAL ACTIVITY QUESTIONNAIRE

Medicine & Science in Sports & Exercise®
Appendix. Continued.

This questionnaire is about activities that you may have done in the past 4 weeks. The questions on the following pages are similar to the example shown below.

INSTRUCTIONS
If you DID the activity in the past 4 weeks:
Step #1 Check the YES box.
Step #2 Think about how many TIMES a week you usually did it, and write your response in the space provided.
Step #3 Circle how many TOTAL HOURS in a typical week you did the activity.

Here is an example of how Mrs. Jones would answer question #1: Mrs. Jones usually visits her friends Maria and Olga twice a week. She usually spends one hour on Monday with Maria and two hours on Wednesday with Olga. Therefore, the total hours a week that she visits with friends is 3 hours a week.

<table>
<thead>
<tr>
<th>In a typical week during the past 4 weeks, did you...</th>
<th>How many TOTAL hours a week did you usually do it?</th>
<th>Less than 1 hour</th>
<th>1-2½ hours</th>
<th>3-4½ hours</th>
<th>5-6½ hours</th>
<th>7-8½ hours</th>
<th>9 or more hours</th>
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<tbody>
<tr>
<td>1. Visit with friends or family (other than those you live with)?</td>
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<td>☑ YES How many TIMES a week? ______________</td>
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</table>

If you DID NOT do the activity:
• Check the NO box and move to the next question

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<td>2. Go to the senior center?</td>
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<td>☐ YES How many TIMES a week? ______________</td>
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| 3. Do volunteer work? | | | | | | | |
| ☐ YES How many TIMES a week? ______________ | | | | | | | |
| ☐ NO | | | | | | | |

| 4. Attend church or take part in church activities? | | | | | | | |
| ☑ YES How many TIMES a week? ______________ | | | | | | | |
| ☐ NO | | | | | | | |

| 5. Attend other club or group meetings? | | | | | | | |
| ☑ YES How many TIMES a week? ______________ | | | | | | | |
| ☐ NO | | | | | | | |

| 6. Use a computer? | | | | | | | |
| ☑ YES How many TIMES a week? ______________ | | | | | | | |
| ☐ NO | | | | | | | |

| 7. Dance (such as square, folk, line, ballroom) (do not count aerobic dance here)? | | | | | | | |
| ☑ YES How many TIMES a week? ______________ | | | | | | | |
| ☐ NO | | | | | | | |
### Appendix. Continued.

#### In a typical week during the past 4 weeks, did you ...

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<tr>
<th>Question</th>
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<th>7-8½ hours</th>
<th>More than 9 hours</th>
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</thead>
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<td>8. Do woodworking, needlework, drawing, or other arts or crafts?</td>
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<td>9. Play golf, carrying or pulling your equipment (count walking time only)?</td>
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<td>10. Play golf, riding a cart (count walking time only)?</td>
<td>□ YES How many TIMES a week?</td>
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<td>11. Attend a concert, movie, lecture, or sport event?</td>
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<td>12. Play cards, bingo, or board games with other people?</td>
<td>□ YES How many TIMES a week?</td>
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<td>13. Shoot pool or billiards?</td>
<td>□ YES How many TIMES a week?</td>
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<th>More than 9 hours</th>
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<tbody>
<tr>
<td>14. Play singles tennis (do not count doubles)?</td>
<td>□ YES How many TIMES a week?</td>
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<td>15. Play doubles tennis (do not count singles)?</td>
<td>□ YES How many TIMES a week?</td>
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<td>16. Skate (ice, roller, in-line)?</td>
<td>□ YES How many TIMES a week?</td>
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<td>17. Play a musical instrument?</td>
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<td>18. Read?</td>
<td>□ YES How many TIMES a week?</td>
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<td>19. Do heavy work around the house (such as washing windows, cleaning gutters)?</td>
<td>□ YES How many TIMES a week?</td>
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<td>20. Do light work around the house (such as sweeping or vacuuming)?</td>
<td>□ YES How many TIMES a week?</td>
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CHAMPS PHYSICAL ACTIVITY QUESTIONNAIRE
### Appendix. Continued.

**In a typical week during the past 4 weeks, did you...**

<table>
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<tr>
<th>Question</th>
<th>How many TOTAL hours a week did you usually do it?</th>
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<th>9 or more hours</th>
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<tr>
<td>21. Do heavy gardening (such as spading, raking)?</td>
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<td>22. Do light gardening (such as watering plants)?</td>
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<td>□ YES How many TIMES a week?</td>
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<td>23. Work on your car, truck, lawn mower, or other machinery?</td>
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*Please note: For the following questions about running and walking, include use of a treadmill.*

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<thead>
<tr>
<th>Question</th>
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<td>24. Jog or run?</td>
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<td>25. Walk uphill or hike uphill (count only uphill part)?</td>
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<td>26. Walk fast or briskly for exercise (do not count walking leisurely or uphill)?</td>
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**In a typical week during the past 4 weeks, did you...**

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<th>9 or more hours</th>
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<tbody>
<tr>
<td>27. Walk to do errands (such as to/from a store or to take children to school) (count walk time only)?</td>
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<td>28. Walk leisurely for exercise or pleasure?</td>
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<td>29. Ride a bicycle or stationary cycle?</td>
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<td>30. Do other aerobic machines such as rowing, or step machines (do not count treadmill or stationary cycle)?</td>
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<td>31. Do water exercises (do not count other swimming)?</td>
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<td>32. Swim moderately or fast?</td>
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<td>□ YES How many TIMES a week?</td>
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<td>33. Swim gently?</td>
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Official Journal of the American College of Sports Medicine

https://www.acsm-msse.org
### Appendix. Continued.

#### In a typical week during the past 4 weeks, did you...

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<tr>
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<tbody>
<tr>
<td>34. Do stretching or flexibility exercises (do not count yoga or Tai-chi)?</td>
<td>☐ YES How many TIMES a week? →</td>
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<tr>
<td>35. Do yoga or Tai-chi?</td>
<td>☐ YES How many TIMES a week? →</td>
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<tr>
<td>36. Do aerobics or aerobic dancing?</td>
<td>☐ YES How many TIMES a week? →</td>
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<tr>
<td>37. Do moderate to heavy strength training (such as hand-held weights of more than 5 lbs., weight machines, or push-ups)?</td>
<td>☐ YES How many TIMES a week? →</td>
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<tr>
<td>38. Do light strength training (such as hand-held weights of 2 lbs. or less or elastic bands)?</td>
<td>☐ YES How many TIMES a week? →</td>
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<tr>
<td>39. Do general conditioning exercises, such as light calisthenics or chair exercises (do not count strength training)?</td>
<td>☐ YES How many TIMES a week? →</td>
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</tr>
</tbody>
</table>

#### In a typical week during the past 4 weeks, did you...

<table>
<thead>
<tr>
<th>Question</th>
<th>How many TOTAL hours a week did you usually do it?</th>
<th>Less than 1 hour</th>
<th>1-2½ hours</th>
<th>3-4½ hours</th>
<th>5-6½ hours</th>
<th>7-8½ hours</th>
<th>9 or more hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>40. Play basketball, soccer, or racquetball (do not count time on sidelines)?</td>
<td>☐ YES How many TIMES a week? →</td>
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<tr>
<td>41. Do other types of physical activity not previously mentioned (please specify)?</td>
<td>☐ YES How many TIMES a week? →</td>
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</tbody>
</table>

*Thank You*
APPENDIX E: IMPULSE OSCILLOMETRY (IOS)

The impulse oscillometry (IOS) apparatus generates small pressure fluctuations applied at the subject’s mouth to identify airways dysfunction (Klug, 1997). It is a non-invasive test lasting approximately 30 seconds during which time the subject is seated and breaths normally over a mouthpiece while the pressure oscillations are applied at the mouth and propagates into the conducting airways (Klug, 1997). As the test commences, the subject is instructed to place his or her hands over the cheeks while wearing a nose clip. Since the IOS is easy to perform and requires minimal cooperation, it can be used in both children and adults for the detection of airway hyperreactivity and airway obstruction (Neve et al. 2006).

Impulse oscillometry measures the impedance ($Z_{rs}$) of the respiratory system, which in turn, is composed of 2 components: pulmonary resistance ($R$) and pulmonary reactance ($X$) (Klug, 1997; Beydon et al. 2007). Resistance ($R$) provides an index of the central and peripheral airway calibers and can be thought of as the energy required to propagate the pressure oscillations throughout the airways (Goldman, 2001; Beydon et al. 2007). The resistance is calculated from pressure and flow signals while the pressure wave is “in phase with flow” (i.e. when the pressure wave is unopposed by lung recoil). In contrast, reactance ($X$) can be thought of as the amount of recoil generated against the applied pressure wave; it is calculated when the pressure wave is “out of phase with flow” (Smith et al. 2005).

The presence of proximal or distal airway obstruction can be determined based on the fact that low-frequency oscillations (5 Hz) travel out to the lung periphery while high-frequency oscillations (20 Hz) only reach the proximal airways (Komarow et al. 2001). In other words, the resistance and reactance measured at 5 Hz ($R_5$ and $X_5$, respectively) provides indices of the entire pulmonary system while the resistance and reactance measured at 20 Hz ($R_{20}$ and $X_{20}$, respectively) provides indices of the central (proximal) airways. Given this, peripheral airways
disease increases R5 much more than the R20. This is called a “frequency-dependant change” and occurs because any change in the proximal resistance (R20) comprises only a small portion of the total change in the respiratory system’s resistance (R5) (Komarow et al. 2001). In clinical and research settings, the frequency-dependant increase present in peripheral obstructive diseases (i.e. COPD) is reported as a high differential change (i.e. high R5 - R20) (Komarow et al. 2001). Lastly, diseases of the peripheral airways also results in a decrease in the pulmonary reactance because the recoil (or signal) generated against the pressure wave and returning from the periphery must travel back through these narrowed airways (Komarow et al. 2001).
APPENDIX F: SINGLE-BREATH NITROGEN WASHOUT TEST

The single-breath nitrogen ($N_2$) washout test determines the pattern of ventilation distribution (Hyatt et al. 2003). In other words, it determines if an inhaled breath is normally distributed throughout the lungs. During this test, the subject is seated and when prompted, exhales to RV. He or she then inhales 100% $O_2$ gas to TLC and then exhales again back to RV at a comfortable pace. As exhalation occurs, the $N_2$ concentration [$N_2$] of the expired gas is continuously recorded.

At RV, before 100% $O_2$ inhalation, the alveoli at the base (gravitationally dependent regions) of the lung are at a relatively smaller volume compared to the apical (superior) regions; the superior alveoli has a relatively larger volume of $N_2$ (Hyatt et al. 2003). Given this, during inhalation of the 100% $O_2$, relatively less $O_2$ will go to the superior alveoli and more $O_2$ will end up at the base of the lung. Therefore, the alveolar $N_2$ is less diluted at the apex and most diluted at the base. As exhalation goes back to RV, the initial gas expired comes from the trachea and upper airways where the [$N_2$] is 0% (Hyatt et al. 2003). Thereafter, alveolar gas empties from the alveoli at the base of the lung and slowly transitions to emptying from the apex, where the [$N_2$] is highest (Hyatt et al. 2003).

Although the [$N_2$] increases at a rate of 1-2.5%/L of expired gas in healthy young individuals (Hyatt et al. 2003), this can be significantly increased in COPD. This is because regions of high airflow resistance cannot appropriately empty during expiration and subsequently receive less $O_2$: the $N_2$ becomes less diluted and the [$N_2$] is therefore greater (Hyatt et al. 2003). This, combined with the fact that COPD patients empty (expire) more slowly, accounts for their elevated [$N_2$] over a given expired volume (i.e. a steeper $N_2$ slope). The more non-uniform the distribution of ventilation (i.e. a greater mal-distribution of ventilation), the steeper this slope.
APPENDIX G: MODIFIED BORG SCALE

10  Extremely strong  (maximal)
9
8
7  Very Strong
6
5  Strong  (heavy)
4  Somewhat strong
3  Moderate
2  Slight  (light)
1  Very slight
0.5  Very, very slight  (just noticeable)
0  Nothing at all
APPENDIX H: DESCRIPTORS OF BREATHELESSNESS

CIRCLE ALL APPLICABLE DESCRIPTORS OF YOUR "UNCOMFORTABLE"

AWARENESS OF BREATHING:

1. My breath does not go in all the way
2. Breathing in requires effort
3. I feel that I am suffocating
4. I feel a need for more air
5. My breathing is heavy
6. I cannot take a deep breath in
7. My chest feels tight
8. My breathing requires more work
9. I feel a hunger for more air
10. I feel that my breathing is rapid
11. My breathing feels shallow
12. I feel that I am breathing more air
13. I cannot get enough air in
14. My breath does not go out all the way
15. Breathing out requires more effort

THE BEST 3 DESCRIPTORS (IN DESCENDING ORDER):
1. _____________________
2. _____________________
3. _____________________