VENTILATORY CONSTRAINTS AND BREATHLESSNESS DURING EXERCISE IN THE ELDERLY, IN THE OBESE, AND IN THOSE WITH MILD AIRFLOW LIMITATION

By

Dror Ofir

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ABSTRACT

Breathlessness during activity is increasingly recognized as a common symptom in the elderly, in older individuals with minor airway obstruction due to tobacco smoking, and in those with obesity. The underlying mechanisms of perceived respiratory difficulty in each of these populations remain unknown and are largely unstudied.

Objective: The main purpose of this original research was to elucidate the alterations in central ventilatory drive and in dynamic ventilatory mechanics that might explain the origin of increased breathlessness during exercise in these three populations.

General Hypothesis: In individuals with largely preserved resting pulmonary function, increased intensity of breathlessness during activity will arise as a result of measurable abnormalities of dynamic ventilatory mechanics, central respiratory drive, or both in combination.

General Methods: We examined sensory-mechanical relationships during cardio-pulmonary exercise testing in each population (total n=146). We compared indices of ventilatory control (ventilation, pulmonary gas exchange and metabolic load), dynamic mechanics (breathing pattern and operating lung volumes) and ratings of dyspnea intensity in three well characterized cohorts: elderly versus younger; smokers with minor airway obstruction versus age-matched non-smokers, and obese versus lean participants.

Results: Individuals across all three study populations had preserved resting pulmonary function. Compared with their respective control groups all three symptomatic groups demonstrated consistent abnormalities in dynamic airway function during exercise [expiratory flow limitation (EFL), dynamic increases in end expiratory lung volume, and restricted tidal volume response]; all had greater ventilatory requirements reflecting
variable ventilation-perfusion and metabolic abnormalities. In all three groups, intensity of breathlessness increased as ventilatory demand approached capacity. In the elderly (with or without airway obstruction), breathlessness intensity ratings at a standardized ventilation during exercise correlated with indices of mechanical volume restriction secondary to EFL. In obese individuals, increased ventilatory drive secondary to increased metabolic loading (and not mechanical abnormalities) was the primary factor contributing to exertional breathlessness.

**Conclusion**: Although the origin of breathlessness during physical exertion in the elderly (with or without minor airway obstruction) and in obese individuals is multi-factorial, we identified the central etiological importance of the combination of increased ventilatory drive and restrictive dynamic mechanical constraints to increasing ventilation.
STATEMENT OF CO-AUTHORSHIP

The contents of this thesis were written by me with input from my supervisor, Dr. O'Donnell and his associate researcher Kathy Webb in the Respiratory Investigation Unit. Each of the published manuscripts within this thesis is the products of experiments done by me. In addition to conducting the experiments, I was also the author of the primary drafts and all the subsequent revisions.
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LIST OF ABBREVIATIONS

A-a DO₂ – alveolar to arterial O₂ difference
BDI – baseline dyspnea index
CC – closing capacity
COPD – chronic obstructive pulmonary disease
CHAMPS – self-reported habitual physical activity questionnaire
CO₂ - carbon dioxide
CV – closing volume
DL CO₂ – diffusion capacity
EELV – end expiratory lung volume
EFL – expiratory flow limitation
EILV – end inspiratory lung volume
ERV – expiratory reserve volume
f – breathing frequency
FEF – force expiratory flow
FEV₁ – force expiratory volume in one second
FRC – functional residual capacity
FVC – force vital capacity
HR – heart rate
IC – inspiratory capacity
IRV – inspiratory reserve volume
MRC – modified medical research council dyspnea scale
MVC – maximal ventilatory capacity
O₂ – oxygen
OCD – oxygen cost diagram
PaCO₂ – arterial partial pressure of carbon dioxide
PaO₂ – arterial partial pressure of oxygen
PCO₂ – partial pressure of oxygen
PEFR – peak expiratory flow rate
P ET CO₂ – partial pressure of end-tidal O₂
P ET O₂ – partial pressure of end-tidal O₂
\( P_{\text{I}_{\text{max}}} \) – maximal inspiratory pressure
\( P_{E_{\text{max}}} \) – maximal expiratory pressure
\( PO_2 \) – partial pressure of carbon dioxide
\( Q \) – cardiac output
RAR – rapidly adapting receptors
RV – residual volume
RER – respiratory exchange ratio
SpO_2 – oxygen saturation
SAR – slowly adapting receptors
sRAW – specific airway resistance
SV – stroke volume
\( T_E \) – expiratory time
\( T_I \) – inspiratory time
TLC – total lung capacity
\( T_{TOT} \) – breath time
\( \dot{V}_A \) – alveolar ventilation
VC – vital capacity
\( \dot{V}_{CO_2} \) – carbon dioxide output
\( V_D \) – dead space
\( \dot{V}_E \) – minute ventilation
\( \dot{V}_{O_2} \) – oxygen consumption
\( V_R \) – relaxation volume
\( V_T \) – tidal volume
VTh – ventilatory threshold
Chapter 1: General Introduction
Introduction

During physical exertion in humans, the acute increases in energy requirements of the active locomotor muscles are met by a carefully orchestrated response from the cardiovascular, ventilatory and neurosensory systems. Thus, demanding physical tasks can be accomplished while ensuring maximal mechanical and metabolic efficiency with preservation of arterial partial pressures of oxygen (O$_2$) and of carbon dioxide (CO$_2$) (PaO$_2$ and PaCO$_2$ respectively) near resting values. Exercise limitation in humans occurs when the cardiovascular system fails to provide the requisite O$_2$ delivery to the active skeletal muscles (Saltin & Calbet, 2006). The respiratory system is regarded as being “overbuilt”: at the peak of exhaustive exercise, substantial ventilatory reserve (exceeding 15% of maximal breathing capacity) is usually present (American Thoracic Society & American College of Chest Physicians, 2003). During exercise, precise chemical and neuromuscular regulation ensures that alveolar ventilation ($\dot{V}A$) rises linearly as a function of CO$_2$ output ($\dot{V}CO_2$) (Eldrige & Waldrop, 1991).

Non-athletic humans have a remarkable ability to increase $\dot{V}E$ to high levels (>10 times the resting value) with minimal perceived breathing difficulty (breathlessness). Near peak exercise, intensity of breathlessness measured by validated scales is generally rated as “severe” and in qualitative terms is described as increased “effort”, “work” or “heaviness” of breathing (Simon et al., 1989). However, breathlessness during heavy exercise is rarely reported to limit performance, at least in healthy young individuals (Jones & Killian, 2000). In fact, several studies have confirmed that intolerable leg discomfort is the proximate exercise-limiting symptom during cycle exercise in the
majority of individuals (Killian et al., 1992; O’Donnell et al., 2000). A possible exception to this is the situation in elite athletes whose ventilatory reserves can become critically eroded at very high peak \( \dot{V}O_2 \). Such individuals may have evidence of diaphragmatic fatigue and experience intolerable breathlessness (Johnson et al., 1996; Babcock et al., 1996; Harms et al., 2000).

While the healthy young are generally spared uncomfortable respiratory symptoms during exercise, there is increasing evidence that troublesome activity-related breathlessness is commonly encountered in such “healthy” populations as the elderly, the overweight and in those with protracted nicotine addiction. It is estimated that >30% of people over 65 years of age experience breathlessness (Horsley et al., 1991; Ho et al., 2001) with exercise and the presence of this symptom (measured by the Medical Research Council scale: see Appendix A) is an independent predictor of morbidity and mortality (Tessier et al., 2001; Vestbo et al., 1988; Sorlie et al., 1989). Epidemiological studies have also documented that breathlessness and activity limitation are common symptoms in obesity (Sjostrom et al., 1992; Bulpitt et al., 1998; Sin et al., 2002). It has long been recognized that smokers, with apparently trivial airway dysfunction, report disproportionate exertional breathlessness and poor health-related quality of life (Jones, 2001).

The focus of this original research is to increase our understanding of the source and mechanisms of breathlessness during physical activity in these specific populations (listed above) in whom this symptom is problematic. The aging demographic and the current epidemic of obesity throughout the western makes this work all the more timely and relevant. Moreover, a better understanding of the nature and mechanisms of
breathlessness in special healthy populations becomes crucial if we are to understand and manage perceived respiratory discomfort in individuals with various cardio-pulmonary disorders, many of whom are elderly smokers who are overweight! In proceeding, we will first consider the neurophysiology of breathlessness from classic psychophysical experiments. We will then review the physiological adaptations to exercise that maximize ventilatory performance and minimize breathing discomfort during the stress of heavy exercise in healthy younger humans. We will consider how current concepts of dyspneogenesis might apply to exertional breathlessness in the elderly, the obese and in those with mild airway obstruction as a result of cigarette smoking. We will then outline the general and specific hypotheses for mechanisms of exertional breathlessness in these various populations. Finally, we will elaborate on the scientific methods that were employed to test the various hypotheses and research questions.

**Neurophysiology of exertional dyspnea**

Dyspnea “is the term used to characterize a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social and environmental factors, and may induce secondary physiological and behavioural responses” (American Thoracic Society, 1999).

Current theories of dyspnea are briefly outlined below and include: 1) direct afferent inputs from chemoreceptors, pulmonary/airway mechanoreceptors, and muscle/chest wall receptors, increased respiratory effort and the corollary discharge, 2) neuromechanical uncoupling of the respiratory system, and 3) respiratory muscle effort
and the corollary discharge.

**Peripheral sources of dyspnea during exercise**

Classic psychophysical experiments have taught us that “external mechanical loading studies in humans have confirmed that the respiratory stimulus has a threshold for detection, that its magnitude can be quantified, and that it is possible to reliably discriminate different qualities of respiratory sensation.” (O'Donnell *et al.*, 2007). The relative importance of the multiple components of the respiratory neurosensory system in contributing to breathlessness during exercise is impossible to determine given the considerable redundancy inherent in all sensory systems. Afferent inputs from chemoreceptors which have direct access to the somatosensory cortex can mediate breathlessness (Campbell *et al.*, 1966; Banzett *et al.*, 1987; Gandevia & Macefield, 1989). However, in healthy young subjects, during light to moderate exercise, hypoxia or hypercapnia is rarely observed; this suggests that chemoreceptor activation does not contribute directly to unpleasant respiratory sensation in this circumstance. However, the hyperventilatory response at higher exercise levels in response to the developing metabolic acidosis is thought to be primarily mediated by increased central and/or peripheral chemoreceptor activation. The attendant breathlessness near the limits of tolerance may be due directly to this increased reflexic drive (increased chemoreceptor activation), to the increased respiratory muscle activity (muscle and chest wall mechanosensors) or a combination of both (Chen *et al.*, 1992; Davenport *et al.*, 1986; Gandevia, 1982).
Lung and airway mechanosensors in exercise

The role of vagal afferents (which project to the somatosensory cortex) in exertional breathlessness in humans remain unknown (Kazakov, 1966; O'Brien et al., 1971). The lungs and the airway are innervated (Sant'Ambrogio, 1982) by 1) the slowly adapting receptors (SARs) (Schelegle & Green, 2001), 2) rapidly adapting receptors (RARs) (Kubin & Davies, 1988), and 3) nonmyelinated C-fiber receptors (Lee & Widdicombe, 2001). Both SARs and RARs respond to lung distension. (Widdicombe, 2001). C-fiber receptors are chemosensors that respond to different chemical substances (e.g. lobeline) as well as lung inflation (Coleridge & Coleridge, 1984; Lee & Widdicombe, 2001).

The strongest evidence of a vagal contribution to dyspnea comes from the work of Guz et al. (1966) and Noble et al. (1970) who demonstrated that partial vagal block can increase breath hold duration and decrease this sensation of dyspnea in health and disease. However, section of the vagi during lung transplantation surgery does not appear to affect the intensity of dyspnea during exercise, measured several months after surgery, indicating that vagal afferents are not obligatory for symptom generation (Sanders et al., 1989; Tapper et al., 1992).

Banzett & Lansing. (1996) reported that vagal receptors have an important role in volume perception, at least in C1-2 quadriplegic subjects when no chest wall mechanosensors are active (Banzett et al., 1987). In this experiment, quadriplegic subjects were able to detect changes in the tidal volume imposed by mechanical ventilator, similar to healthy subjects. Similarly, Lougheed et al. (2002) demonstrated that dyspnea intensity during methacholine induced bronchoconstriction/lung hyperinflation was similar in patients with low cervical cord section (who were deprived
of afferent input from the chest wall and its musculature) and neurologically intact controls. These investigators could not therefore rule out an important contribution from the vagus in dyspnea causation during bronchoprovocation. Pulmonary vagal afferents are ideally suited to provide precise simultaneous proprioceptive feedback about change in flows and volume within the lung. During the high tidal volume expansion of exercise, vagal afferent activity increases. It is reasonable to assume that any increased respiratory system impedance may disrupt the normal pattern of vagal activation and convey this information to consciousness. What is not known is whether in certain circumstances, abnormal vagal feedback can become “nociceptive” and directly cause dyspnea.

Chest wall mechanoreceptors

Receptors in the chest wall include the costovertebral joints, Golgi tendon organs, and muscle spindle receptors in intercostal muscles and diaphragm (Berne, 2007) all of which signal the position and dynamic displacement of the chest wall during breathing. Restriction of inspiratory movements (in disease or during extrinsic loading experiments) causes compensatory increases in afferent activity which reflexly increases inspiratory muscle force to help preserve tidal volume within the same breath (Mithoefer et al., 1953; Fowler, 1954; Gandevia, 1982; Berne, 2007). In COPD, patients, vibration of the chest wall in phase with inspiration can alleviate dyspnea (Manning et al., 1991). Aspiration of pleural fluid in patients with pleural effusions leads to immediate relief of dyspnea and is thought to reflect partial restoration of the chest wall dynamic compliance (Estenne et al., 1983) and local mechanosensor feedback inputs. Chest wall restriction during exercise in healthy volunteers causes dyspnea but it remains unclear whether this reflects altered
sensory inputs arising directly from the chest wall to the sensorium. It is possible that information from the restricted chest wall may represent only one of the multiple sensory components that culminate in a global awareness of neuromechanical uncoupling of the respiratory system (Mithoefer et al., 1953; Fowler, 1954).

Neuromechanical uncoupling

For more than 100 years, it has been suggested that the chemoreceptors contribute to the sensation of dyspnea, especially during volitional breathholding (Hill & Flack, 1908) when PCO$_2$ rises abruptly and PO$_2$ falls. However, in these experiments the concomitant altered feedback related to absence of normal respiration (i.e., thoracic volume displacement and muscle activation) also likely contributed to perceived respiratory difficulty. In the Fowler (1954) experiments, resumption of spontaneous breathing after breathhold was associated with immediate alleviation of dyspnea despite worsening of arterial blood gases (8.2% O$_2$ and 7.5% CO$_2$) and chemical drive. It would appear that integrated sensory information related to the reflex increase in central respiratory drive and simultaneous altered sensory feedback from multiple mechanoreceptors collectively modulate dyspnea under many circumstances. It follows that disruption of the relationship between central respiratory drive and the mechanical/muscular response of the respiratory system is fundamental to the origin of dyspnea. Campbell & Howell (1963) presented what they described as an irrefutable hypothesis, that dyspnea arises from “length-tension inappropriateness” at the level of the muscle spindle. Campbell & Howell (1963) reasoned that the respiratory muscles (weakened or overloaded by disease) are the proximate source of sensory information
which conveys that a disparity exists between the activation (or tension) in the muscle and the associated volume displacement (change in muscle length). Subsequent studies have found that when thoracic volume is restricted (either voluntarily or by imposition) in the face of a normal or increased central drive, dyspnea quickly escalates to intolerable levels. This theory of dyspnea was further refined to describe the concept of mismatch between efferent and afferent signals (Schwartzstein et al., 1989).

O’Donnell et al. (2000) were the first to suggest that neuro-mechanical dissociation might explain perceived respiratory difficulty during exercise under conditions of external loading. In healthy young subjects, chest wall strapping which constrained the normal $V_T$ response to exercise (compared with unloaded control) resulted in severe dyspnea described as “unsatisfied inspiration” which correlated with the attendant high effort-displacement (the relationship between the change in pleural pressure and the change in tidal volume) ratios. The combination of increased chemostimulation (by deadspace loading) and volume restriction, further disrupted effort-displacement ratios and thus amplified perceived inspiratory difficulty (Fowler, 1954; Harty et al., 1999; O’Donnell et al., 2000). Subsequent studies in patients with chronic obstructive lung disease, interstitial lung disease and congestive heart failure have bolstered the contention that neuromechanical dissociation contributes to the intensity and quality of dyspnea during exercise in patients with these conditions (O’Donnell et al. 1998a; O’Donnell et al. 2006b).

Respiratory muscle effort and the corollary discharge

The sense of respiratory muscle effort, “is the conscious awareness of the voluntary activation of skeletal muscles” (Manning & Schwartzstein, 1995). Recent
theories about the mechanisms of dyspnea during exercise have emphasized the central importance of the perception of increased contractile inspiratory muscle effort (Killian et al., 1984; el-Manshawi et al., 1986; Chen et al., 1992). As $\dot{V}_E$ increases relative to the maximal possible ventilation, then the associated muscular effort must increase in proportion. Exertional dyspnea intensity correlates well with $\dot{V}_E$/maximal ventilatory capacity (MVC) (the original dyspnea index) (Gandevia & Hugh-Jones, 1957) and respiratory effort relative to maximum (measured by esophageal pressure) (LeBlanc et al., 1988). During cycle exercise, the sense of effort increases linearly with the power output (Killian et al., 1992). At a given power output, the perceived work/effort of breathing is affected by the strength of the respiratory muscle, lung volume, gender, and age (Killian et al., 1992). Based on animal studies, increased motor output is thought to be accompanied by increased corollary discharge to the somatosensory cortex, where it is directly perceived as a heightened sense of effort (Davenport et al., 1986; Gandevia & Macefield, 1989; Chen et al., 1992). Qualitative descriptors of breathlessness at the end of exercise in healthy subjects allude mainly to increased “effort” or “work” or “heaviness” of breathing. These descriptors are also pervasive at end-exercise in subjects with cardiopulmonary disease (Lougheed et al., 1993; O'Donnell et al., 1998a; O'Donnell et al., 2000). Increased corollary discharge therefore remains a plausible mechanistic explanation for exertional breathlessness linked to higher ventilation levels.

However, a sense of heightened effort is clearly not the only source of exertional breathlessness in healthy subjects. Breathlessness arises abruptly in healthy individuals who are subject to chemostimulation under conditions of ventilatory muscle paralysis at rest when contractile effort is absent (Gandevia, 1982). Moreover ventilatory assistance
that reduces muscular effort does not consistently abolish the sense of dyspnea suggesting that other sources of unpleasant respiratory sensation exist (Lansing et al., 2000; Moosavi et al., 2000).

In summary little is known about the precise neurophysiological underpinnings of exertional breathlessness in healthy young adults. We do know that perceived intensity of breathlessness rises as ventilation approaches MVC and the attendant contractile muscular effort rises towards its levels. Increased central corollary discharge from the motor cortex remains one plausible mechanism of exertional breathlessness. However, at high ventilation levels near the limits of tolerance (when tidal volume expansion is maximal and acid-base disturbances develop), we cannot rule out additional dyspneogenic sensory inputs arising directly from chemoreceptors and multiple mechanosensors throughout the respiratory system. Based on the experimental data on the sensitivity of neurosensory systems (peripheral and central mechanosensors) to detect any disruption to the act of spontaneous breathing (described above), it is remarkable that healthy humans have the ability to generate very high ventilation levels (>100 L/min) during the high metabolic demands of exercise with minimal respiratory distress. The next section explores possible physiological adaptations that explain why breathlessness is rarely the locus of sensory limitation during exercise in healthy young adults.

**Ventilatory adaptations to avoid breathlessness during exercise in normal healthy subjects**

The regulation of $\dot{V}_A$ to match metabolic demand ($\dot{V}O_2, \dot{V}CO_2$) is achieved by three important neural control mechanisms: 1) a feed-forward mechanism from higher
locomotor centers of the central nervous system which drives the medullary respiratory pattern generator in parallel with increasing locomotor muscle activity, 2) a feedback signal from exercising muscles to the respiratory pattern generator in the medulla which drives ventilation with increasing muscular contraction (Eldridge & Waldrop, 1991; Kaufman & Forster, 1996), and 3) additional afferent inputs to the respiratory centers from the central and peripheral chemoreceptors in response to arterial acid base perturbations at the extreme of exercise. Several acute ventilatory adaptations ensure that the ventilatory system will be able to respond to the increased metabolic demand with a minimal increase in the work of breathing and in the sensation of breathing discomfort. These include control of airway caliber, control of operating lung volumes, optimization of breathing pattern, and minimization of pulmonary gas exchange inefficiency.

Control of airway caliber during exercise

In healthy subjects, the increased respiratory flow rates occur in the absence of a significant increase in airway resistance (Warren et al., 1984). This is achieved by an increase in the caliber of both the upper and lower airways. Reduced upper airways resistance is achieved by recruitment of inspiratory muscles in the laryngeal passage (England & Bartlett, 1982), tongue (Williams et al., 2000), and nasal passages (Williams et al., 2000). This mechanism protects the upper airways from narrowing during high negative intrathoracic inspiratory pressure of heavy exercise (Rodman et al., 2002). Similarly, the change from nasal breathing to oral-nasal breathing contributes to the decrease in upper airway resistance (Clanton et al., 1987). Withdrawal of parasympathetic tone during exercise reduces resistance in the smaller airways (Warren et al., 1984).
Control of operating lung volumes

During exercise in young healthy individuals, increased tidal volume is accomplished by encroaching on both the inspiratory reserve volume (IRV) and the expiratory reserve volume (ERV) (Kagawa & Kerr, 1970; Sharratt et al., 1987; Henke et al., 1988). A decrease in end-expiratory lung volume (EELV) early in the exercise, secondary to expiratory muscle recruitment, has several important advantages during exercise. EELV reduction allows tidal volume to be maintained within the most compliant (linear portion) of the respiratory system’s pressure-volume (P-V) relation, thus minimizing the increase in the elastic work of breathing. Forceful expiratory muscle recruitment means that the inspiratory muscles are assisted by the outwards recoil of the lower ribcage at the onset of each inspiration. Moreover, abdominal muscle recruitment causes cephaloic displacement of the diaphragm which improves the length-tension relationships of the latter.

Quantitative flow-volume loop analysis with serial inspiratory capacity measurements throughout exercise provides an indirect evaluation of dynamic ventilatory mechanics. Thus serial measurement of IC allows an assessment of the proximity of tidal volume to TLC and the upper extreme of the P-V relation. During exercise in healthy young subjects, the ratio between effort (change in pressure relative to maximal capacity) and volume displacement (change in volume relative to volume capacity) is constant (O'Donnell et al., 2000). This suggests that optimization of operating lung volumes during exercise in health allows the preservation of the harmonious relationship between effort and volume displacement.
Optimization of breathing pattern

Increase in $V_E$ during exercise is achieved by both an increase in tidal volume and increase in breathing frequency ($f$). The larger increase in tidal volume as compared with $f$ early in exercise minimizes the wasted ventilation with each inspiration. This pattern of breathing also reduces the flow-resistive work that is more related to $f$ (Younes & Kivinen, 1984). During exercise in healthy people, tidal volume reaches a plateau close to 75% of IC (or 50% of VC) (Hey et al., 1966; Cotes, 1970; Younes & Kivinen, 1984). This helps to minimize the elastic work of the respiratory muscles by avoiding the less compliant portion of the respiratory system (close to TLC).

Several psychophysical experiments have shown that breathing pattern during external mechanical loading is optimized both by behavioural and reflex mechanisms (el-Manshawi et al., 1986; Kayser et al., 1997). Thus, the compensatory response to inspiratory resistive loading is prolongation of inspiratory time with reduced flow to minimizes intra-thoracic pressure perturbations and presumably the attendant discomfort (el-Manshawi et al., 1986). Similarly, the sensory consequence of elastic loading obviated by adopting a shallow breathing pattern (Kayser et al., 1997). The theory of optimization of breathing pattern for comfort during extrinsic and intrinsic mechanical loading is supported by several previous studies and can be extrapolated to the physiological stress of exercise (Otis, 1954; Mead, 1960; el-Manshawi et al., 1986; Poon, 1989a; 1989b).

Maximize gas exchange inefficiency

The efficiency of pulmonary gas exchange for oxygen within the lung is calculated from the difference between the alveolar and the arterial partial pressure of $O_2$ ($A-a DO_2$) (Haverkamp et al., 2002). During exercise a small increase $A-a DO_2$ is present
mainly due to alveolar ventilation ($\dot{V}_A$) and pulmonary blood flow ($\dot{Q}$) inequality (West & Dollery, 1960; West, 1985; Hakim et al., 1988), diffusion limitation of $O_2$, and small right-to-left intrapulmonary and intracardiac shunts (Gale et al., 1985; Hammond et al., 1986). The overall small $\dot{V}_A/\dot{Q}$ inequality is present due to maldistributed regions in lungs. However, the increase in $\dot{V}_A$ out of proportion to $\dot{Q}$ ensures a more uniform ventilation of the lungs. Diffusion limitation is suggested to occur only at very high exercise intensity ($\dot{V}O_2$: 2.5-3 L/min) and mainly in athletes, when transit time of the blood cell is lower than 0.5 second. Small right to left shunts were found not to contribute to gas exchange inefficiency. With advanced aged especially in smokers, increase in $\dot{V}_A/\dot{Q}$ inequality and decrease in diffusion capacity has been reported (Wagner et al., 1974; Barbera et al., 1994). Both indices may contribute to increase ventilatory drive at a given metabolic demand.

In summary, to the extent that the above-mentioned ventilatory adaptations successfully obviate respiratory discomfort during exercise in healthy young, it is reasonable to suggest that any disruption of these adaptations (increased airway resistance, abnormal operating lung volumes and $\dot{V}_A/\dot{Q}$ derangements) will have negative sensory consequences. In the healthy elderly population, increased ventilatory requirements due to increased $\dot{V}_A/\dot{Q}$ abnormalities and alterations in the behaviour of operating lung volumes would lead to earlier onset of breathlessness and exercise limitation. These changes may be more pronounced in elderly women whose maximal ventilatory capacity is reduced relative to age-matched men.
General hypothesis

It is hypothesized that in individuals with preserved resting pulmonary function, increased intensity of breathlessness during activity will arise as a result of measurable abnormalities of dynamic ventilatory mechanics, central respiratory drive, or both in combination. In specific populations with documented troublesome exertional breathlessness (i.e., the elderly, older individuals with mild COPD and those with obesity), consistent abnormalities of dynamic airway function and in the behaviour of operating lung volumes during exercise will culminate in significant mechanical constraints to increasing ventilation. The effects of these mechanical constraints on perceived respiratory difficulty during exercise will be further amplified by the attendant increase in central respiratory drive as a result of variable abnormalities in pulmonary gas exchange and in metabolic loading.

Specific hypotheses

Chapter 2: It was hypothesized that aging will be associated with an increase in exertional breathlessness at a given metabolic rate as compared to control. This increase in exertional breathlessness will be associated with increased ventilatory drive, increased mechanical restriction or some combination of the two. Further, the relatively reduced baseline ventilatory capacity in females will have more pronounced negative effects on subjective dyspnea during exercise compared with age-matched males.
Chapter 3: It was hypothesized that in mild COPD, a higher intensity of exertional breathlessness compared with age-matched healthy participants will be associated with: 
1) greater ventilatory demand, 2) increased mechanical loading of the ventilatory muscles during exercise or 3) a combination of both.

Chapter 4: It was hypothesized that inhaled bronchodilator therapy will improve airway function and lung volumes at rest and reduces the rate of dynamic pulmonary hyperinflation during exercise, thus permitting greater tidal volume expansion and higher submaximal ventilation. These mechanical improvements reduce breathlessness intensity ratings at standardized exercise $\dot{V}_E$.

Chapter 5: It was also hypothesized that if the intensity of breathlessness at any given $\dot{V}_E$ and $\dot{V}O_2$ is not different between obese and normal-weight control subjects, then respiratory mechanical factors are unlikely to contribute to breathlessness. Alternatively, an increase in the breathlessness/$\dot{V}_E$ and breathlessness/$\dot{V}O_2$ slopes during cycle exercise in obese compared with normal-weight participants indicates that restrictive ventilatory mechanics in obesity contribute to increased breathing discomfort.
Summary of Scientific Methods

Exercise-induced increases in ventilatory demand were used to challenge the available limits of the respiratory control system in the above-mentioned experimental groups (to determine potential mechanical ventilatory constraints), while provoking an increase in perceived breathing discomfort to mimic that experienced during activities of daily living (Horsley et al., 1991; Sjostrom et al., 1992; Bulpitt et al., 1998; Tessier et al., 2001; Ho et al., 2001; Jones, 2001; Sin et al., 2002).

Maximal symptom-limited cycling or treadmill exercise tests were evaluated for: 1) the normalcy of the physiological response patterns and maximal capacity, 2) perceived symptoms of breathing and leg discomfort during exercise, at a standardized load, and at peak exercise, and 3) relationships between physiological measurements and symptom perception.

To examine the normalcy of the physiological responses, we compared the response patterns and capacity measurements to those of “non-breathless” control groups and to acceptable reference values (American Thoracic Society & American College of Chest Physicians, 2003; Palange et al., 2007). Physiological measurements included metabolic, cardiovascular, ventilatory responses, as well as the integration of these responses (see Chapter 2,3,4,5 results and discussion).

Prior to evaluating the ventilatory adaptations to exercise, we first verified that subjects gave their maximal effort according to accepted guidelines (American Thoracic Society & American College of Chest Physicians, 2003). We then examined the normalcy of the metabolic and the cardiovascular responses to exercise. Metabolic responses were measured based on the relationship between $\dot{V}O_2$ uptake $\dot{V}CO_2$
elimination for a given exercise load. Cardiovascular parameters were evaluated based on the accepted criteria for such parameters as heart rate (HR), \( O_2 \) pulse (for estimation of stroke volume (SV)), blood pressure (systolic and diastolic) and the normalcy of the electrocardiogram. The ventilatory threshold (VTh) (where \( V\dot{CO}_2 \) and \( V\dot{O}_2 \) relationship become nonlinear, and that was verified by the relationship between \( V_{E}/V\dot{O}_2 \) and \( V_{E}/V\dot{CO}_2 \) as well as \( P_{ET}CO_2 \) and \( P_{ET}O_2 \); as described in Chapter 5 methods; Wassereman et al., 1999) was determined in all the experiments so as to eliminate other potential contributors to exercise limitation and to compare some ventilatory and metabolic parameters at that point.

### Measurements of symptom perception

Perceived dyspnea during daily activities and exercise was measured using the following instruments: 1) chronic dyspnea using the modified Medical Research Council (MRC) dyspnea scale (Appendix A), the oxygen cost diagram (OCD) (Appendix B), and the Baseline Dyspnea Index (BDI) (Appendix C) (Fletcher et al., 1959; McGavin et al., 1978; Mahler et al., 1984; Brooks, 1982), 2) dyspnea and leg discomfort during exercise using the Borg scale (0-10) (Borg, 1982), 3) qualitative descriptors of dyspnea at the end of exercise using a questionnaire modified by O’Donnell and coworkers (1998a) from that of Simon et al. (1989; 1990).

The MRC scale, OCD, and BDI were designed to evaluate chronic activity-related dyspnea. These clinical tools have been examined for validity and reliability using accepted guidelines (Stoller et al., 1986; Guyatt et al., 1987; Mahler et al., 1987; Mahler et al., 1989). The MRC and OCD use unidimensional scales: “category or analog scale focused on a single dimension that provoked breathlessness” (Mahler, 2005b). The BDI
is a multidimensional instrument that evaluates three different aspects of dyspnea: functional impairment, magnitude of effort, and magnitude of task. The MRC scale, OCD and BDI aim to discriminate between people on the basis of the severity of dyspnea during different daily activities. The BDI is thought to be more sensitive to small but clinically relevant changes than the unidimensional instruments such as the MRC and OCD (Mahler, 2005b). This is even more relevant when dealing with populations with only mild increases in symptoms of breathlessness such as occurred in the present study.

*Dyspnea perceived during acute bouts of exercise* was measured using the modified 10-point Borg scale (Borg, 1982). This is a widely used scale for measurement of dyspnea during exercise (Mador et al., 1995; O'Donnell et al., 1998b; O'Donnell et al., 2000; Weiner et al., 2002). The modified Borg scale is constructed of numbers ranging from 0 to 10 with corresponding word descriptors of intensity/severity (*Appendix D*). Participants are asked to select a number between 0 and 10 that reflects the intensity of their perceived breathing (or leg/limb) discomfort (Borg, 1990). The Borg scale is reproducible between different tests (Muza et al., 1990; Mador et al., 1995; O'Donnell et al., 1998b). In addition, it is to medical interventions such as administration of bronchodilators (Ayers et al., 2001; Belman et al., 1996; O'Donnell et al., 1998b) and exercise conditioning (Gigliotti et al., 2003; O'Donnell et al., 1995). Descriptors of breathing discomfort correspond to the number chosen by the subjects allow comparisons across different populations when using the Borg scale (Mahler, 2005a).

*Qualitative aspects of perceived breathing discomfort* at peak exercise were described by completion of a questionnaire modified from Simon et al. (1990). Dyspnea includes several qualitatively distinct sensations (“descriptors”) that vary in intensity and
is influenced by a wide variety of factors (Simon et al., 1989; Simon et al., 1990; Elliott et al., 1991). These studies suggest that different sensations can arise from different pathophysiological mechanisms and that the use of verbal descriptors of dyspnea may contribute to the understanding of the mechanisms of dyspnea and assist in identifying or predicting a specific diagnosis.

**Ventilatory responses to exercise**

We evaluated ventilatory responses to exercise specifically ventilation, breathing pattern, and operating lung volumes, quantitative flow-volume loop analysis, and in a small subset, esophageal-pressure-derived ventilatory mechanics. The appropriateness of the ventilatory response to metabolic demand during exercise was evaluated using the relationships between $V_E$ and $\dot{V}CO_2$ and $\dot{V}O_2$ based on accepted criteria (American Thoracic Society; American College of Chest Physicians, 2003), the ventilatory threshold (VTh) (Beaver et al., 1986), as well as $V_E/\dot{V}CO_2$ and $V_E/\dot{V}O_2$ ratios. These relationships were evaluated in response to increasing exercise intensity, both below and above the anaerobic threshold (estimated based on the V-slope method for ventilatory threshold detection). VTh was detected individually using the V-slope method (Wasserman et al. 1999) and verified against other points, i.e., the $\dot{V}O_2$ at which the ventilatory equivalent for oxygen $V_E/\dot{V}CO_2$ begins to increase systematically without an increase in $V_E/\dot{V}CO_2$ and where $P_{ET}O_2$ begins to increase without a decrease in $P_{ET}CO_2$ (Wasserman et al. 1999).

Arterial oxygen saturation ($SpO_2$) was estimated using pulse oximetry. Pulse oximetry gives accurate measurement of oxygen saturation as compared with gold
standard measurements of arterial O$_2$ saturation (Ries et al., 1985). Significant haemoglobin desaturation is present when a fall of $\geq 5\%$ in SpO$_2$ lasts at least 2 min (American Association for Respiratory Care, 1992).

**Breathing pattern** was evaluated for the change in $V_T$, $f$ and duration of inspiration ($T_i$) and expiration ($T_e$) and duty cycle ($T_i/T_{TOT}$). We evaluated these parameters based on the established relationship between $V_T$ and $V_{E}$, and $f$ and $V_{E}$ (Hey et al., 1966; Cotes, 1970). Similarly the ratio between anatomical dead space ($V_D$), measured using the Jones (1988) prediction equation, and $V_T$ was examined to evaluate the relative and absolute volume of air (ml) that is not participating in pulmonary gas exchange.

Breathing pattern was also evaluated by plotting $V_T$ within the maximal flow-volume loop at rest and at the end of exercise, as recommended by Johnson et al. (1999). This analysis provides valuable insights into the nature and extent of abnormalities of ventilatory mechanics and their contribution to exercise limitation. Based on this analysis, we determined the percent of $V_T$ that encroached on the iso-volume expiratory or inspiratory loop of the maximal flow-volume loop (% tidal expiratory flow limitation).

**Operating lung volumes** at rest and during exercise were derived from measurements of dynamic inspiratory capacity (IC). Assuming that TLC remained constant (Stubbing et al., 1980a; 1980b), changes in IC reflect changes in end-expiratory lung volume ($EELV=TLC-IC$), and changes in inspiratory reserve. This has been found to be a reliable and reproducible method of tracking acute changes in lung volumes in patients with respiratory diseases (Yan et al., 1997; O’Donnell et al., 1998b). Regardless of the behaviour of TLC, a decrease in IC and IRV indicates increasing proximity of the
$V_T$ to TLC and the upper non-compliant portion of the respiratory system pressure-volume relationship where there is increased elastic and inspiratory threshold loading.

**Evaluating the interaction between physiological responses to exercise and perceived symptoms**

To evaluate the interaction between physiological parameters (stimulus) and the perceptual responses (response), we performed the following steps: 1) plotted ratings of dyspnea intensity versus either power output (in cycling) or $\dot{V}O_2$ (walking), 2) plotted dyspnea versus $V_E$, and 3) to identify important contributors to dyspnea at a standardized stimulus. Compared with the control group, a significant increase in the slope of dyspnea/work rate (or $\dot{V}O_2$) and/or an increase in dyspnea at a standardized load confirmed our hypothesis that symptoms of dyspnea during physical activity increase in the experimental groups. Evaluation of dyspnea/$\dot{V}E$ relationships and correlative analysis allowed us to examine the following potential contributors to exertional dyspnea in the experimental groups: 1) ventilatory demand, 2) abnormalities of dynamic ventilatory mechanics, or 3) a combination of both of these.

To determine the importance of chemical (i.e., ventilatory demand) and/or respiratory mechanical factors to exertional breathlessness in the elderly (Chapter 2), obese women (Chapter 5), symptomatic mild COPD (Chapter 3), with and without acute bronchodilator therapy (Chapter 4), we compared dyspnea/$\dot{V}E$ relationships throughout exercise with those of appropriately matched control groups. Previous studies from our laboratory have shown that, compared with control conditions, dyspnea/$\dot{V}E$ relationships
were not altered by either increasing (by dead space, i.e., chemical (or CO$_2$) loading) or decreasing (by hyperoxia) chemostimulation (and thus ventilatory demand) during exercise in healthy men (O’Donnell et al., 2000) and in patients with moderate-to-severe COPD (Peters et al., 2006), respectively. However, both Harty et al. (1999) and O’Donnell et al. (2000) showed that external thoracic restriction (i.e., chest wall strapping) imposing a mechanical constraint which limit $V_T$ and resulted a significant increased (vs. unloaded control) dyspnea intensity ratings at any given $V_E$ during exercise in healthy men. Similarly, studies of pharmacological (i.e., bronchodilators (O’Donnell et al., 1998a; Belman et al., 1996), and surgical (i.e., lung volume reduction surgery (Young et al., 1999; Laghi et al., 1998) mechanical respiratory unloading in patients with chronic pulmonary disease have demonstrated consistent reductions in dyspnea intensity at any given $V_E$ during exercise compared with control. These findings strongly support a central role for respiratory mechanical factors (or muscle weakness) in dyspnea causation (or relief). Alternatively, an increase (or decrease) in dyspnea intensity at any given work rate during exercise compared with control supports a central role for central reflexic ventilatory drive in dyspnea causation (or relief), provided that the dyspnea/$V_E$ relationship is preserved.

The final portion of each investigation included correlative analysis. We examined associations between dyspnea at a given stimulus (dependent variable) and various relevant physiological indices (independent variables) that were known or potentially implicated in dyspnea causation (based on previous work from the Respiratory Investigation Unit and other studies). Regression analysis also took into
account potential inter-relationship between independent variables.

The resultant correlations provided us with a list of parameters that had a significant association with dyspnea. To examine these associations or generate new hypotheses based on the study results of Chapter 4, we designed an experiment in which the independent variable could be modified. In this regard, the use of an anticholinergic bronchodilator in mild COPD was used to decrease hyperinflation during exercise and thereby improve ventilatory mechanics and decrease exertional dyspnea intensity. The higher IC and VT, as well as the associated decrease in breathlessness on the iprterium bromide visit compared with placebo visit in this study confirm that mechanical factors play an important role in exercise limitation and exertional dyspnea.
Chapter 2: Gender Differences in the Perceived Intensity of Breathlessness during Exercise with Advancing Age

Dror Ofir, Pierantonio Laveneziana, Katherine A. Webb, Yuk-Miu Lam, Denis E. O’Donnell

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ABSTRACT

The prevalence of activity-related breathlessness increases with age, particularly in females, but the specific underlying mechanisms have not been studied. This novel cross-sectional study was undertaken to examine the effects of age, gender and their interaction on the perceptual and ventilatory responses to incremental treadmill exercise in 73 healthy participants (age range 40-80 years) with normal pulmonary function. Age-related changes at a standardized oxygen uptake ($\dot{V}O_2$) during exercise included: significant increases in breathlessness ratings (Borg scale), ventilation ($\dot{V}_E$), ventilatory equivalent for carbon dioxide and the ratio of tidal volume ($V_T$) to dynamic inspiratory capacity (IC) (all $p<0.05$). These changes were quantitatively similar in females ($n=39$) and in males ($n=34$). For the entire group, exertional breathlessness ratings increased as resting static inspiratory muscle strength diminished ($p=0.05$), as exercise $\dot{V}_E$ increased relative to capacity ($p=0.013$) and as the $V_T$/IC ratio increased ($p=0.003$) during exercise. Older females (60-80 years, $n=23$) reported greater ($p<0.05$) intensity of exertional breathlessness at a standardized $\dot{V}O_2$ and $\dot{V}_E$ than age-matched males ($n=16$), despite similar age-related changes in ventilatory demand and dynamic ventilatory mechanics. These increases in breathlessness ratings in older females disappeared when gender-differences in baseline maximal ventilatory capacity were accounted for. Conclusion: Although increased exertional breathlessness with advancing age is multifactorial, contributory factors included: higher ventilatory requirements during exercise, progressive inspiratory muscle weakness and restrictive mechanical constraints on $V_T$ expansion related to the reduced IC. The sensory consequences of this age-related
respiratory impairment were more pronounced in females who, by nature, have relatively reduced maximal ventilatory reserve.

INTRODUCTION

Cardiovascular factors are widely accepted as a proximate limit to maximal oxygen uptake ($\dot{V}O_2$) during weight-bearing exercise in healthy humans (Wagner et al., 1974; Wagner et al., 1996; Saltin & Calbet, 2006). By contrast, the respiratory system is regarded as relatively “overbuilt” and less likely to contribute to exercise limitation except in elite athletes at very high power outputs (Dempsey et al., 1984; Harms et al., 2000). However, in sedentary older individuals, intolerable exertional breathlessness may contribute to exercise limitation even before physiological maxima are attained (Ofir et al., 2008). Several studies have reported that more than 30% of the elderly (>65 years) experience breathlessness during activities of daily living (Horsley et al., 1991; Ho et al., 2001; Tessier et al., 2001; Mahler & Baird, 2005). The nature and mechanisms of exertional breathlessness in older healthy humans are poorly understood. While the physiological effects of aging on the respiratory system are well established (Johnson et al., 1991a; Johnson et al., 1991b; Delorey & Babb, 1999; Pride, 2005), the interaction between the changes in respiratory system compliance, muscle function and ventilation/perfusion ($V_A/Q$) matching and the perceptual responses to physical exertion is largely unknown. Psychophysical studies of external mechanical loading have indicated that sensory thresholds for imposed external load detection are increased in the elderly compared with youth (Tack et al., 1983; Pride, 2005) but the impact of aging on magnitude estimation of respiratory sensation during a variety of physiological
perturbations (including exercise) is uncertain. This information becomes important if we are to improve the evaluation and management of exertional breathlessness in the healthy elderly or in patients with chronic cardiopulmonary conditions, many of whom are elderly.

The complaint of activity-related breathlessness appears to be more common in older women than in older men (Becklake & Kauffmann, 1999; Tessier et al., 2001). Women report greater intensity of breathlessness at a given power output during incremental cycle exercise (Killian et al., 1992). Population studies in patients with various cardiopulmonary conditions have similarly indicated that, when matched for disease severity, women experience greater levels of respiratory difficulty, greater exercise intolerance and poorer perceived health status than their male counterparts (Watson et al., 2004; de Torres et al., 2005; Pride, 2005; Han et al., 2007). The mechanisms underlying the propensity for women to experience more disabling symptoms than men with similar disease staging are unknown.

This is the first study to explore potential mechanisms underlying gender differences in exertional breathlessness in healthy individuals. Our objective was to determine if possible gender differences in the nature or degree of age-related respiratory impairment accounted for differences in respiratory sensation at a standardized exercise stimulus. We wished to determine if the increased intensity of exertional breathlessness in elderly women compared to age-matched men was associated with greater dynamic mechanical constraints during exercise secondary to relatively reduced inspiratory capacity and static inspiratory muscle strength in women. We hypothesized that, regardless of any gender based differences in the progressive respiratory impairment of
aging, the relatively reduced baseline ventilatory capacity in females would result in more pronounced negative effects on subjective breathlessness during exercise compared with age-matched males.

We undertook a cross-sectional study to compare the effects of aging on perceptual and ventilatory responses to incremental treadmill exercise in healthy male and female participants whose ages ranged from 40 to 80 years. We completed within- and between-gender comparisons of: 1) age-related changes in resting pulmonary function and skeletal (ventilatory and peripheral) muscle strength and 2) age-related changes in expiratory flow limitation, breathing pattern, operating lung volumes, and pulmonary gas exchange during exercise. We conducted correlative analyses to determine the main independent contributory factors to exertional breathlessness and examined the interaction between the effects of age and gender on symptom perception.

METHODS

Subjects

Subjects were recruited by advertising for research volunteers in the community. Males and females between 40 and 80 years of age were included if they had normal spirometry [forced expiratory volume in 1 second (FEV$_1$) $\geq$ 80 %predicted, ratio between FEV$_1$ and forced vital capacity (FEV$_1$/FVC) > 70 %] and no evidence of respiratory diseases such as chronic obstructive pulmonary disease (COPD) or bronchial asthma. Subjects were excluded if they had: 1) a medical condition which could cause or contribute to breathlessness, i.e., metabolic or cardiovascular disease or 2) other disorders which could interfere with exercise testing such as neuromuscular or musculoskeletal
disorders. Subjects were divided into four groups based on sex and age: younger females 40-59 years (YF), younger males 40-59 years (YM), older females 60-80 years (OF), and older males 60-80 years (OM).

Study Design

This was a controlled, cross-sectional study in which informed consent was obtained from all subjects and ethical approval was received from the University and Hospital Health Sciences Human Research Ethics Board. Subjects attended the laboratory once for a 4-6 hour visit. Medical, smoking and symptom histories were obtained by questionnaire. Chronic activity-related dyspnea was assessed using the Medical Research Council (MRC) dyspnea scale, Baseline Dyspnea Index (BDI) and an oxygen cost diagram (Fletcher et al., 1959; McGavin et al., 1978; Mahler et al., 1984). Habitual physical activity was assessed as either “active” (exercised at least twice per week on a regular basis) or “sedentary” (exercised less than twice per week on a regular basis) at the time of questionnaire completion. Procedures at this visit included: anthropometric measurements (height, weight, circumferences, skinfold thicknesses), complete pulmonary function tests, symptom-limited incremental treadmill test and, after an appropriate recovery period of 60-90 min, peripheral muscle strength tests.

Pulmonary Function Testing

Routine spirometry, constant-volume body plethysmography, single-breath diffusing capacity for carbon monoxide (DLCO), and maximum inspiratory and expiratory mouth pressures [PImax and PEmax; measured at functional residual capacity (FRC) and total lung capacity (TLC), respectively] were performed using an automated pulmonary
function testing system (6200 Autobox DL or Vmax229d; SensorMedics, Yorba Linda, CA) in accordance with recommended techniques (American Thoracic Society; European Respiratory Society, 2002; MacIntyre et al., 2005; Miller et al., 2005a; Miller et al., 2005b; Pride, 2005; Wanger et al., 2005; Han et al., 2007). Pulmonary function measurements were expressed as percentages of predicted normal values (Burrows et al., 1961; Crapo et al., 1982; Morris et al., 1988); predicted normal inspiratory capacity (IC) was calculated as predicted TLC minus predicted FRC.

Peripheral Muscle Strength

Peripheral muscle strength was assessed using a computerized isokinetic dynamometer (LIDO Active System; Loredan Biomedical, West Sacramento, CA). Maximal knee and elbow torques were measured in the sitting position, with movement patterns ranging from 90° of flexion to full extension, at an angular velocity of 60°/s. Mid-upper arm and thigh circumference were measured to account for muscle mass.

Cardiopulmonary Exercise Testing

Symptom-limited exercise tests were conducted on an electronically controlled treadmill (MedTrack ST55; Quinton Instrument Co., Bothell, WA) using a metabolic cart (Vmax229 Cardiopulmonary Exercise Testing Instrument; SensorMedics, Yorba Linda, CA). Exercise tests were performed using an incremental protocol (Balady et al., 2000; Pride, 2005): either a Bruce, modified Bruce or modified Naughton protocol was selected depending upon individual body size and level of fitness. Exercise tests were terminated at the point of symptom limitation (i.e., peak exercise) or if participants were unable to maintain the treadmill speed. A maximal effort was confirmed based on
accepted criteria (American Thoracic Society; American College of Chest Physicians, 2003). Cardiopulmonary exercise test parameters were collected on a breath-by-breath basis while subjects breathed through a mouthpiece with nasal passages occluded by a nose-clip. Pulse oximetry using a finger sensor (SatTrak; SensorMedics) and electrocardiographic monitoring (Q710; Quinton Instrument Co., Bothell, WA) were carried out continuously; and blood pressure was measured at rest and at regular intervals throughout exercise testing.

**Symptom evaluation:** Exertional breathlessness was defined as “the sensation of labored or difficult breathing” and leg discomfort as “the level of leg difficulty/discomfort experienced during exercise.” Before exercise testing, subjects were familiarized with the modified Borg scale (Borg, 1982) and its endpoints were anchored such that zero represented “no breathlessness (leg discomfort)” and 10 was “the most severe breathlessness (leg discomfort) that they had ever experienced or could imagine experiencing.” By pointing to the Borg scale, subjects rated the magnitude of their perceived breathlessness and leg discomfort at rest, every 2 to 3 minutes and at the peak exercise. Upon exercise cessation, subjects were also asked to verbalize their main reason for stopping exercise (i.e., breathlessness, leg discomfort, both breathing and legs, or other) and this reason was documented. In addition, the sensory aspects of perceived breathing discomfort at peak exercise were described by completion of a questionnaire modified from Simon et al. (1990).

**Breathing pattern and operating lung volumes:** Breathing pattern (timing, flow and volume measurements) and dynamic IC were measured using the SensorMedics Vmax229 system as previously described (O’Donnell et al., 2001). Operating lung
volumes and their changes during exercise were derived from measurements of dynamic IC that were performed at rest, within the last 30 s period of each increment of exercise and at peak exercise. Assuming that TLC remained constant (Stubbing et al., 1980a, Stubbing et al., 1980b), changes in IC reflect changes in end-expiratory lung volume (EELV=TLC-IC), and changes in inspiratory reserve volume (IRV=IC-VT) reflected changes in end-inspiratory lung volume (EILV=TLC-IRV). This has been found to be a reliable method of tracking acute changes in lung volumes (Yan et al., 1997; O'Donnell et al., 1998b). Tidal flow-volume curves at baseline, at each stage during testing, and at peak exercise were constructed for each patient and placed within their respective maximal flow-volume envelopes using the coinciding IC measurements. Estimates of expiratory flow limitation were made from these flow-volume loops using a previously described method (Johnson et al., 1999).

**Exercise endpoints:** Exercise variables were measured and averaged in 30 s intervals throughout each test stage and at peak exercise; peak exercise was defined as the last 30 s of loaded exercise. The ventilatory threshold (VTh) was detected individually using the V-slope method (Beaver et al., 1986) and verified by combining three methods (Gaskill et al., 2001). Relationships between VT and ventilation (VE) were examined and a point of inflection was determined for each subject (Hey et al., 1966). We compared our measurements of peak VO2 with predicted normal values accounting for sex, age, height and weight; a correction factor of 1.09 was applied to estimate the difference between predicted values obtained with cycle versus treadmill ergometry since treadmill testing results in higher values for peak VO2 (Blackie et al., 1989). Other exercise
parameters were compared with predicted normal values of Jones (1988). Maximum ventilatory capacity (MVC) was estimated as \(\text{FEV}_1\) multiplied by 35 (Gandevia & Hugh-Jones, 1957).

Statistical Analysis

A sample size of 16 provides a statistical power (80%) to detect a significant difference in dyspnea intensity (Borg Scale) measured at a standardized work-load during incremental treadmill exercise based on a relevant difference in Borg ratings of ±1, a SD of 1 for Borg ratings changes found at our laboratory, \(\alpha=0.05\), and a two-tailed t-test of significance. Values are reported as means ± SD unless otherwise specified. The conventional level of statistical significance of 0.05 was used for all analyses.

Qualitative descriptors of breathlessness were analyzed as frequency statistics; group comparisons were made using Pearson’s chi-square test. Borg dyspnea ratings, cardiorespiratory parameters, metabolic parameters, breathing pattern and operating lung volumes were compared at rest, at peak exercise and at a standardized \(\dot{V}O_2\) during exercise (the highest equivalent \(\dot{V}O_2\) achieved for comparison between the female age groups and between the 60-80 y/o groups was 20 ml/kg/min; a \(\dot{V}O_2\) of 25 ml/kg/min was used for comparisons between the male age groups). Exercise response slopes were studied using linear regression analysis of data sets from each individual. Summary statistics were compared using a 2×2 ANOVA for gender and age differences between the four groups. In case of a significant interaction between age and gender from the 2×2 ANOVA, four pairwise comparisons (YF versus OF, YM versus OM, YF versus YM, and OF versus OM) were performed using the post-hoc multiple
comparison approach; Bonferroni adjustment was applied to adjust the p-values for these four comparisons.

Relationships between exertional dyspnea intensity (Borg ratings at a standardized $\dot{VO}_2$) and possible physiological contributors (concurrent exercise measurements and baseline pulmonary function) were determined by Pearson correlations. To test the possibility of a different relationship between the dependent variable and the independent variable across groups, an interaction term was incorporated into the regression model.

RESULTS
Subjects

A total of 73 subjects completed the study: YF (n=16), OF (n=23), YM (n=18), and OM (n=16). Subject characteristics are summarized in Table 2.1. There were no significant differences in the baseline characteristics of the four study groups, other than size differences between male and females. Cigarette smoking history and current smoking status are reported in Table 2.1. The majority of subjects were never smokers or were remote ex-smokers, although one subject in the younger male group was a current smoker with a 13 pack-year smoking history. No subjects with a smoking history had clinical or spirometric evidence of COPD. Chronic activity-related dyspnea measured by the BDI focal score was significantly (p<0.05) lower by approximately one unit in OF compared with either YF or age-matched males (OM). Physical activity levels were similar (p=0.42) across groups with the majority (79-100%) of subjects in each group participating in some form of regular activity.
Table 2.1. Baseline subject characteristics and activity-related dyspnea questionnaires

<table>
<thead>
<tr>
<th></th>
<th>40-59 y/o males (n = 18)</th>
<th>60-80 y/o males (n = 16)</th>
<th>40-59 y/o females (n = 16)</th>
<th>60-80 y/o females (n = 23)</th>
<th>Gender effect p value</th>
<th>Aging effect p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>48 ± 5</td>
<td>67 ± 6</td>
<td>50 ± 6</td>
<td>68 ± 6</td>
<td>0.423</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Height, cm</td>
<td>176.2 ± 8.1</td>
<td>173.8 ± 6.6</td>
<td>164.1 ± 5.2</td>
<td>161.7 ± 5.4</td>
<td>&lt;0.0005</td>
<td>0.117</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.1 ± 4.0</td>
<td>27.5 ± 4.9</td>
<td>25.0 ± 4.1</td>
<td>27.0 ± 4.2</td>
<td>0.124</td>
<td>0.299</td>
</tr>
<tr>
<td>BDI focal score, 1-12</td>
<td>11.4 ± 1.2</td>
<td>11.3 ± 0.9</td>
<td>11.7 ± 0.9</td>
<td>10.3 ± 1.7*</td>
<td>0.355</td>
<td>0.033</td>
</tr>
<tr>
<td>MRC dyspnea scale, 1-5</td>
<td>1.6 ± 0.6</td>
<td>1.6 ± 0.6</td>
<td>1.9 ± 0.6</td>
<td>1.9 ± 0.7</td>
<td>0.070</td>
<td>0.863</td>
</tr>
<tr>
<td>Oxygen cost diagram, 0-100 mm</td>
<td>88 ± 7</td>
<td>86 ± 11</td>
<td>87 ± 9</td>
<td>85 ± 11</td>
<td>0.609</td>
<td>0.416</td>
</tr>
<tr>
<td>Cigarette smoking history, pack-yrs</td>
<td>4.8 ± 9.0</td>
<td>10.6 ± 12.9</td>
<td>0.8 ± 2.0</td>
<td>5.0 ± 7.0</td>
<td>0.026</td>
<td>0.020</td>
</tr>
</tbody>
</table>

Cigarette smoking status, n:
- Current smoker: 1, 0, 0, 0
- Ex-smoker: 7, 9, 5, 11
- Never smoked: 10, 7, 11, 12

Values are means ± SD. Abbreviations: BDI, modified Baseline Dyspnea Index; MRC, Medical Research Council. * p<0.05 males versus females within same age group.
Resting pulmonary function measurements for all groups were in keeping with their normal predicted values and are summarized in Table 2.2. There were significant age-related changes in maximal expiratory flows, lung volumes, diffusing capacity and respiratory muscle strength measurements. Across age groups, measurements were also consistently greater in males than females. However, there were no interaction effects between age and gender, i.e., age-related declines in pulmonary function were similar across genders.

The FEF$_{25-75}$/FVC ratio was used as an index of dysanapsis, a term referring to a dissociation between airway size and lung size (Mead, 1980). There was a significant age-related decrease in this ratio (p=0.001) with no gender effect or interaction between age and gender: in the older subgroups, the FEF$_{25-75}$/FVC ratio reached a similar value of 0.62±0.21 and 0.59±0.05 in females and males, respectively.

Significant age-related decreases in maximal torque measurements for the knee and elbow were found in both males and females (Table 2.2). As expected, knee and elbow torque measurements were significantly (p<0.0005) greater in males than females for both age groups. There was no interaction effect between age and gender in these measurements.

**Exertional Breathlessness**

The primary reasons for stopping exercise are summarized in Table 2.3. Breathing discomfort was identified as the primary reason for stopping exercise in 57% of the OF group (p=0.006). Within each of the YF, YM and OM groups, the selection frequency of reasons for stopping exercise were not significantly different. At peak
Table 2.2. Pulmonary function and muscle strength

<table>
<thead>
<tr>
<th></th>
<th>40-59 y/o males</th>
<th>60-80 y/o males</th>
<th>40-59 y/o females</th>
<th>60-80 y/o females</th>
<th>Gender effect</th>
<th>Aging effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 18)</td>
<td>(n = 16)</td>
<td>(n = 16)</td>
<td>(n = 23)</td>
<td>p value</td>
<td>p value</td>
</tr>
<tr>
<td>FEV\textsubscript{1}, L</td>
<td>3.90 ± 0.48</td>
<td>3.16 ± 0.52</td>
<td>2.95 ± 0.41</td>
<td>2.31 ± 0.35</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>FEV\textsubscript{1}, %</td>
<td>110 ± 13</td>
<td>112 ± 23</td>
<td>115 ± 17</td>
<td>115 ± 13</td>
<td>0.265</td>
<td>0.799</td>
</tr>
<tr>
<td>FEV\textsubscript{1}/FVC, %</td>
<td>77 ± 5</td>
<td>74 ± 6</td>
<td>80 ± 4</td>
<td>75 ± 6</td>
<td>0.134</td>
<td>0.001</td>
</tr>
<tr>
<td>PEF, L/min</td>
<td>10.5 ± 1.4</td>
<td>9.2 ± 1.9</td>
<td>7.1 ± 1.2</td>
<td>6.08 ± 0.86</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>FEF\textsubscript{25-75%}, L/min</td>
<td>3.56 ± 1.04</td>
<td>2.51 ± 0.98</td>
<td>3.04 ± 0.72</td>
<td>1.91 ± 0.59</td>
<td>0.006</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>FVC, L</td>
<td>5.06 ± 0.76</td>
<td>4.24 ± 0.55</td>
<td>3.67 ± 0.51</td>
<td>3.10 ± 0.47</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>IC, L</td>
<td>3.63 ± 0.70</td>
<td>3.07 ± 0.68</td>
<td>2.57 ± 0.52</td>
<td>2.21 ± 0.32</td>
<td>&lt;0.0005</td>
<td>0.001</td>
</tr>
<tr>
<td>FRC, L</td>
<td>3.41 ± 0.75</td>
<td>3.61 ± 0.69</td>
<td>2.95 ± 0.51</td>
<td>2.91 ± 0.51</td>
<td>&lt;0.0005</td>
<td>0.565</td>
</tr>
<tr>
<td>RV, L</td>
<td>1.96 ± 0.37</td>
<td>2.28 ± 0.40</td>
<td>1.89 ± 0.49</td>
<td>1.95 ± 0.31</td>
<td>0.031</td>
<td>0.045</td>
</tr>
<tr>
<td>TLC, L</td>
<td>7.04 ± 1.03</td>
<td>6.67 ± 0.81</td>
<td>5.51 ± 0.68</td>
<td>5.12 ± 0.51</td>
<td>&lt;0.0005</td>
<td>0.040</td>
</tr>
<tr>
<td>sRaw, cmH\textsubscript{2}O·s</td>
<td>6.4 ± 2.5</td>
<td>6.6 ± 2.2</td>
<td>4.9 ± 1.6</td>
<td>6.8 ± 3.0</td>
<td>0.293</td>
<td>0.069</td>
</tr>
<tr>
<td>DL\textsubscript{CO}, ml/min/mmHg</td>
<td>31.3 ± 3.9</td>
<td>25.8 ± 3.8</td>
<td>22.4 ± 2.8</td>
<td>18.2 ± 2.9</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>DL\textsubscript{CO}/V\textsubscript{A}</td>
<td>4.98 ± 0.47</td>
<td>4.47 ± 0.92</td>
<td>4.80 ± 0.95</td>
<td>4.15 ± 0.48</td>
<td>0.143</td>
<td>0.001</td>
</tr>
<tr>
<td>PI\textsubscript{max}, cmH\textsubscript{2}O</td>
<td>108 ± 41</td>
<td>86 ± 27</td>
<td>82 ± 22</td>
<td>61 ± 25</td>
<td>&lt;0.0005</td>
<td>0.003</td>
</tr>
<tr>
<td>PE\textsubscript{max}, cmH\textsubscript{2}O</td>
<td>193 ± 52</td>
<td>145 ± 31</td>
<td>118 ± 29</td>
<td>91 ± 31</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Maximal torque, Nm:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee extension</td>
<td>178 ± 50</td>
<td>146 ± 30</td>
<td>128 ± 26</td>
<td>94 ± 19</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Knee flexion</td>
<td>79 ± 22</td>
<td>63 ± 11</td>
<td>54 ± 15</td>
<td>35 ± 11</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Elbow extension</td>
<td>48 ± 11</td>
<td>42 ± 9</td>
<td>28 ± 5</td>
<td>26 ± 6</td>
<td>&lt;0.0005</td>
<td>0.051</td>
</tr>
<tr>
<td>Elbow flexion</td>
<td>54 ± 11</td>
<td>46 ± 10</td>
<td>32 ± 4</td>
<td>28 ± 4</td>
<td>&lt;0.0005</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Values are means ± SD. There were no interaction effects between gender and aging. FEV\textsubscript{1}, forced expiratory volume in one second; FVC, forced vital capacity; PEF, peak expiratory flow rate; FEF\textsubscript{25-75%}, mean forced expiratory flow between 25 and 7% of FVC; IC, inspiratory capacity; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; sRaw, specific airway resistance; DL\textsubscript{CO}/V\textsubscript{A}, diffusing capacity of the lung for carbon monoxide per unit of alveolar volume; PI\textsubscript{max}, maximal inspiratory pressure; PE\textsubscript{max}, maximal expiratory pressure.
Table 2.3. Measurements at peak exercise and at the ventilatory threshold

<table>
<thead>
<tr>
<th></th>
<th>40-59 y/o males n = 18</th>
<th>60-80 y/o males n = 16</th>
<th>40-59 y/o females n = 16</th>
<th>60-80 y/o females n = 23</th>
<th>Gender effect P</th>
<th>Aging effect P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peak exercise:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \dot{V}O_2 ), l/min</td>
<td>3.49 ± 0.46</td>
<td>2.71 ± 0.62</td>
<td>2.47 ± 0.43</td>
<td>1.74 ± 0.26</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>( \dot{V}O_2 ), % predicted*</td>
<td>108 ± 12</td>
<td>101 ± 22</td>
<td>116 ± 19</td>
<td>106 ± 11</td>
<td>0.100</td>
<td>0.022</td>
</tr>
<tr>
<td>( \dot{V}O_2 ), ml/kg/min</td>
<td>42.5 ± 8.0</td>
<td>33.0 ± 8.1</td>
<td>37.3 ± 7.5</td>
<td>25.2 ± 3.5</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>164 ± 16</td>
<td>154 ± 23</td>
<td>163 ± 16</td>
<td>155 ± 14</td>
<td>0.972</td>
<td>0.031</td>
</tr>
<tr>
<td>Heart rate, % predicted</td>
<td>92 ± 9</td>
<td>94 ± 14</td>
<td>92 ± 8</td>
<td>94 ± 9</td>
<td>0.871</td>
<td>0.547</td>
</tr>
<tr>
<td>( \dot{V}E ), l/min</td>
<td>98.3 ± 18.7</td>
<td>82.1 ± 22.1</td>
<td>70.3 ± 13.5</td>
<td>56.4 ± 10.1</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>( \dot{V}E / \dot{V}CO_2 )</td>
<td>24.8 ± 2.9</td>
<td>27.0 ± 2.9</td>
<td>25.6 ± 4.2</td>
<td>30.4 ± 3.8</td>
<td>0.017</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>( P_{ET}CO_2 ), mmHg</td>
<td>46.6 ± 5.1</td>
<td>44.8 ± 1.0</td>
<td>47.0 ± 5.1</td>
<td>42.4 ± 4.5</td>
<td>0.006</td>
<td>0.389</td>
</tr>
<tr>
<td>RER</td>
<td>1.13 ± 0.08</td>
<td>1.11 ± 0.08</td>
<td>1.12 ± 0.09</td>
<td>1.08 ± 0.08</td>
<td>0.215</td>
<td>0.116</td>
</tr>
<tr>
<td>( \text{SpO}_2 ), %</td>
<td>93.6 ± 2.3</td>
<td>93.9 ± 1.8</td>
<td>92.8 ± 2.9</td>
<td>94.0 ± 2.2</td>
<td>0.419</td>
<td>0.986</td>
</tr>
<tr>
<td>( f ), breaths/min</td>
<td>35.5 ± 5.7</td>
<td>33.6 ± 7.2</td>
<td>36.3 ± 7.1</td>
<td>35.9 ± 7.0</td>
<td>0.338</td>
<td>0.481</td>
</tr>
<tr>
<td>( V_T ), L</td>
<td>2.79 ± 0.49</td>
<td>2.43 ± 0.42</td>
<td>1.95 ± 0.28</td>
<td>1.59 ± 0.21</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>( \Delta IC ) peak-rest, L</td>
<td>-0.37 ± 0.52</td>
<td>-0.31 ± 0.28</td>
<td>-0.26 ± 0.35</td>
<td>-0.22 ± 0.28</td>
<td>0.273</td>
<td>0.598</td>
</tr>
<tr>
<td>( IRV ), L</td>
<td>0.48 ± 0.47</td>
<td>0.32 ± 0.28</td>
<td>0.36 ± 0.23</td>
<td>0.48 ± 0.20</td>
<td>0.818</td>
<td>0.803</td>
</tr>
<tr>
<td>( EELV ), L</td>
<td>3.65 ± 0.76</td>
<td>3.92 ± 0.62</td>
<td>3.21 ± 0.56</td>
<td>3.06 ± 0.45</td>
<td>&lt;0.0005</td>
<td>0.682</td>
</tr>
<tr>
<td><strong>Ventilatory threshold:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \dot{V}O_2 ), l/min</td>
<td>1.91 ± 0.32</td>
<td>1.63 ± 0.34</td>
<td>1.48 ± 0.37</td>
<td>1.08 ± 0.24</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>( \dot{V}O_2 ), % of peak ( \dot{V}O_2 )</td>
<td>55 ± 8</td>
<td>62 ± 13</td>
<td>60 ± 13</td>
<td>63 ± 10</td>
<td>0.244</td>
<td>0.096</td>
</tr>
<tr>
<td>( \dot{V}O_2 ), ml/kg/min</td>
<td>23.3 ± 5.0</td>
<td>19.8 ± 3.6</td>
<td>22.1 ± 4.5</td>
<td>15.5 ± 3.1</td>
<td>0.007</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>( \dot{V}E ), l/min</td>
<td>38.8 ± 6.6</td>
<td>36.7 ± 7.2</td>
<td>30.8 ± 7.6</td>
<td>27.2 ± 6.5</td>
<td>&lt;0.0005</td>
<td>0.091</td>
</tr>
<tr>
<td>( \dot{V}E / \dot{V}CO_2 )</td>
<td>24.1 ± 1.8</td>
<td>27.2 ± 4.0</td>
<td>25.2 ± 2.9</td>
<td>31.5 ± 5.5</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>( P_{ET}CO_2 ), mmHg</td>
<td>49.3 ± 3.5</td>
<td>47.6 ± 4.7</td>
<td>48.4 ± 4.2</td>
<td>45.3 ± 4.7</td>
<td>0.124</td>
<td>0.024</td>
</tr>
<tr>
<td>Reasons for stopping exercise, n (%)</td>
<td>40-59 y/o males n = 18</td>
<td>60-80 y/o males n = 16</td>
<td>40-59 y/o females n = 16</td>
<td>60-80 y/o females n = 23</td>
<td>Gender effect P</td>
<td>Aging effect P</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-------------------------</td>
<td>-------------------------</td>
<td>--------------------------</td>
<td>---------------------------</td>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Breathing discomfort</td>
<td>7 (41)</td>
<td>7 (44)</td>
<td>7 (44)</td>
<td>13 (57) †</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg discomfort</td>
<td>6 (35)</td>
<td>3 (19)</td>
<td>4 (25)</td>
<td>3 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>breathing &amp; leg discomfort</td>
<td>3 (18)</td>
<td>4 (25)</td>
<td>3 (19)</td>
<td>3 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (6)</td>
<td>2 (13)</td>
<td>2 (13)</td>
<td>4 (17)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD unless otherwise specified. There were no interaction effects between gender and aging. \( \dot{V}_O_2 \), oxygen uptake; \( \dot{V}_E \), minute ventilation; MVC, maximal ventilatory capacity; RER, respiratory exchange ratio, VCO\(_2\), carbon dioxide output; \( V_T \), tidal volume; VC, vital capacity; IC, inspiratory capacity; \( f \), breathing frequency; IRV, inspiratory reserve volume; TLC, total lung capacity; RER, respiratory exchange ratio. * Predicted peak \( \dot{V}_O_2 \) of Blackie et al. (1989) with 9% correction for treadmill from cycle values. † \( p<0.05 \) significantly different within-group.
exercise, Borg ratings of breathlessness and perceived leg discomfort were not different across all groups. Breathlessness/\dot{V}\textsubscript{O}_2 slopes showed a significant aging effect (p<0.05) with no significant gender effect; slopes were greater in OF compared with YF (p<0.05) but not in OM compared with YM (p=0.29) (Figure 2.1). Likewise, Borg ratings of breathlessness intensity at a standardized \dot{V}\textsubscript{O}_2 of 20 ml/kg/min showed a significant age effect (p=0.003) as well as a significant interaction between aging and gender (p=0.041), i.e., the age-related increase in breathlessness ratings was greater in females. Ratings of breathlessness were significantly (p<0.05) greater by >1 Borg unit on average at a standardized \dot{V}\textsubscript{O}_2 in the 60-80 year old group compared with the 40-59 year old group in both males and females. Analysis of breathlessness/\dot{V}\textsubscript{E} slopes indicated a significant gender effect only (p=0.037) such that females had steeper slopes than males (Figure 2.1): slopes were 0.11±0.05, 0.08±0.06, 0.08±0.05 and 0.06±0.03 Borg units/(L/min) in OF, OM, YF and YM, respectively. There were no significant gender or age effects for breathlessness/\dot{V}\textsubscript{E} slopes when \dot{V}\textsubscript{E} was expressed as a percentage of estimated MVC.

At the end of symptom-limited exercise, shallow breathing was the only descriptor of breathing discomfort that was significantly (p<0.05) different across the four groups: this descriptor was chosen by 39% of the OF group, by 31% of the YF group, and by only one subject in each of the OM and YM groups. Rapid breathing was reported by 75% of OM compared with 43% of OF (p=0.051).

**Physiological Responses to Exercise**

Measurements at peak exercise are provided in Table 2.3. All groups reached a peak \dot{V}\textsubscript{O}_2 that corresponded well with the normal predicted value of Blackie et al. (1989)
Breathlessness/VO₂ slopes showed a significant aging effect (p<0.05) with no significant gender effect: slopes were greater in 60-80 year old females (OF) compared with 40-59 year old females (YF) (p<0.05) but not in 60-80 year old males (OM) compared with 40-59 year old males (YM). Breathlessness/VE slopes showed a significant (p<0.05) gender effect only, such that females had steeper slopes than males. * Ratings of dyspnea intensity at a standardized VO₂ of 20 ml/kg/min showed a significant age effect (p=0.003) as well as a significant interaction between aging and gender (p=0.041): the age-related increase in dyspnea ratings was greater in females. Values are means ± SEM for measurements at rest, during each stage of exercise and at peak exercise.

Figure 2.1. The relationship between breathlessness and VO₂ and VE.
(with a 9% correction for treadmill). At peak exercise, significant (p<0.05) age and gender effects were found for $\dot{V}O_2$, $\dot{V}_E$, $\dot{V}_E/\dot{V}CO_2$ and $V_T$. However, peak differences in $\dot{V}O_2$, $\dot{V}_E$ and $V_T$ disappeared once variables were expressed as % of their respective predicted capacity. There was a significant (p=0.031) age effect for peak heart rate but this also disappeared when evaluated as % of predicted maximum. Minimal hypoxemia was noted during exercise: mean reductions in SpO$_2$ of 2-4% were occurred within each group, while one OM and two YF had an SpO$_2$ that fell to a transient nadir of 87% at end-exercise. All groups reached a similar minimal IRV at the end of exercise; therefore differences in absolute $V_T$ during exercise could be explained by differences in IC. There were no interaction effects between aging and gender for any measured variable at peak exercise.

Ventilatory responses to exercise are shown in Figure 2.2. At a standardized $\dot{V}O_2$, there was a significant (p≤0.01) aging effect for $\dot{V}_E$, $\dot{V}_E/\dot{V}CO_2$ and $P_{ET}CO_2$; a significant (p≤0.01) gender effect was also found for $\dot{V}_E/\dot{V}CO_2$ and $P_{ET}CO_2$. Slopes of $\dot{V}_E$ over $\dot{V}CO_2$ showed significant age (p<0.0005), gender (p=0.034) and interaction (p=0.023) effects: the age-related increase in these slopes was greatest in females. A significant (p<0.01) age- and gender-related increase was also found for $\dot{V}_E/\dot{V}CO_2$ at the VTh (Table 2.3). Although there was a significant age-related decline in the absolute $\dot{V}O_2$ at the VTh in both males and females, this difference disappeared when $\dot{V}O_2$ was expressed as a % of actual peak $\dot{V}O_2$. Breathing pattern and operating lung volume responses to exercise
Figure 2.2. Ventilatory demand, minute ventilation to carbon dioxide production ratio (V̇E/V̇CO₂), and end-tidal carbon dioxide (ṖETCO₂) during incremental exercise. Ventilatory responses to incremental treadmill exercise in adult males and females show significant (p<0.05) age-related increases in ventilation (V̇E), the ratio of V̇E to carbon dioxide production (V̇CO₂), partial pressure of end-tidal carbon dioxide (ṖETCO₂). * Significant (p<0.05) difference at a standardized oxygen consumption (VO₂) of 25 and 20 ml/kg/min within males and females, respectively. Values are means ± SEM for measurements at rest, during each stage of exercise and at peak exercise.
are shown in Figure 2.3. There were no significant gender, age or interaction effects for slopes of $V_T$ over $\dot{V}_E$; however, females had significantly ($p<0.0005$) greater slopes of $F$ over $\dot{V}_E$ than males. An inflection in the $V_T/\dot{V}_E$ relationship occurred when IRV had reached a similarly reduced level in all groups: at this point, mean IRV ranged from 0.55-0.75 L or 8-12 %TLC. There were also no age- or gender-related differences across groups in dyspnea intensity at this inflection point. However, there were significant age- ($p<0.01$) and gender-related ($p<0.0005$) decreases in the absolute $\dot{V}O_2$, $\dot{V}_E$ and $V_T$ where this inflection occurred. Similar to the breathlessness intensity differences, these breathing pattern differences disappeared when measurements were expressed as percentages of their respective capacity, i.e., $\dot{V}O_2$ as % of predicted maximum, $\dot{V}_E$ as a % of estimated MVC, and $V_T$ as % of predicted VC (Figure 2.4). Breathing pattern and operating volume measurements at a standardized $\dot{V}O_2$ showed: significant age-related decreases in IRV ($p<0.0005$) and IC ($p<0.0005$), increases in $V_T/IC$ ($p<0.0005$) and increases in $f$ ($p=0.014$); significantly smaller IRV ($p<0.0005$) and IC ($p<0.0005$) and greater $f$ ($p=0.002$) in females compared with males; with no significant interaction between aging and gender effects.

Examination of tidal versus isovolume maximal expiratory flows at rest, showed no evidence of expiratory flow limitation (EFL) in the YF or YM groups. In contrast, EFL at rest was evident in 6 (26%) and 4 (25%) subjects from the OF and OM groups, respectively. At the peak of exercise when ventilations were high, EFL was evident in 12 (52%) of the OF group, 11 (67%) of the OM group, 5 (31%) of the YF group, and 12 (69%) of the YM group. There was a significant age ($p=0.013$) and gender ($p=0.010$)
Figure 2.3. Breathing pattern and operating lung volumes during incremental exercise. Breathing pattern and operating volume measurements are shown as ventilation increased during exercise in the younger female (YF), older female (OF), younger male (YM) and older male (OM) groups. Significant (p<0.05) age-related reductions in tidal volume ($V_T$), inspiratory reserve volume (IRV) and inspiratory capacity (IC) were present in both males and females. There were also significant (p<0.05) gender effects for peak $V_T$ and IC and for slopes of breathing frequency ($f$) over $V_E$. Values are means ± SEM for measurements at rest, the first two stages of exercise, the $V_T$/ventilation inflection point and peak exercise.
Figure 2.4. Breathing pattern, inspiratory reserve volume, and symptoms of breathing discomfort during exercise. There were no age or gender differences found when measurements of tidal volume (VT) and inspiratory reserve volume (IRV) were normalized for age and gender (i.e., expressed as percentages of predicted vital capacity (VC) and total lung capacity (TLC), respectively) and plotted against ventilation as a fraction of maximal ventilatory capacity (MVC). Similarly, exertional breathlessness intensity was not different across groups when expressed against ventilation/MVC or against IRV. YM, younger males aged 40-59 years; OM, older males aged 60-80 years; YF, younger females aged 40-59 years; OF, older females aged 60-80 years.
effect in the $\dot{V}_E$ at which the onset of EFL was noted in these subjects: the onset of EFL by this method occurred at a greater $\dot{V}_E$ in the younger versus older groups, and in men versus women. The magnitude of dynamic hyperinflation (reduction in IC) from rest to peak exercise was similar across all groups (Table 2.3). Representative samples of flow-volume loops during exercise in each group are shown in Figure 2.5.

**Correlates of Exertional Breathlessness**

Correlates of breathlessness intensity at a standardized $\dot{V}O_2$ during exercise are provided in Table 2.4. In females, the strongest correlates of breathlessness intensity at the highest standardized $\dot{V}O_2$ (20 ml/kg/min) were $V_T/IC$ and $V_T$ expressed as % of predicted VC; these relationships were similar across age groups. In males, the strongest correlates of breathlessness intensity at the highest standardized $\dot{V}O_2$ (25 ml/kg/min) were $V_T/IC$ and IRV expressed as % of predicted TLC; these relationships were consistent across age groups. Within all older (60-80 years) subjects, the strongest correlates of breathlessness intensity at a standardized $\dot{V}O_2$ of 20 ml/kg/min were $V_T/IC$ and $V_T$ expressed as % of predicted VC; there was no effect of gender on these relationships in this age group. Across all groups, breathlessness ratings also correlated with $\dot{V}_E$ (partial $r=0.33$, $p=0.005$) and $\dot{V}_E/MVC$ (partial $r=0.26$, $p=0.032$) at a standardized $\dot{V}O_2$. Standardized Borg ratings of intensity of breathlessness and perceived leg discomfort also correlated across groups with $P_{I_{\text{max}}}$ (partial $r= 0.22$, $p=0.05$) and maximal knee torque (partial $r=0.41$, $p=0.010$), respectively. Relationships between Borg ratings of
Figure 2.5. Individual resting and exercise tidal volume plotted within the resting maximal flow volume loops. Tidal flow-volume loops at rest, the ventilatory threshold (VTh) and at peak exercise are plotted within the respective maximal loops in representative subjects from each group. Inspiratory capacity (IC) decreases with increasing age, thereby reducing inspiratory reserve volume (IRV) and limiting the tidal volume response to exercise. This mechanical restriction is greater in females, i.e., reduced resting IC. Dynamic pulmonary hyperinflation is shown by a decrease in IC during exercise. The IRV is shown at VTh (heavy line on the volume axis) when the relative exercise intensity was comparable across groups.
Table 2.4. Pearson correlation coefficients for variables measured at a standardized VO$_2$* during exercise and tested against concurrent breathlessness intensity ratings (Borg scale)

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>Older subjects (60-80 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\dot{V}_E$, L/min</td>
<td>0.415 †</td>
<td>0.498 ‡</td>
<td>0.304</td>
</tr>
<tr>
<td>$\dot{V}_E$, % MVC</td>
<td>0.608 §</td>
<td>0.384 †</td>
<td>0.333 †</td>
</tr>
<tr>
<td>$f$, breaths/min</td>
<td>0.144</td>
<td>0.237</td>
<td>0.211</td>
</tr>
<tr>
<td>$V_T$, % predicted VC</td>
<td>0.413 †</td>
<td>0.526 §</td>
<td>0.440 ‡</td>
</tr>
<tr>
<td>$V_T$, % IC</td>
<td>0.637 §</td>
<td>0.564 §</td>
<td>0.449 §</td>
</tr>
<tr>
<td>IC, L</td>
<td>-0.297</td>
<td>-0.341 †</td>
<td>-0.288</td>
</tr>
<tr>
<td>IC, % predicted</td>
<td>-0.378 †</td>
<td>-0.249</td>
<td>-0.040</td>
</tr>
<tr>
<td>$\Delta$IC exercise-rest, L</td>
<td>-0.131</td>
<td>-0.264</td>
<td>-0.284</td>
</tr>
<tr>
<td>IRV, % predicted TLC</td>
<td>-0.621 §</td>
<td>-0.495 §</td>
<td>-0.284</td>
</tr>
<tr>
<td>EELV, % TLC</td>
<td>0.143</td>
<td>0.340 †</td>
<td>0.162</td>
</tr>
<tr>
<td>EFL, % of $V_T$ overlapping maximal flow-volume curve</td>
<td>0.521 ‡</td>
<td>-0.080</td>
<td>-0.092</td>
</tr>
<tr>
<td>SpO$_2$, %</td>
<td>0.122</td>
<td>0.044</td>
<td>-0.026</td>
</tr>
<tr>
<td>$P_{ET}CO_2$, mmHg</td>
<td>-0.088</td>
<td>-0.341 †</td>
<td>-0.327 †</td>
</tr>
</tbody>
</table>

* A VO$_2$ of 20 ml/kg/min in females and in older subjects, and 25 ml/kg/min in males.
† p<0.05, ‡ p<0.01, § p≤0.001. VO$_2$, oxygen uptake; $\dot{V}_E$, minute ventilation; MVC, maximal ventilatory capacity; $f$, breathing frequency; $V_T$, tidal volume; VC, vital capacity; IC, inspiratory capacity; $\Delta$IC, change in IC; IRV, inspiratory reserve volume; TLC, total lung capacity; EELV, end-expiratory lung volume; EFL, expiratory flow limitation; SpO$_2$, oxygen saturation; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide.
breathlessness intensity and IRV (% predicted TLC) or $\dot{V}_E$/MVC were superimposed for all groups: breathlessness increased as IRV decreased or as $\dot{V}_E$/MVC increased (Figure 2.4).

**DISCUSSION**

The main findings of this study are as follows: 1) perceptual responses to incremental treadmill exercise were similar in males and females in the 40-59 y/o groups; 2) breathlessness intensity ratings were higher at a standardized metabolic load during exercise in the 60-80 year old (y/o) compared with the 40–59 y/o age groups in both males and females; 3) in both genders, the higher levels of exertional breathlessness with advancing age were associated with reduced static inspiratory muscle strength, greater ventilatory mechanical constraints and higher ventilatory demand during exercise; and 4) ratings of breathlessness intensity at a standardized metabolic load were higher in 60-80 y/o females (OF) than age-matched males (OM) reflecting the interaction of the increased ventilatory constraints of aging and the relatively reduced baseline ventilatory capacity in females.

During incremental treadmill testing, all four groups reached their predicted peak $\dot{V}O_2$ without apparent ventilatory limitation but nevertheless experienced significant exertional symptoms. The intensity of breathlessness and the cardiopulmonary responses throughout incremental exercise were similar in males and females in the 40-59 y/o age groups. However, females in this age group were more likely to report the qualitative descriptor “shallow” at end-exercise than males. In females of this age range, small
differences in breathing pattern responses (i.e. lower $V_T$) to exercise and in the ventilatory demand/capacity ratio (i.e., higher at a given $\dot{V}O_2$) are likely explained by their anatomically smaller lungs, airways and respiratory musculature.

In OF compared with YF, the intensity of breathing discomfort was higher at a standardized $\dot{V}O_2$ during exercise (by 1.5 Borg units at 20 ml/kg/min), and breathlessness/$\dot{V}O_2$ slopes were, on average, ~40% steeper ($p<0.05$) (Figure 2.1). In OM, exertional breathlessness intensity was greater than in YM only at higher metabolic loads ($\geq 25$ mLO$_2$/kg/min); breathlessness/$\dot{V}O_2$ slopes were not significantly different.

The following potential contributors to increased exertional breathlessness in the 60-80 y/o group of both genders were considered: 1) greater age-related muscular weakness and mechanical ventilatory constraints during exercise; 2) increased ventilatory demand during exercise reflecting greater ventilation/perfusion mismatching and metabolic alterations; and 3) a combination of these factors.

**Age-related Abnormalities in Ventilatory Mechanics**

Cross-sectional comparison (within both genders) of resting pulmonary function parameters between the 60-80 y/o and the 40-59 y/o groups confirmed the expected age-related reductions in FEV$_1$, FVC, IC, DL$CO$ and maximal respiratory pressures. The magnitude of change in these parameters was similar in male and female participants.

Age-related changes in cardiopulmonary responses to treadmill exercise were quantitatively similar in males and females. In the 60-80 y/o groups, symptom-limited peak $\dot{V}O_2$ and $\dot{V}_E$ were reduced by an average of 33% and 19% in OF and by 22% and
17% in OM, compared with their respective younger groups. It is noteworthy that in the 60-80 y/o group, the resting IC, which represents the operating limit for $V_T$ expansion during exercise in the presence of EFL, was reduced by an average of 15% compared with the 40-59 y/o group. The IC reduction was the result of a combination of variable increases in FRC (particularly in males) and a reduction in TLC, possibly due to age-related reductions in height and $P_{l_{\text{max}}}$ or both in combination. During exercise, the rest to peak decreases in IC, reflecting the extent of air trapping secondary to EFL, were similar in the 40-60 y/o group and the 60-80 y/o group and averaged -0.3 L. The oldest groups appeared to have greater EFL as crudely assessed by the $V_T$ overlap method during flow-volume loop analysis. Greater “restrictive” mechanical constraints were evident during exercise in the 60-80 y/o group by the relatively higher $V_T$/IC ratios and the reduced dynamic IRV at lower metabolic rates compared with the 40-59 y/o group. In the OF group the lower baseline resting IC (reduced by 14% compared with the YF group) with further reduction during exercise resulted in a relatively more rapid and shallow breathing pattern compared to YF group. Such age-related differences in breathing pattern responses to exercise were less evident in the OM compared with the YM group, likely reflecting the relatively larger lung volume reserve in males.

**Mechanical/Muscular Factors and Exertional Breathlessness**

Ventilatory muscle strength diminished with advancing age in both men and women. This likely reflects generalized skeletal muscle weakness with aging, as peripheral muscle strength was reduced in tandem. Thus, the effort expended to drive both muscle groups must represent a higher fraction of their maximal possible effort in the older groups. Indeed, exertional symptom intensity correlated significantly (albeit
weakly) with muscle strength measurements across groups: breathlessness increased as $P_{\text{tmax}}$ decreased and perceived leg discomfort increased as leg strength decreased. The neurophysiological basis of exertional breathlessness (and perhaps also leg discomfort) in this circumstance is thought to be increased central motor command output with increased central corollary discharge to the somatosensory cortex (Davenport et al. 1986; Gandevia & Macefield, 1989; Chen et al. 1992).

At the highest standardized $\dot{V}O_2$ for both genders, indices of volume restriction such as high $V_T/IC$ ratios and reduced dynamic IRV correlated well with breathlessness intensity ratings. Breathlessness/IRV relationships were superimposed in the 60-80 y/o groups and 40-59 y/o groups of both genders. However, at a standardized $\dot{V}O_2$, breathlessness intensity was significantly higher and the dynamic IRV was proportionately diminished in the older groups compared to their younger counterparts. The relatively lower dynamic IRV at a given $\dot{V}O_2$ in the older groups points to a higher operating position of the $V_T$ on the upper reaches of the respiratory system’s pressure-volume relationship where there is increased elastic loading and functional weakness of the inspiratory muscles.

**Increased Ventilatory Demand and Exertional Breathlessness**

Ventilation was increased significantly by ~30% for any given submaximal $\dot{V}O_2$ in the 60-80 y/o groups of both genders compared to the 40-59 y/o groups. Consistent with previous studies (DeLorey & Babb, 1999; Prioux et al. 2000), $V_T/\dot{V}CO_2$ ratios were significantly elevated before and at the ventilatory threshold in the 60-80 y/o groups (at a
point where $P_{ET^{}}CO_2$ was stable) in both genders compared with their younger counterparts. In both genders, the finding of a significant reduction in $DL_{CO}$ in the 60-80 y/o group compared with the younger groups is also in keeping with the well described age-related decreases in the alveolar/capillary surface area for gas exchange and increased $\dot{V}/\dot{Q}$ non-uniformity (Wagner et al. 1974; DeLorey & Babb, 1999). However, ventilatory inefficiency in the elderly was not of sufficient magnitude to compromise $CO_2$ elimination or result in significant arterial $O_2$ desaturation, even at the peak of symptom-limited exercise. Ventilatory thresholds, heart rate/$\dot{V}O_2$ slopes, peak heart rate reserve and peak $\dot{V}O_2$ remained within the predicted normal range for these older participants, essentially excluding significant peripheral skeletal muscle deconditioning and/or impaired cardiac function as additional sources of ventilatory stimulation.

To what degree did the small increases in $\dot{V}_E$ seen in the 60-80 y/o groups contribute to greater exertional breathlessness intensity compared to the 40-59 y/o groups? Certainly, younger healthy individuals can tolerate increases in exercise $\dot{V}_E$ during dead space loading which are comparable to the age-related increases in this study with minimal or no increase in breathing discomfort (DeLorey & Babb, 1999; O'Donnell et al. 2000). However, we cannot exclude the possibility that even small increases in ventilatory demand (and therefore muscular effort) of this magnitude, in the setting of progressive age-related decline in respiratory muscle strength and dynamic mechanical restriction, may lead to greater respiratory difficulty in the elderly. At a $\dot{V}O_2$ of 20
ml/kg/min, age-related increases in breathlessness intensity were associated with increases in $\dot{V}_E$ and the $\dot{V}_E$/MVC ratio across groups.

**Gender Differences in Perceived Breathlessness in the Older Age Group**

The effect of aging on breathlessness/$\dot{V}O_2$ and $\dot{V}_E$/$\dot{V}CO_2$ slopes was greater in females than males. Breathlessness was also more frequently reported as the primary exercise-limiting symptom in the OF group. These findings are in keeping with previous reports on gender influences on symptom perception in both health and cardiopulmonary disease (Becklake & Kauffmann, 1999; Horsley *et al.* 1999; Ho *et al.* 2001; Tessier *et al.* 2001; Watson *et al.* 2004; de Torres *et al.* 2005; Han *et al.* 2007). As expected, females in the OF group, whose average height was 12 cm less than age-matched males, had significantly smaller (in absolute terms) lung volumes, maximal expiratory flow rates, $DL_{CO}$ and static inspiratory muscle strength. The question arises whether the intrinsically smaller airway size relative to lung volume in females (i.e., dysanapsis), described by Jere Mead (1980), predisposes them to greater exertional breathlessness with advancing age. In our study, there was an age-related decline in the ratio of $FEF_{25-75\%}$ to FVC (a surrogate measure of dysanapsis) but with no significant gender effect. Older men and older women had similar such ratios and showed no differences in measured expiratory flow limitation during exercise to account for differences in breathlessness. Moreover, we were unable to demonstrate that the increased breathlessness in elderly women compared with age-matched men was the result of greater derangements of dynamic mechanics (related to reduced IC), reduced inspiratory muscle strength or abnormal pulmonary gas exchange. Future studies that compare the effect of manipulation of
ventilatory mechanics (bronchodilators, helium/oxygen or increased chemostimulation) on breathlessness in men and women are likely to provide greater insights into the relative importance of such mechanical factors in causation.

While the age-related respiratory muscle weakness and dynamic ventilatory constraints were broadly similar in males and females, the sensory consequences of these changes were proportionately greater in the oldest female group who had the lowest estimated MVC of all four subgroups. It is noteworthy that the increase in breathlessness at any given $\dot{V}_E$ or $\dot{V}O_2$ in OF compared with OM disappeared when these variables were expressed as %MVC and % predicted, respectively. It follows that in OF, the ventilation required to support any physical task represents a higher fraction of their MVC than age-matched males, with attendant proportionate increases in relative contractile muscle effort and perceived breathlessness.

We acknowledge that our study did not address the important question of whether gender differences in subjective responses to exercise could be accounted for by non-physiological factors (psychological, sociocultural and environmental) that are known to shape the expression of breathlessness on an individual basis (Dale et al. 1989; Becklake & Kauffmann, 1999).

In summary, the intensity of breathlessness during weight-bearing exercise in males and females in the 40-59 y/o groups were similar. Cross-sectional comparisons within each gender revealed that participants in the 60-80 y/o groups experienced greater breathing difficulty at a standardized $\dot{V}O_2$ than their younger counterparts and occurred more consistently in females. Although the origin of breathlessness is multifactorial, correlative analysis identified age-related ventilatory muscular/mechanical constraints
and higher ventilatory requirements as potential contributory factors in the oldest groups. The impact of the progressive age-related decline in respiratory function on perceived exertional symptoms was most pronounced in the OF group whose baseline maximal ventilatory capacity was, by nature, relatively diminished compared with their male counterparts.
Chapter 3: Mechanisms of Dyspnea during Cycle Exercise in Symptomatic Patients with GOLD Stage I Chronic Obstructive Pulmonary Disease

Dror Ofir, Pierantonio Laveneziana, Katherine A. Webb, Yuk-Miu Lam, Denis E. O’Donnell

ABSTRACT

**Rationale:** Smokers with a relatively preserved forced expiratory volume in one second (FEV₁) may experience dyspnea and activity limitation but little is known about underlying mechanisms.

**Objectives:** To examine ventilatory constraints during exercise in symptomatic smokers with GOLD stage I COPD so as to uncover potential mechanisms of dyspnea and exercise curtailment.

**Methods:** We compared resting pulmonary function and ventilatory responses (breathing pattern, operating lung volumes, pulmonary gas exchange) to incremental cycle exercise as well as Borg scale ratings of dyspnea intensity in 21 patients (post-bronchodilator FEV₁ 91 ± 7 %predicted and FEV₁/FVC 60 ± 6 %; mean±SD) with significant breathlessness and 21 healthy age- and gender-matched control subjects with normal spirometry.

**Results:** In COPD compared with control, peak oxygen consumption and power output were significantly reduced by more than 20% and dyspnea ratings were higher for a given work rate and ventilation (p<0.05). Compared with the control group, the COPD group had evidence of extensive small airway dysfunction with increased ventilatory requirements during exercise, likely on the basis of greater ventilation-perfusion abnormalities. Changes in end-expiratory lung volume during exercise were greater in COPD than in health (0.54 ± 0.34 vs 0.06 ± 0.32 L, respectively; p<0.05) and breathing pattern was correspondingly more shallow and rapid. Across groups, dyspnea intensity increased as ventilation expressed as a percentage of capacity increased (p<0.0005) and as inspiratory reserve volume decreased (p<0.0005).
**Conclusion:** Exertional dyspnea in symptomatic patients with mild COPD is associated with the combined deleterious effects of higher ventilatory demand and abnormal dynamic ventilatory mechanics, both of which are potentially amenable to treatment.

**INTRODUCTION**

Recent studies have confirmed that patients with mild airflow obstruction as defined by traditional spirometric criteria have evidence of airway inflammation (Hogg *et al.*, 2004). Moreover, patients with relatively preserved FEV$_1$ may have extensive small airway dysfunction as measured by closing volume and tests of abnormal distribution of ventilation (Buist & Ross, 1973b; Stanescu *et al.*, 1998; Verbanck *et al.*, 2006). In such patients significant ventilation-perfusion inequalities may exist as a result of inflammation of the lung parenchyma and its vasculature (Barbera *et al.*, 1994). This, in turn, may contribute to a higher ventilatory requirement than normal during exercise. It is known that patients with apparently mild airflow obstruction may report poor perceived health status, chronic activity-related dyspnea (Jones, 2001) and reduced activity levels. Such patients may seek medical attention for relief of dyspnea but the underlying mechanisms and the impact of therapeutic interventions other than successful smoking cessation remains unknown (Anthonisen *et al.*, 2002).

The GOLD definition of mild COPD based on a fixed FEV$_1$/FVC ratio (<0.7) has recently been criticized because of the risk of false positive diagnosis, particularly in the elderly. The added concern is that over-diagnosis could lead to inappropriate treatment with expensive inhaled bronchodilator and corticosteroid treatment. This view is further justified by the absence of proof of the long term safety and efficacy of these medications.
in patients with milder disease (FEV$_1$ $>$ 60 % predicted). However, this must be balanced by the clinical experience that some symptomatic smokers who fit the mild GOLD criteria may indeed have extensive physiological impairment that is obscured by a relatively preserved FEV$_1$. It is reasonable to assume that in older smokers, widespread small airway bronchiolitis, in conjunction with the natural pulmonary impairment associated with aging, will give rise to perceived greater breathing difficulty during exercise than in healthy non-smoking controls. The main purpose of this study was, therefore, to increase our understanding of the mechanisms of exertional dyspnea and activity limitation in this population.

Previous studies have demonstrated that exercise capacity is abnormally diminished in subjects with a mildly reduced post-bronchodilator FEV$_1$ (<80 % predicted) (Babb et al., 1991b; Carter et al., 1993). In this study we extend these observations by examining ventilatory constraints during exercise in symptomatic patients with GOLD stage I COPD (post-bronchodilator FEV$_1$ $\geq$ 80% predicted and FEV$_1$/FVC < 0.7) so as to uncover potential mechanisms of dyspnea and exercise curtailment. We reasoned that in mild COPD a higher intensity of exertional dyspnea compared with age-matched healthy participants would be associated with: 1) greater ventilatory demand, 2) increased mechanical loading of the ventilatory muscles during exercise, or 3) a combination of both. We therefore compared ventilatory responses (breathing pattern, operating lung volumes and gas exchange parameters) to incremental cycle exercise in 21 patients and 21 healthy age- and gender-matched control subjects. We then conducted a correlative analysis to examine possible contributors to exertional dyspnea intensity.
METHODS

Subjects

We studied 21 symptomatic patients with GOLD stage I COPD (post-bronchodilator FEV$_1$ ≥ 80 % predicted and FEV$_1$/FVC < 0.7) (Rabe et al., 2007) who were referred to the COPD Centre at our institution. Patients were excluded if they had: 1) other unstable medical conditions which could cause or contribute to breathlessness, i.e., metabolic, cardiovascular or other respiratory diseases, or 2) other disorders which could interfere with exercise testing such as neuromuscular diseases or musculoskeletal problems. In addition, a group of 21 healthy age-and gender-matched subjects was included with: 1) normal baseline spirometry (FEV$_1$ ≥ 80% predicted, FEV$_1$/FVC ≥ 0.7), and 2) absence of any health problems, including cardiovascular, neuromuscular, musculoskeletal or respiratory diseases which may contribute to breathlessness or exercise limitation. Healthy subjects were recruited from the local community using word-of-mouth, notices posted in community health care facilities and newspaper advertisements.

Study Design

This was a controlled, cross-sectional study in which informed consent was obtained from all subjects and ethical approval was received from the University and Hospital Health Sciences Human Research Ethics Board. Subjects were tested on two occasions. On the first visit, after informed consent and appropriate screening of medical history, all subjects completed pulmonary function testing pre- and post-bronchodilator (400 µg salbutamol) and a variety of questionnaires: chronic activity-related dyspnea questionnaires included the Baseline Dyspnea Index (BDI) (Mahler et al., 1984) and the
Medical Research Council (MRC) scale (Fletcher et al., 1959) and a self-reported habitual physical activity questionnaire (CHAMPS) which was used to evaluate each subject’s weekly caloric expenditure in physical activities (Stewart et al., 2001). On the second visit, subjects completed pulmonary function testing and cardiopulmonary exercise testing.

Subjects with COPD were asked to withdraw from any respiratory-related medications between 8 and 72 hours, based on the medication used (short- or long-acting), prior to any of the visits to eliminate any effect on exercise or pulmonary function. All subjects were required to eat a normal mixed diet prior to laboratory visits to provide valid experimental/metabolic results during exercise. Subjects were also asked to avoid the ingestion of alcohol, caffeine-containing products and a heavy meal for at least four hours and to refrain from strenuous activity (e.g., cycling, running) for at least 12 hours prior to testing. Experimental visits were conducted at the same time of day for each subject.

**Procedures**

Routine spirometry, constant-volume body plethysmography, single breath diffusing capacity (DL\textsubscript{CO}), and maximum inspiratory and expiratory mouth pressures (PI\textsubscript{max} and PE\textsubscript{max}, measured at FRC and TLC, respectively) were performed in accordance with recommended techniques (American Thoracic Society; European Respiratory Society, 2002; Miller et al., 2005a; Miller et al., 2005b. Wanger et al., 2005; MacIntyre et al., 2005) using an automated pulmonary function testing system (6200 Autobox DL and Vmax229d; SensorMedics, Yorba Linda, CA). Closing volumes were measured using the single-breath nitrogen test as modified by Anthonisen et al. (1969).
Measurements were repeated 30 minutes post-bronchodilator (400 µg salbutamol) in all mild COPD patients and in 10 healthy subjects. Measurements were standardized as percentages of predicted normal values (Briscoe & Dubois, 1958; Burrows et al., 1961; Black & Hyatt, 1969; Buist & Ross, 1973a; Crapo et al., 1982; Hamilton et al., 1995; Morris et al., 1998); predicted normal values for inspiratory capacity (IC) were calculated as predicted TLC minus predicted FRC.

Symptom-limited incremental exercise testing was conducted on an electronically braked cycle ergometer (Ergometrics 800S; SensorMedics, Yorba Linda, CA) using the Vmax229d Cardiopulmonary Exercise Testing System (SensorMedics) according to recommended guidelines (American Thoracic Society; American College of Chest Physicians, 2003) as previously described (Ofir et al., 2007). Exercise tests consisted of a steady-state resting period and a 1 minute warm-up of unloaded pedalling followed by a stepwise protocol in which the work rate was increased in 2-minute intervals by increments of 20 watts. All exercise tests were terminated at the point of symptom-limitation (peak exercise). Upon exercise cessation, subjects were asked to verbalize their main reason for stopping exercise, i.e., breathing discomfort, leg discomfort, both breathing and leg discomfort, or some other reason to be documented.

Subjects rated the magnitude of their perceived breathing and leg discomfort at rest, every minute during exercise, and at peak exercise by pointing to the 10-point Borg scale. Oxygen saturation (SpO2) by pulse oximetry, electrocardiographic monitoring of heart rate (HR), rhythm and ST-segment changes, and blood pressure by indirect sphygmomanometry were carried out at rest and throughout exercise testing. Breath-by-breath data was collected at baseline and throughout exercise while subjects breathed
through a mouthpiece with nasal passages occluded by a nose-clip: computer software calculated minute ventilation ($\dot{V}_E$), oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), end-tidal carbon dioxide partial pressure ($P_{ET}CO_2$), tidal volume ($V_T$), breathing frequency ($F$), inspiratory and expiratory time ($T_I$ and $T_E$, respectively), duty cycle ($T_I/T_{TOT}$), and mean inspiratory and expiratory flow ($V_T/T_I$ and $V_T/T_E$, respectively).

Exercise variables were measured and averaged over the last 30 seconds of each minute and at peak exercise. Exercise parameters were compared with the predicted normal values of Blackie (1989) and Jones et al. (1985). Changes in end-expiratory lung volume (EELV) were estimated from IC measurements at rest, at the end of each 2-minute increment of exercise and at peak exercise (O’Donnell et al., 2001). Ventilation was also compared with the maximal ventilatory capacity (MVC) that was estimated by multiplying the measured FEV$_1$ by 35 (Gandevia & Hugh-Jones, 1957). The ventilatory threshold (VTh) was detected individually using the V-slope method (Wasserman et al., 1999). Breathing pattern was evaluated by examining individual Hey plots (Hey et al., 1966). Additional detail on the method for performing pulmonary function and exercise test measurements is provided in an online data supplement (see Appendix E).

**Statistical Analysis**

A sample size of 16 was used to provide the power (80%) to detect a significant difference in dyspnea intensity (Borg Scale) measured at a standardized work-rate during incremental cycle exercise based on a relevant difference in Borg ratings of ±1, a SD of 1 for Borg ratings changes found at our laboratory, $\alpha=0.05$. Results were expressed as means ± SD. A $p<0.05$ level of statistical significance was used for all analyses.

Group responses at different time points and/or intensities during exercise were
compared using t-tests with appropriate Bonferroni adjustments for multiple comparisons. Dyspnea descriptors were analysed as frequency statistics and compared using the Fisher’s exact test. Physiological contributors to exertional dyspnea intensity in subjects with COPD were determined by multiple regression analysis. In this analysis, Borg dyspnea ratings at a standardized exercise work rate (dependent variable) were analyzed against concurrent relevant independent variables (which were determined based on correlation coefficient analysis and previous knowledge (literature), i.e., exercise measurements of ventilation, breathing pattern, operating lung volumes, cardiovascular and metabolic parameters, and baseline pulmonary function measurements.

RESULTS

Subject characteristics are summarized in Table 3.1. Compared with the healthy control group, the COPD group showed: significant expiratory airflow limitation and lung hyperinflation; a reduced DLCO; a greater closing capacity and N₂ slope; and significantly greater chronic activity-related dyspnea. The healthy control subjects had normal spirometry and were well matched for age, sex, body mass index and habitual physical activities, when compared to the COPD subjects. All COPD subjects were symptomatic and had a diagnosis of COPD; the majority (15 out of 21) had a diagnosis made within the previous 5 years. Eleven COPD subjects were prescribed respiratory medication: 9 subjects used their inhalers on a regular basis (n=9 long- and/or short-acting β₂-agonist bronchodilators, n=5 long- and/or short-acting anticholinergic bronchodilators, n=7 inhaled corticosteroid/long-acting β₂-agonist combination) and 2
| Table 3.1. Subject characteristics and pulmonary function in patients with GOLD stage I COPD and in healthy control subjects |
|-----------------------------------------------|---------------|-----------|
|                                | Control | COPD | P value |
| Male %                          | 57      | 64      | NS       |
| Age, years                      | 63 ± 9  | 64 ± 7  | NS       |
| Body mass index, kg/m²          | 26.2 ± 3.4 | 27.7 ± 4.1 | NS |
| BDI focal score (0-12)          | 11.5 ± 0.7 | 8.3 ± 2.0 | <0.0005 |
| MRC dyspnea scale (1-5)         | 1.1 ± 0.1 | 1.9 ± 0.1 | <0.0005 |
| CHAMPS, kcal/week consumed at moderate activities * | 1744 ± 880 | 2820 ± 2103 | NS |
| FEV₁, L (% predicted)           | 2.77 ± 0.48 (117 ± 9) | 2.28 ± 0.56 (85 ± 11) | <0.05 | <0.0005 |
| FEV₁ post-β₂ agonist, L (%predicted) | 2.88 ± 0.52 (124 ± 12) | 2.47 ± 0.54 (91 ± 7) | NS | <0.0005 |
| FEV₁/FVC post-β₂ agonist,%     | 82 ± 4 | 60 ± 6 | <0.0005 |
| FVC, L (% predicted)            | 3.79 ± 0.67 (106 ± 13) | 3.93 ± 0.98 (102 ± 11) | NS | NS |
| PEFR, % predicted               | 120 ± 15 | 89 ± 16 | <0.0005 |
| FEF₂₅₋₇₅%, % predicted          | 99 ± 27 | 34 ± 12 | <0.0005 |
| IC, % predicted                 | 109 ± 13 | 105 ± 19 | NS |
| FRC, % predicted                | 102 ± 21 | 121 ± 20 | <0.005 |
| TLC, % predicted                | 105 ± 13 | 114 ± 9 | 0.01 |
| RV, % predicted                 | 97 ± 20 | 129 ± 21 | <0.0005 |
| RV/TLC, %                       | 33 ± 4 | 41 ± 6 | <0.0005 |
| sRaw, % predicted               | 132 ± 42 | 290 ± 97 | <0.0005 |
| PImax at FRC, % predicted       | 132 ± 46 | 109 ± 35 | NS |
| PImax at TLC, % predicted       | 94 ± 25 | 81 ± 23 | NS |
| DLCO, % predicted               | 118 ± 20 | 98 ± 21 | <0.005 |
| CV/VC, % predicted *            | 103 ± 21 | 128 ± 47 | NS |
| CC/TLC % predicted *            | 97 ± 12 | 118 ± 18 | <0.005 |
| Estimated MVC, L/min            | 102.0 ± 16.4 | 79.6 ± 19.3 | <0.0005 |

Values are means ± SD. * Data only collected in 10 of the 21 healthy control subjects. Abbreviations: NS, not significant; BDI, modified Baseline Dyspnea Index; MRC, Medical Research Council; CHAMPS, Community Healthy Activities Model Program for Seniors; FEV₁, force expired volume in one second; FVC, force vital capacity; PEFR, peak expiratory flow; FEF₂₅₋₇₅%, force expiratory flow between 25 and 75% of FVC; PImax, maximal inspiratory pressure; PEmax, maximal expiratory pressure; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; IC, inspiratory capacity; DLCO, diffusing capacity of the lung for carbon monoxide; sRaw, specific airways resistance; CV, closing volume; VC, vital capacity; CC, closing capacity; MVC, maximal ventilatory capacity estimated as 35 × FEV₁.
subjects used a short-acting $\beta_2$-agonist bronchodilator on an “as needed” basis only. Comorbidities in the COPD group included: stable coronary artery disease (n=2), diabetes mellitus type 2 (n=1), well controlled hypertension (n=2), and varying degrees of osteoarthritis (n=4). Comorbidities in the control group included: mild osteoarthritis (n=4), and diabetes mellitus type 2 (n=1). See the online data supplement (Appendix E) for more detail on subjects.

All of the COPD patients had a significant ($\geq$15 pack-years) smoking history (46.4 ± 19.8 pack-years, range 15-100 pack-years). Five patients were current smokers and 16 were ex-smokers who had stopped smoking at least two years prior to the study. In the control group, there were no current smokers and all four ex-smokers had less than a 10 pack-year smoking history and had stopped smoking for more than 10 years.

**Symptom-limited Incremental Cycle Exercise**

The majority of patients with COPD (60%) stopped exercise due to severe breathing discomfort, either alone or in combination with leg discomfort (Figure 3.1). In contrast, the majority of healthy control subjects (81%) stopped exercise primarily because of leg discomfort. Dyspnea intensity was higher in the COPD group during exercise at a given work rate (Figure 3.2); group mean differences were greater than 1 Borg unit at 60 watts and thereafter during exercise (p<0.05). Dyspnea/$\dot{V}O_2$ and dyspnea/$\dot{V}E$ slopes were also greater in COPD than control by 49% and 51%, respectively (p<0.05). At the end of exercise, dyspnea intensity was rated 1.5 Borg units higher in COPD compared to control (p=0.08) and a significantly greater number of COPD patients described their breathing as rapid compared to control subjects (45% versus 5%, respectively; p<0.05).
Figure 3.1. Selection frequency of the reason for stopping cycle exercise in the GOLD stage I COPD group and healthy control group. *p<0.05 COPD vs Control.
Figure 3.2. The relationships between exertional dyspnea, exercise work rate, and minute ventilation. Exertional dyspnea intensity was greater during cycle exercise in mild COPD than in healthy control subjects. Dyspnea/work rate and dyspnea/ventilation slopes were significantly (#: p<0.05) steeper in COPD patients than in health. Graphs represent mean±SE values at rest, at 20, 40, 60 and 80 watts during exercise, and at peak exercise. *p<0.05 COPD vs Control at a standardized work rate in watts.
Measurements at the ventilatory threshold (VTh) and at peak exercise are shown in Table 3.2. Patients with COPD stopped exercise at a lower peak VO$_2$, work rate and HR than healthy control subjects: VO$_2$/work rate (Figure 3.3) and HR/work rate relationships were not different between the two groups throughout the exercise. Compared with the control group, VE in the COPD group was significantly higher at any submaximal exercise intensity: mean differences in VE ranged from ~5 L/min at 20 watt (p<0.0005) and became greater with increasing work rate (Figure 3.3). At the VTh, VE was similar in both groups; however, patients with COPD reached their VTh at a lower VO$_2$ as well as lower work rate. More COPD subjects (n=10) than control subjects (n=5) had a VTh below 50% of the predicted maximum work rate, while more COPD subjects also had a VTh in the lower VO$_2$ range (n=5 between 40-49%, n=8 between 50-59% of predicted peak VO$_2$) than control subjects (n=3 between 40-49%, n=3 between 50-59% of predicted peak VO$_2$). PETCO$_2$ was lower in the COPD group compared with the control group at rest (36.0 ± 4.3 vs. 39.5 ± 4.5 mmHg, respectively), at any given work rate during exercise (see Figure 3.4) and at VTh (Table 3.2).

During exercise in COPD, IC decreased significantly by 0.54 ± 0.34 L (p<0.0001), with changes in IC ranging between +0.26 L (9% predicted) and -1.11 L (-41% predicted). In contrast to COPD, there was no significant change in IC from rest to peak exercise in the normal group (0.06 ± 0.32 L or 1 ± 9 % predicted). While 19 out of 21 (90%) patients with COPD decreased their IC during exercise by more than 0.2 L, only 24% of the control subjects decreased IC, 29% increased IC, and 47% did not change IC. Upon evaluation of individual Hey plots (Hey et al., 1966), the average VE at
Figure 3.3. $\dot{V}_E$, $\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$, and oxygen saturation during incremental exercise. $\dot{V}_E$, $\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$, and oxygen saturation by pulse oximetry (SpO$_2$) are shown in response to symptom-limited incremental cycle exercise in patients with mild COPD and in healthy control subjects. Graphs represent mean ± SE values at rest, at 20, 40, 60 and 80 watts during exercise, and at peak exercise. *p<0.05 COPD vs Control at a standardized work rate in watts.
Figure 3.4. $\dot{V}_E$ and $P_{ET}CO_2$ in responses to incremental exercise. $\dot{V}_E$ expressed as a fraction of the estimated maximal ventilatory capacity (MVC) was increased significantly and $P_{ET}CO_2$ was decreased significantly at rest and at a given work rate during incremental cycle exercise testing. * $p<0.05$ in patients with mild COPD compared with the healthy control group.
Table 3.2. Measurements at the ventilatory threshold and at the peak of symptom-limited incremental cycle exercise

<table>
<thead>
<tr>
<th></th>
<th>Ventilatory threshold</th>
<th>Peak exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>COPD</td>
</tr>
<tr>
<td>Dyspnea, Borg scale</td>
<td>1.8 ± 1.5</td>
<td>3.0 ± 1.9</td>
</tr>
<tr>
<td>Leg discomfort, Borg scale</td>
<td>2.4 ± 1.5</td>
<td>3.6 ± 1.9</td>
</tr>
<tr>
<td>Work rate, watt (%) predicted maximum</td>
<td>91 ± 32 (62 ± 18)</td>
<td>79 ± 13 (49 ± 13*)</td>
</tr>
<tr>
<td>VO2, L/min (%) predicted maximum</td>
<td>1.34 ± 0.29 (65 ± 12)</td>
<td>1.25 ± 0.33 (56 ± 9*)</td>
</tr>
<tr>
<td>VO2, ml/kg/min</td>
<td>18.7 ± 4.9</td>
<td>15.6 ± 3.8*</td>
</tr>
<tr>
<td>HR, beats/min (%) predicted maximum</td>
<td>121 ± 17 (72 ± 9)</td>
<td>118 ± 19 (70 ± 11)</td>
</tr>
<tr>
<td>O2 pulse, mlO2/beat</td>
<td>11.2 ± 2.9</td>
<td>10.8 ± 2.9</td>
</tr>
<tr>
<td>SpO2, %</td>
<td>97 ± 1</td>
<td>96 ± 2</td>
</tr>
<tr>
<td>VE, L/min (% estimated MVC)</td>
<td>36.2 ± 7.8 (36 ± 6)</td>
<td>39.8 ± 10.6 (51 ± 13*)</td>
</tr>
<tr>
<td>VE/VO2</td>
<td>28.9 ± 4.2</td>
<td>34.3 ± 6.0*</td>
</tr>
<tr>
<td>VE/VCO2</td>
<td>27.7 ± 3.6</td>
<td>32.0 ± 5.2*</td>
</tr>
<tr>
<td>PETCO2, mmHg</td>
<td>45.6 ± 4.2</td>
<td>41.0 ± 5.7*</td>
</tr>
<tr>
<td>R, breaths/min</td>
<td>24 ± 4</td>
<td>25 ± 5</td>
</tr>
<tr>
<td>VT, L (% predicted VC)</td>
<td>1.55 ± 0.35 (44 ± 7)</td>
<td>1.64 ± 0.48 (42 ± 8)</td>
</tr>
<tr>
<td>IC, L (% predicted)</td>
<td>2.84 ± 0.51 (105 ± 9)</td>
<td>2.82 ± 0.72 (95 ± 16*)</td>
</tr>
<tr>
<td>ΔIC from rest, L (% predicted)</td>
<td>0.02 ± 0.28 (1 ± 11)</td>
<td>-0.28 ± 0.27* (-10 ± 9*)</td>
</tr>
<tr>
<td>IRV, L (% predicted TLC)</td>
<td>1.29 ± 0.48 (22 ± 8)</td>
<td>1.18 ± 0.47 (19 ± 7)</td>
</tr>
<tr>
<td>EFL, % of VT overlapping maximal flow-volume curve</td>
<td>25 ± 27</td>
<td>63 ± 25 *</td>
</tr>
</tbody>
</table>

Values are means ± SD. * p<0.05 COPD vs Control within the given stage of exercise. Abbreviations: VO2, oxygen consumption; HR, heart rate; SpO2, arterial oxygen saturation; VE, minute ventilation; MVC, maximal ventilatory capacity estimated as 35×FEV1; VCO2, carbon dioxide production; PETCO2, partial pressure of end tidal CO2; F, breathing frequency; VT, tidal volume; VC, vital capacity; IC, inspiratory capacity; IRV, inspiratory reserve volume; EFL, expiratory flow-limitation.
the $V_T$ inflection point was similar at 44 and 45 L/min in the control and COPD group, respectively (Figure 3.5); however, this inflection occurred at a significantly ($p<0.05$) lower $\dot{V}O_2$ and work rate in COPD. Between-group differences in breathing pattern were found beyond this $\dot{V}_E$: in COPD, there was a plateau in $V_T$ at this point so that further increases in $\dot{V}_E$ were achieved by increasing $F$ alone; in the control group, further increases in $\dot{V}_E$ were achieved by increasing both $V_T$ and $F$. In COPD, $V_T$ after the inflection point was constrained by further reductions in IC of 0.23 L ($p<0.0005$). Interestingly, the IRV at the $V_T/\dot{V}_E$ inflection point was similar across groups.

**Mechanisms of Exertional Dyspnea**

The relationships between Borg ratings of dyspnea intensity and $\dot{V}_E$ (% estimated MVC) or IRV (% predicted TLC) during exercise were both superimposed in COPD and control, indicating that dyspnea intensity increased as a function of each of these independent variables. This concept is supported by the strong correlation across groups between ratings of exertional dyspnea at the highest common work rate (80 watts) and the concurrent $\dot{V}_E$ expressed as % estimated MVC ($r=0.61$, $p<0.0005$) and IRV standardized as % predicted TLC ($r=-0.62$, $p<0.0005$); the best physiological correlate of dyspnea intensity at this work rate was the concurrent IC expressed %predicted ($r= -0.63$, $p<0.0005$). Although $\dot{V}_E$ (% estimated MVC) and IRV (% predicted TLC) were moderately inter-related ($r=-0.58$, $p<0.005$), each variable explained an additional 10% to the variance in dyspnea ratings after accounting first for the other. Dyspnea intensity and absolute values of $\dot{V}_E$ at this work rate were not as strongly correlated ($r=0.39$, $p=0.013$);
however, $V_E$ explained an additional 8% of the variance in dyspnea intensity after accounting for the concurrent IC%predicted. By stepwise multiple regression analysis, dyspnea intensity at 80 watts was best described by the combination of concurrent measurements of IC %predicted and peak tidal expiratory flow ($r^2=0.56$, $p<0.0001$). Within the COPD group, the strongest correlates of exertional dyspnea intensity at a given work rate (80 watts) were the simultaneous measurements of IC %predicted ($r=-0.57$, $p=0.011$), IRV expressed % predicted TLC ($r=-0.51$, $p=0.025$) and the $V_T$/IC ratio ($r=0.47$, $p=0.042$).

**DISCUSSION**

The main findings of this study are as follows: 1) exercise capacity was significantly reduced and exertional dyspnea ratings were higher at a given work rate in symptomatic patients with GOLD stage I COPD, compared with healthy controls; 2) resting pulmonary function tests confirmed that patients had significant small airway dysfunction; 3) ventilatory abnormalities during exercise in patients with mild COPD included higher ventilatory demand, significant dynamic lung hyperinflation and a relatively rapid and shallow breathing pattern.

Our COPD patients with a relatively preserved FEV$_1$ had mild to moderate chronic activity-related dyspnea as measured by validated questionnaires. In fact, 11/21 had previously sought medical attention for dyspnea and were receiving regular or as needed inhaled bronchodilator therapy. Peak symptom-limited $\dot{V}O_2$ was reduced by 22% of the predicted normal value (Table 3.2), and patients were more likely to report dyspnea (and less likely to report leg discomfort) as an exercise-limiting symptom compared with
age- and gender-matched healthy participants (Figure 3.1). We are satisfied that the reduced exercise performance in our COPD patients was not the result of reduced motivational effort because the patients reported intolerable exertional symptoms at the peak of exercise and generally demonstrated significant encroachment on their cardiopulmonary and metabolic reserves. Although exercise limitation was multifactorial and the proximate cause likely varied among individuals, significant ventilatory constraints and attendant respiratory difficulty were evident in the majority of patients.

During exercise, dyspnea intensity ratings were higher at a given power output (e.g., by 2 Borg units at 80 watts) (Figure 3.2), while both dyspnea/VO₂ and dyspnea/Vₑ slopes were ~50% steeper in COPD than in the healthy control group. We considered the following potential contributors to exertional dyspnea in mild COPD patients; 1) higher ventilatory demand as a result of pulmonary gas exchange or metabolic abnormalities, 2) greater abnormalities of dynamic ventilatory mechanics and muscle function which would cause dyspnea to increase for any given ventilation compared with health, or 3) a combination of both of these.

**Increased Ventilatory Demand**

Ventilation was increased significantly by ~30% or more for any given power output throughout exercise in patients with mild COPD compared with control (Figure 3.3). VO₂/work rate slopes were similar and well within the normal range in both groups as has previously been described (Lewis et al., 1994) (Figure 3.3). The DLCO in the COPD group was slightly but significantly diminished compared with the healthy group but remained within the predicted normal range. Five patients had a DLCO value that was
lower than 80% predicted, indicating some reduction in the surface area for gas exchange in these heavy smokers. The ventilatory equivalents for CO\textsubscript{2} and O\textsubscript{2} were significantly elevated throughout exercise compared with in health, suggesting greater ventilation/perfusion (V/Q) abnormalities. Thus, the higher \( \dot{V}_{E}/\dot{V}_{CO_{2}} \) and \( \dot{V}_{E}/\dot{V}_{O_{2}} \) in our COPD group likely reflects an impaired ability to reduce a higher physiological dead-space during exercise. The contention that V/Q inequality contributed to the accelerated ventilatory response in COPD patients is supported by the findings that: \( V_{E} \) was increased early in exercise before the onset of metabolic acidosis; and \( \dot{V}_{E}/\dot{V}_{CO_{2}} \) ratios were also significantly (p<0.05) elevated early in exercise (by 10 and 15% at 40 and 60 watts, respectively) as well as at the ventilatory threshold (by 19%) in COPD patients compared with in health. Barbera \textit{et al.} (1994) originally described significant V/Q inequalities during exercise in a group of patients with mild COPD (mean FEV\textsubscript{1}/FVC = 59%) but found that gas exchange in these individuals was largely preserved through increased alveolar ventilation. Similarly, ventilatory efficiency was not critically compromised in COPD and pulmonary gas exchange abnormalities were not sufficiently pronounced to cause greater arterial oxygen desaturation during the activity. It is noteworthy that \( P_{ET}CO_{2} \) was decreased at rest and remained similarly decreased throughout all exercise work rates (by ~4 mmHg) in COPD patients compared with in health, suggesting alveolar hyperventilation and possible alteration in the ventilatory control system.

Earlier metabolic acidosis secondary to the effects of skeletal muscle deconditioning was considered as a potential explanation for the earlier rise in \( \dot{V}_{E} \) and
dyspnea in patients with COPD. Ventilatory thresholds occurred at a significantly lower \( \dot{V}O_2 \) in COPD (by 16%) than in health but these values were within the expected normal range (Table 3.2). However, there was considerable overlap in the range and more COPD subjects than control subjects had a VTh below 50% of the predicted maximum work rate or in the lower range of \( \dot{V}O_2 \). Perceived exertional leg discomfort was relatively increased in patients with COPD. However, other indications of the effects of deconditioning such as increased HR/\( \dot{V}O_2 \) slopes were not discernible in our COPD patients. Moreover, our estimates of habitual physical activity using the CHAMPS questionnaire (Stewart et al., 2001) were similar in both groups (Table 3.1). Significant cardiac impairment was also unlikely to contribute to the relatively reduced ventilatory threshold in COPD since patients with active cardiac comorbidity were carefully excluded from this group and heart rate responses and reserve at peak exercise were normal as were \( O_2 \) pulse and blood pressure measurements. We can postulate, therefore, that pulmonary \( \dot{V}A/\dot{Q} \) abnormalities stimulated ventilation during exercise in COPD and that this was likely compounded later in exercise by the effects of metabolic acidosis.

Regardless of the mechanism, the increased ventilatory demand likely contributed to the greater dyspnea intensity and exercise curtailment in COPD patients. Thirteen out of 21 patients with COPD reached a \( \dot{V}E/MVC > 85\% \) at a lower peak exercise capacity than in health, suggesting clinically significant ventilatory constraints to exercise in these individuals (Palange et al. 2004). A high ventilatory index (\( \dot{V}E/MVC \)) has traditionally been linked to higher levels of exertional dyspnea during exercise (Gandevia &
Macefield, 1989). In this study, a correlative analysis confirmed an association between dyspnea intensity ratings and the $\dot{V}_E$/MVC ratio ($r=0.61$, $p<0.05$). The higher ventilatory demand in COPD patients ultimately reflects a relatively increased central neural drive and contractile muscular effort (relative to the maximal possible value) for the ventilatory muscles. Neurophysiologically, the perception of increased effort is thought to be conveyed via central corollary discharge from the motor centres to the somato-sensory cortex where it is consciously appreciated as unpleasant (Davenport et al. 1986; Gandevia & Macefield, 1989; Chen et al., 1992).

**Abnormal Dynamic Ventilatory Mechanics**

Dyspnea/$\dot{V}_E$ slopes were consistently elevated during exercise in COPD suggesting increased intrinsic mechanical loading and/or functional weakness of the ventilatory muscles. Resting pulmonary function tests confirmed important mechanical abnormalities in the setting of a relatively preserved FEV₁, VC, IC and maximal static respiratory muscle strength. The presence of clinically significant small airway dysfunction was suggested by the following: 1) maximal expiratory flow rates were uniformly diminished over the effort-independent portion of the maximal flow-volume curve, 2) closing capacity was increased, 3) maldistribution of ventilation was suggested by the nitrogen washout test, and 4) all plethysmographic lung volumes were elevated. The time course of change in the various lung volume and capacity components with disease progression is unknown. In our sample, TLC and FRC were increased in proportion (suggesting increased lung compliance) such that IC was preserved. Tantucci et al. (1998) have previously shown that reduction of resting IC (<80% predicted) in
patients with moderate to severe COPD indicated the presence of expiratory flow limitation at rest (measured by the negative expiratory pressure technique) with negative implications for exercise performance. It follows that our COPD patients were unlikely to manifest expiratory flow limitation at rest but nevertheless encroached on their maximal expiratory flow reserve relatively early in exercise. During the accelerated ventilatory response to exercise in COPD, EELV increased by an average of 0.54 L from rest to peak exercise whereas in healthy participants it increased by an average of 0.06 L. These findings are consistent with the previous report by Babb et al. (1991b) who demonstrated dynamic pulmonary hyperinflation by 0.42 L in a group of patients with GOLD stage 2 COPD. Similar levels of dynamic pulmonary hyperinflation (DH) have been reported in patients with moderate to severe COPD but at much lower ventilations and work rates than our milder patients (O’Donnell et al., 2001). The presence of this degree of DH suggests that the respiratory system’s mechanical time constant for lung emptying was delayed even in mild COPD. Thus, in the setting of exercise tachypnea (and reduction of expiratory time) progressive air trapping is the inevitable consequence. Our older control group showed an inability to decrease EELV during higher exercise intensities likely reflecting the well-documented effects of aging on lung compliance which predisposes them to expiratory flow limitation (Johnson et al., 1991b; Delorey & Babb, 1999). It follows that the superimposition of small airway bronchiolitis and possibly regional emphysema, as a result of smoking, on the already impaired physiology of the aging lung may amplify the negative clinical consequences. Whether the impact of similar smoking damage on the lungs and airways of younger individuals is less marked has not been studied but is a reasonable postulation.
Dynamic hyperinflation in our COPD group was associated with a more rapid, shallow breathing at ventilations beyond 45 L/min (Figure 3.5). Consequently, the $V_T$ inflection point on individual Hey plots happened at an earlier $\dot{V}O_2$ and work rate (but at a similar dynamic IRV) in COPD than in health. Thus, in COPD patients, $V_T$ did not increase further from the inflection point to peak $\dot{V}E$ (an increase of 23 L/min) and increases in $\dot{V}E$ near end-exercise were achieved mainly by increasing breathing frequency. In this regard, it is interesting that at end-exercise, patients with COPD selected the qualitative dyspnea descriptor “rapid” more frequently than the healthy group. By contrast, $V_T$ expansion in health continued after the $V_T$ inflection point (by a further 0.23 L) and tachypnea was relatively delayed.

Mechanical abnormalities contributed to perceived exertional respiratory difficulty in COPD. Based on the result of a previous mechanical study in moderate to severe COPD (O’Donnell et al., 2006), we speculate that dynamic hyperinflation was likely advantageous early in exercise by attenuating expiratory flow limitation at the relatively higher absolute lung volume. This may have permitted our COPD patients to increase $\dot{V}E$ to ~ 40 L/min over the first few minutes of exercise with only mild increases in perceived respiratory discomfort (i.e., Borg ~2 units). Thereafter, further lung hyperinflation would be expected to cause increased elastic loading and functional weakness of the inspiratory muscles (already burdened with increased resistive loading) and to constrain $V_T$ expansion in the setting of a progressively increasing central neural drive (O’Donnell et al., 2006). Over the final minutes of exercise it is clear that in our COPD patients, central respiratory drive was relatively increased whereas $V_T$ expansion
Figure 3.5 Breathing pattern and operating lung volume changes in response to incremental exercise. Tidal volume ($V_T$), breathing frequency ($F$), inspiratory capacity (IC), and inspiratory reserve volume (IRV) are shown in response to increasing minute ventilation or work rate during incremental cycle exercise in patients with mild COPD (closed circles) and in healthy control subjects (open circles). Graphs represent mean±SE values at rest, at 20, 40, 60 and 80 watts during exercise, and at peak exercise. *$p<0.05$
was more restricted compared with healthy participants. We have previously argued that this increasing disparity between respiratory effort (or neural drive) and simultaneous thoracic volume displacement (i.e., neuromechanical dissociation) may, in part, form the basis for the perception of greater respiratory difficulty in patients with COPD (O’Donnell et al., 2006b). In the current study, dyspnea/IRV relationships were superimposed in the COPD and control groups. However, it is noteworthy that at a standardized power output of 80 watts, dyspnea intensity was significantly higher and dynamic IRV was proportionately lower in the COPD group than in the healthy group, indicating deleterious mechanical effects on respiratory sensation. The notion that dynamic hyperinflation contributes to exertional dyspnea is bolstered by the finding that within the COPD group, ratings of dyspnea intensity increased as dynamic IRV diminished during exercise ($r = -0.51$, $p < 0.05$). Moreover, consistent with a number of previous studies in patients with moderate to severe COPD, increased dyspnea intensity ratings at a standardized exercise stimulus correlated well with reduced dynamic IC expressed as % predicted (Marin et al., 2001; Puente-Maestu et al., 2005; O’Donnell et al., 2006). Thus, mechanical factors contributed more to the variance of exertional dyspnea intensity than the increased ventilation, although ventilation explained an additional 8% of the variance in dyspnea ratings after accounting for IC in a stepwise regression analysis.

It is important to emphasize that even among this small group of COPD patients, considerable pathophysiological heterogeneity was evident. For example, three patients had a disproportionate reduction of $D_{LCO}$ (<70% predicted) and were subsequently found to have radiographic evidence of localized emphysema. The extent to which our results
can be generalized to the larger population of less symptomatic GOLD stage I COPD patients (e.g., those identified by screening spirometry) remains to be determined. We can conclude, however, that in older symptomatic smokers with a largely preserved FEV₁, clinically significant physiological impairment and exertional symptoms may be present.

In summary, this is the first study to examine mechanisms of exertional dyspnea in patients with mild COPD as judged by traditional spirometric criteria. Our study demonstrates that extensive small airway dysfunction may exist in symptomatic patients with mild COPD with relatively preserved FEV₁, FVC and resting IC. When abnormal airway function and increased V/Q mismatching are superimposed on pre-existing age-related pulmonary impairment, greater exercise curtailment and troublesome exertional symptoms are the result. Dyspnea causation is multifactorial but our results indicate that the combination of increased ventilatory demand and abnormal dynamic ventilatory mechanics is likely important. For smokers who experience persistent and apparently disproportionate dyspnea (with reference to FEV₁), cardiopulmonary exercise testing is useful in uncovering the severity and mechanisms of this symptom, on an individual basis.
Chapter 4: Evaluation of Acute Bronchodilator Reversibility in GOLD Stage I COPD


Submitted to the American Journal of Respiratory and Critical Care Medicine
ABSTRACT

Symptomatic patients with GOLD stage I COPD can have significant abnormalities of ventilatory mechanics with greater exertional symptoms and exercise limitation than age-matched healthy subjects. In such patients, the impact of bronchodilator therapy remains unknown and is difficult to evaluate. We measured the acute effects of nebulized ipratropium bromide 500 µg (IB) on resting pulmonary function and on dyspnea and ventilatory parameters during symptom-limited constant work-rate cycle exercise. In a randomized, double-blind, crossover study, 16 patients with COPD [post-bronchodilator forced expiratory volume in one second (FEV$_1$) = 90 ± 7 % predicted; FEV$_1$/forced vital capacity (FVC) = 59 ± 7 %; mean ± SD] with a significant smoking history (44±16 pack-years) inhaled either IB or placebo (PL) on each of two separate visits. Pulmonary function tests and cycle exercise at 80-85% of each subject’s maximal work capacity were performed 2-hours after dosing. Results: Differences after IB compared with PL included: FEV$_1$ increased by 0.16 ± 0.23 L or 5 ± 9 % predicted; residual volume decreased by -12 ± 20 %predicted; and specific airway resistance fell by -81±93 % predicted (all p<0.05). During exercise, dynamic inspiratory capacity (IC) and tidal volume (V$_T$) significantly increased in tandem by 0.12 and 0.16 L, respectively (each p<0.05); and the abdominal contribution to V$_T$ increased by 0.16 L (n=12; p<0.05). The attendant fall in dyspnea intensity ratings at a standardized time correlated with the concurrent decrease in dynamic end-expiratory lung volume (p<0.05). Conclusion: In symptomatic GOLD stage I COPD, IB administration was associated with modest but consistent improvements in airway function at rest and during exercise with alleviation of dyspnea at the higher ventilation levels.
INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) who have relatively preserved measurements of forced expiratory flows, may have extensive small airway dysfunction (Buist & Ross, 1973b; Anthonisen et al., 2002; Hogg et al., 2004; Verbanck et al., 2006). Such patients report greater exertional dyspnea than healthy age-matched controls as a result of the combined effects of abnormal dynamic ventilatory mechanics and higher ventilatory requirements during exercise (Ofir et al., 2008). This physiological impairment of the respiratory system may explain, at least in part, reports of poor perceived health status in subpopulations of patients with apparently mild airway obstruction (Jones, 2001). Successful smoking cessation is the only proven intervention for these patients and improves small airway function (Anthonisen et al., 2002; Verbanck et al., 2006). However, the optimal clinical management of these symptomatic smokers with mild COPD is not established and remains largely unstudied. It is not known, for example, whether inhaled bronchodilator therapy, which has established efficacy in moderate to severe COPD (O’Donnell et al., 1998b; Ayers et al., 2001; Oga et al., 2003), is effective in alleviating activity-related dyspnea in those with milder disease. Moreover, it remains uncertain whether traditional spirometric criteria for bronchodilator reversibility, based on arbitrary improvement in the forced expiratory volume in one second (FEV₁), are applicable in mild COPD. This information becomes important for clinical practice and for the design of future clinical trials to evaluate the efficacy of therapeutic interventions in early COPD.

The purpose of the present study was therefore to evaluate the acute effects of an anticholinergic bronchodilator on airway function and exertional dyspnea in patients with
mild COPD, as defined by GOLD stage I criteria (Rabe et al., 2007). Based on the results of a previous mechanistic study in symptomatic mild COPD (Ofir et al., 2008), we hypothesized that inhaled bronchodilator therapy would improve airway function and lung volumes at rest and reduce the rate of dynamic pulmonary hyperinflation during exercise, thus permitting greater tidal volume expansion and higher submaximal ventilation. These mechanical improvements would result in reduced dyspnea intensity ratings at standardized exercise ventilation. To test this hypothesis we undertook a randomized placebo-controlled study in 16 well-characterized symptomatic patients with mild COPD. We compared the acute effects of nebulized ipratropium bromide (IB) and placebo (PL) on resting pulmonary function measurements, as well as dyspnea ratings, operating lung volumes, breathing pattern and pulmonary gas exchange during constant work cycle exercise. To explore potential mechanisms of dyspnea relief, we also measured esophageal pressure (Pes)-derived indices of dynamic ventilatory mechanics in a small subsample of consenting patients.

METHODS

Subjects

We studied sixteen symptomatic patients with GOLD stage I COPD (post-bronchodilator FEV₁ ≥ 80 % predicted and FEV₁/forced vital capacity (FVC) ratio < 0.7) (Rabe et al., 2007) who were referred to the COPD Centre at our institution. Patients were excluded if they had any of the following: 1) other unstable medical conditions which could cause or contribute to breathlessness, i.e., metabolic, cardiovascular or other
respiratory diseases, or 2) other disorders which could interfere with exercise testing, such as neuromuscular diseases or musculoskeletal problems.

**Study Design**

This randomized, double blind, placebo controlled, crossover study was approved by the Queen’s University and Affiliated Hospitals Research Ethics Board. After informed consent and the screening of medical history, patients were familiarized with all procedures and completed four visits conducted 2-7 days apart. At Visit 1, subjects completed pulmonary function tests and a symptom-limited incremental cycle exercise test, followed after 60 min of rest by a familiarization constant-load cycle endurance test at 80-85% of their maximal achieved power output ($W_{\text{max}}$). At Visit 2, the constant-load cycle endurance test was repeated and, after 60 min of recovery, subjects performed pulmonary function tests pre- and 20 min post-salbutamol (400 µg). At Visits 3 and 4, subjects were randomized to receive either nebulized ipratropium bromide 500 µg (IB) or a placebo (PL). Subjects performed pulmonary function tests before and 60 min after nebulization, followed by a constant-load exercise test. All symptom-limited constant-load exercise tests were conducted at the same work rate for each subject. Subjects adhered to the following withdrawal of bronchodilators before testing at each visit: short-acting $\beta_2$-agonists (8 h), short-acting anticholinergics (8 h), long-acting $\beta_2$-agonists (48 h), and long-acting anticholinergics (72 h). Subjects avoided caffeine, alcohol, and heavy meals for 4 h before testing and avoided major physical exertion entirely on visit days.
Interventions

IB and PL were administered by nebulizer (Parimaster compressor with Pari LC Jet+ nebuliser; PARI Respiratory Equipment Inc, Richmond, VA, USA) in a double-blind fashion. A 3.5 mL solution containing either 500µg IB or PL consisting of sterile 0.9% saline was nebulized over 15-20 min in a double-blind fashion.

Pulmonary Function Testing

Routine spirometry, constant-volume body plethysmography, single-breath diffusing capacity for carbon monoxide (DLCO), and maximum inspiratory and expiratory mouth pressures [MIP and MEP; measured at functional residual capacity (FRC) and total lung capacity (TLC), respectively] were performed using an automated pulmonary function testing system (6200 Autobox DL or Vmax229d; SensorMedics, Yorba Linda, CA) in accordance with recommended techniques (American Thoracic Society; European Respiratory Society, 2002; MacIntyre et al., 2005; Miller et al., 2005a; Miller et al., 2005b; Wanger et al., 2005; Han et al., 2007). Pulmonary function measurements were expressed as percentages of predicted normal values (Burrows et al., 1961; Crapo et al., 1982; Morris et al., 1988); predicted normal inspiratory capacity (IC) was calculated as predicted TLC minus predicted FRC.

Cardiopulmonary Exercise Testing

Symptom-limited exercise tests were conducted on an electronically-braked cycle ergometer in accordance with clinical exercise testing guidelines (Palange et al., 2007) as previously described (O’Donnell et al., 2006; Ofir et al., 2007; Ofir et al., 2008). An
incremental exercise test was performed at the first visit using 2-min increments of 20 W to the point of symptom limitation; \( W_{\text{max}} \) was defined as the greatest work rate that the subject could maintain for at least 30 s. Constant-load tests at 80-85% \( W_{\text{max}} \) were performed during all four visits; endurance time was defined as the duration of loaded pedaling. Cardiopulmonary exercise test parameters and detailed breathing pattern measurements were collected in a breath-by-breath fashion while subjects breathed through a mouthpiece with nasal passages occluded by a nose-clip using a cardiopulmonary exercise testing system (SensorMedics Vmax229d). Pulse oximetry, electrocardiography and blood pressure measurements were also performed.

**Exertional symptoms.** Subjects rated the intensity of their “breathing discomfort” and “leg discomfort” at rest, every minute during exercise and at end-exercise using the modified 10-point Borg scale (Borg, 1982). Immediately after exercise, subjects were asked why they needed to stop exercising, i.e., breathing discomfort, leg discomfort, a combination of breathing and leg discomfort, or some other reason to be specified. Qualitative descriptors of dyspnea were collected at end-exercise by completion of a questionnaire that we modified (O’Donnell *et al.*, 2000) from that of Simon *et al.* (1990).

**Breathing pattern and operating lung volumes.** Operating lung volumes were derived from IC measurements performed at rest, at every second minute during exercise and at end-exercise as previously described (O’Donnell *et al.*, 1998b). Flow and integrated volume were recorded continuously during exercise testing. Tidal flow-volume curves at rest, every 2 minutes during exercise and at peak exercise were constructed for each patient and placed within their respective maximal flow-volume envelopes measured at the end of their exercise test according to coinciding IC
measurements. Maximal flow-volume loops were performed at rest and immediately after exercise for this analysis. The presence or absence of expiratory flow-limitation was assessed by calculating the percent of tidal volume ($V_T$) that encroached on the maximal flow envelope (Johnson et al., 1991a; Johnson et al., 1999). We compared mid-tidal expiratory flow, maximal flow corresponding to this volume, and the expiratory reserve area (expiratory tidal volume area/ expiratory flow volume loop above the tidal volume). In 12 subjects, respiratory inductance plethysmography (LifeShirt®; VivoMetrics Inc., Ventura, CA) was used to identify breath-by-breath differences in breathing pattern and thoraco-abdominal contributions to breathing (Clarenbach et al., 2005). Volume calibration was performed by aligning volumes measured during quiet breathing on the SensorMedics Vmax systems with those measured concurrently by the LifeShirt®.

**Respiratory mechanics.** In a subgroup of 6 subjects, esophageal pressure ($P_{es}$) was recorded continuously during constant-load exercise tests using an integrated data acquisition set-up as described elsewhere (O’Donnell et al., 2006). An adult balloon-tipped catheter (Ackrad Laboratories, Cranford, NJ) was placed according to an accepted technique (Baydur et al., 1982). $P_{es}$ was sampled continuously at a rate of 100 Hz using a differential pressure transducer (MP45; Validyne Engineering, Northridge, CA), a signal conditioner (Carrier amplifier; Gould Electronics, Chandler, AZ), and computer data-acquisition software (CODAS; Dataq Instruments, Akron, OH). The continuous flow signal from the Vmax229d system was simultaneously input into this system for further analysis. Maximum inspiratory sniff maneuvers were performed pre-exercise at rest and immediately at end-exercise to obtain maximum values for $P_{es}$ ($P_{I_{max}}$). The inspiratory threshold load was calculated as the difference between $P_{es}$ at the onset of inspiratory
flow and at isovolume on the predicted chest-wall compliance curve (Estenne et al., 1985). The resistance to flow across the lung (lung tissue and airways) was calculated based on the differences in pressure and flow between two isovolume (mid-tidal) points as described by Tobin (1997). Campbell’s diagrams were constructed to calculate work of breathing measurements (Fleury et al., 1985). An index of neuromechanical coupling was calculated as the ratio of respiratory effort (tidal \( P_{es}/P_{m,ax} \)) to thoracic displacement (\( V_T/predicted \ VC \)) (O’Donnell et al., 2006b).

**End-points for exercise test analysis.** Three main time points were evaluated, i.e., pre-exercise rest, a standardized time during exercise (isotime), and peak exercise. Rest was defined as the steady-state period after at least 3 min of breathing on the mouthpiece while seated at rest on the cycle ergometer before exercise started: cardiolpulmonary parameters were averaged over the last 30 s of this period; resting IC measurements were collected while breathing on the same circuit immediately after completion of the quiet breathing period. Peak was defined as the last 30 s of loaded pedaling: cardiolpulmonary parameters were averaged over this time period; Borg ratings and IC were collected immediately at the end of this period. Isotime was defined as the duration of the shortest exercise test of the two tests rounded down to the nearest full minute, i.e., the highest equivalent isotime: cardiolpulmonary measurements were averaged over the first 30 s of this minute, while Borg ratings and IC were captured within the second 30-s period of this minute.

**Statistical Analysis**

A sample size of 16 was used to provide the power (80%) to detect a significant
difference in dyspnea intensity (Borg Scale) measured at a standardized work-rate during incremental cycle exercise based on a relevant difference in Borg ratings of ±1, a SD of 1 for Borg ratings changes found at our laboratory, \( \alpha = 0.05 \). Results were expressed as means ± SD. A \( p < 0.05 \) level of statistical significance was used for all analyses.

Treatment comparisons were made using paired t-tests with appropriate Bonferroni adjustments for multiple comparisons. Responses at rest and at different time points and/or intensities during exercise were compared. Dyspnea descriptors were analysed as frequency statistics and compared using the Fisher’s exact test. Physiological contributors to exertional dyspnea intensity in subjects with COPD were determined by forward stepwise multiple regression analysis. In this analysis, Borg dyspnea ratings at a standardized exercise work rate (dependent variable) were analyzed against concurrent relevant independent variables, i.e., exercise measurements of ventilation, breathing pattern, operating lung volumes, cardiovascular and metabolic parameters, and baseline pulmonary function measurements.

RESULTS

Subjects

Subject characteristics are summarized in Table 4.1. All subjects were symptomatic and had a diagnosis of COPD; the majority (11 of 16) had a diagnosis made within the previous 5 y. Seven subjects did not use any respiratory medications, two subjects only used a short-acting \( \beta_2 \)-agonist bronchodilator on an “as needed” basis, and seven subjects used inhalers on a regular basis. Of these latter seven subjects: all used short-acting \( \beta_2 \)-agonists, five used a long-acting \( \beta_2 \)-agonist, five used an anticholinergic
(one short-acting, four long-acting), and six used an inhaled corticosteroid (five in combination with a long-acting β<sub>2</sub>-agonist). Comorbidities included: stable coronary artery disease (n=2), well controlled diabetes mellitus type 2 (n=1), treated hypertension (n=1), and varying degrees of osteoarthritis (n=4). All subjects had a smoking history ≥15 pack-years (range 15-63 pack-years) (Table 4.1): four subjects were current smokers and twelve subjects were ex-smokers who had stopped smoking at least 2 y prior to the study.

Symptoms of breathing discomfort were confirmed by activity-related dyspnea questionnaires: Baseline Dyspnea Index (BDI) (Mahler et al., 1984), Medical Research Council (MRC) dyspnea scale (Fletcher et al., 1959), and the oxygen cost diagram (McGavin et al., 1978). BDI focal scores ranged from 5 to 12; nine subjects reported a BDI ≤ 8 and seven subjects reported a BDI ≥ 9. The majority (11 of 16) of subjects had a rating ≥ 2 on the MRC dyspnea scale.
### Table 4.1. Subjects characteristics

<table>
<thead>
<tr>
<th></th>
<th>Enrolled subjects (n = 16)</th>
<th>Subjects with respiratory inductance plethysmography (n = 12)</th>
<th>Subjects with complete mechanical measurements (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (males/females)</td>
<td>63% male (10/6)</td>
<td>66% male (8/4)</td>
<td>83% male (5/1)</td>
</tr>
<tr>
<td>Age, y</td>
<td>63 ± 8</td>
<td>63 ± 7</td>
<td>67 ± 8</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.8 ± 4.6</td>
<td>26.6 ± 4.0</td>
<td>26.4 ± 3.8</td>
</tr>
<tr>
<td>Cigarette smoking history, pack-years</td>
<td>44 ± 16</td>
<td>44 ± 16</td>
<td>43 ± 18</td>
</tr>
<tr>
<td>BDI focal score (0 -12)</td>
<td>8.3 ± 2.0</td>
<td>8.3 ± 2.2</td>
<td>8.3 ± 1.9</td>
</tr>
<tr>
<td>MRC dyspnea scale (1-5)</td>
<td>1.8 ± 0.7</td>
<td>1.7 ± 0.7</td>
<td>1.5 ± 0.5</td>
</tr>
<tr>
<td>CHAMPS, kcal/week consumed at moderate activities</td>
<td>2123 ± 2221</td>
<td>2861± 2167</td>
<td>1736 ± 1974</td>
</tr>
</tbody>
</table>

**Symptom-limited peak exercise (%predicted maximum):**

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<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Power output, W</td>
<td>121 ± 39 (72)</td>
<td>131 ± 38 (75)</td>
<td>119 ± 30 (74)</td>
</tr>
<tr>
<td>VO₂ L/min</td>
<td>1.84 ± 0.58 (79)</td>
<td>1.99 ± 0.56 (83)</td>
<td>1.79 ± 0.58 (79)</td>
</tr>
</tbody>
</table>

**Pulmonary function (%predicted maximum):**

<p>| | | | |</p>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ post-bronchodilator, L</td>
<td>2.50 ± 0.58 (90)</td>
<td>2.71 ± 0.48 (92)</td>
<td>2.44 ± 0.64 (86)</td>
</tr>
<tr>
<td>FVC post-bronchodilator, L</td>
<td>4.25 ± 1.08 (108)</td>
<td>4.56 ± 0.98 (109)</td>
<td>4.39 ± 1.18 (108)</td>
</tr>
<tr>
<td>FEV₁/FVC post-bronchodilator, %</td>
<td>59 ± 7 (84)</td>
<td>60 ± 6 (85)</td>
<td>56 ± 8 (80)</td>
</tr>
<tr>
<td>IC, L</td>
<td>3.01 ± 0.97 (103)</td>
<td>3.26 ± 0.98 (106)</td>
<td>3.34 ± 1.13 (106)</td>
</tr>
<tr>
<td>FRC, L</td>
<td>4.10 ± 0.91 (122)</td>
<td>4.26 ± 0.91 (120)</td>
<td>4.45 ± 0.71 (126)</td>
</tr>
<tr>
<td>TLC, L</td>
<td>7.11 ± 1.50 (113)</td>
<td>7.52 ± 1.44 (113)</td>
<td>7.79 ± 1.32 (117)</td>
</tr>
<tr>
<td>RV, L</td>
<td>2.83 ± 0.48 (129)</td>
<td>2.88 ± 0.48 (128)</td>
<td>3.08 ± 0.32 (131)</td>
</tr>
<tr>
<td>MIP, cmH₂O</td>
<td>95 ± 32 (115)</td>
<td>102 ± 31 (119)</td>
<td>87 ± 23 (95)</td>
</tr>
<tr>
<td>MEP, cmH₂O</td>
<td>149 ± 59 (83)</td>
<td>158 ± 64 (87)</td>
<td>139 ± 44 (100)</td>
</tr>
<tr>
<td>D₃CO, ml/min/mmHg</td>
<td>21.2 ± 5.9 (95)</td>
<td>22.1 ± 6.1 (96)</td>
<td>22.4 ± 4.5 (106)</td>
</tr>
<tr>
<td>sRaw, cmH₂O·s</td>
<td>12.3 ± 4.0 (294)</td>
<td>11.7 ± 3.8 (278)</td>
<td>13.3 ± 2.9 (303)</td>
</tr>
</tbody>
</table>

Values are described as means ± SD. BDI, Baseline Dyspnea Index; MRC, Medical Research Council; CHAMPS, Community Healthy Activities Model Program for Seniors; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IC, inspiratory capacity; FRC, functional reserve capacity; TLC, total lung capacity; RV, residual volume; MIP, maximal inspiratory mouth pressure; MEP, maximal expiratory mouth pressure; sRaw, specific airway resistance.
All subjects had a normal post-bronchodilator FEV$_1$ (90±7 % predicted) and a FEV$_1$/FVC ratio < 70 % (59±7 %). Lung volume measurements showed mild static lung hyperinflation (mean FRC and RV > 120 % predicted) with a preserved VC and IC (Table 4.1). Symptom-limited incremental exercise testing showed a reduced peak VO$_2$ and work rate. The subgroups of subjects with P$_{es}$-derived measurements and with LifeShirt® measurements had comparable baseline characteristics and pulmonary function to the group as a whole (Table 4.1).

**Pulmonary Function Responses**

Differences in spirometry and body plethysmography after IB compared with PL are shown in Table 4.2. There were significant improvements in maximal expiratory flows (FEV$_1$, FEF$_{25-75\%}$) and FVC, with no significant difference in FEV$_1$/FVC; there was a significant decrease in lung hyperinflation (FRC, RV). There were no significant treatment differences in respiratory muscle strength (MIP and MEP) or in IC; and specific airway resistance (sRaw) decreased by more than a third from baseline values. Maximal expiratory flows measured at FRC after PL were compared with the maximal flow at the same absolute volume after IB within each individual; these isovolume flows improved from 0.27±0.18 to 0.43±0.30 L/s after PL and IB, respectively (p=0.006).

**Responses to Constant-Load Exercise**

Distribution of reasons for stopping exercise was not different between the two treatments. In both visits, leg discomfort was reported as the primary reason for stopping exercise, 2- to 3-times more often than breathing discomfort (Table 4.3).
Table 4.2. The effect of placebo (PL) and ipratropium bromide (IB) on pulmonary function tests in GOLD stage I COPD

<table>
<thead>
<tr>
<th></th>
<th>Post PL</th>
<th>Post IB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV₁, L</strong></td>
<td>2.30 ± 0.60 (83)</td>
<td>2.46 ± 0.59 (88)*</td>
</tr>
<tr>
<td>Δ FEV₁, L</td>
<td>0.07 ± 0.09 (3)‡</td>
<td>0.26 ± 0.19 (9)‡ §</td>
</tr>
<tr>
<td><strong>FVC, L</strong></td>
<td>4.07 ± 1.13 (103)</td>
<td>4.20 ± 1.17 (106)*</td>
</tr>
<tr>
<td>Δ FVC, L</td>
<td>0.02 ± 0.18 (1)</td>
<td>0.23 ± 0.21 (6)‡ §</td>
</tr>
<tr>
<td><strong>FEV₁/FVC, %</strong></td>
<td>57 ± 7 (81)</td>
<td>59 ± 7 (83)</td>
</tr>
<tr>
<td>Δ FEV₁/FVC, %</td>
<td>1.3 ± 2.0 (2)‡</td>
<td>2.9 ± 3.2 (4)‡</td>
</tr>
<tr>
<td><strong>FEF₂₅₋₇₅%, L/sec</strong></td>
<td>0.93 ± 0.39 (33)</td>
<td>1.06 ± 0.33 (37)</td>
</tr>
<tr>
<td>Δ FEF₂₅₋₇₅%, L/sec</td>
<td>0.10 ± 0.20 (4)‡</td>
<td>0.24 ± 0.24 (8)‡</td>
</tr>
<tr>
<td><strong>DlCO, ml/min/mmHg</strong></td>
<td>21.0 ± 6.2 (94)</td>
<td>20.2 ± 6.5 (90)</td>
</tr>
<tr>
<td>Δ DlCO</td>
<td>-0.11 ± 1.37 (-1)</td>
<td>-1.09 ± 2.32 (-5)</td>
</tr>
<tr>
<td><strong>MIP, cmH₂O</strong></td>
<td>96 ± 20 (120)</td>
<td>98 ± 21 (121)</td>
</tr>
<tr>
<td>Δ MIP, cmH₂O</td>
<td>-1 ± 11 (-2)</td>
<td>1.6 ± 7.7 (1)</td>
</tr>
<tr>
<td><strong>MEP, cmH₂O</strong></td>
<td>148.2 ± 54.5 (82)</td>
<td>148 ± 48 (83)</td>
</tr>
<tr>
<td>Δ MEP, cmH₂O</td>
<td>0.7 ± 12.2 (1)</td>
<td>-5.9 ± 13.2 (-10)</td>
</tr>
<tr>
<td><strong>TLC, L</strong></td>
<td>7.16 ± 1.49 (114)</td>
<td>7.04 ± 1.42 (112)</td>
</tr>
<tr>
<td>Δ TLC, L</td>
<td>-0.03 ± 0.26 (-1)</td>
<td>-0.15 ± 0.20 (-3)‡</td>
</tr>
<tr>
<td><strong>RV, L</strong></td>
<td>2.73 ± 0.34 (125)</td>
<td>2.49 ± 0.47 (113)*</td>
</tr>
<tr>
<td>Δ RV, L</td>
<td>-0.14 ± 0.19 (-6)‡</td>
<td>-0.38 ± 0.22 (-19)‡ §</td>
</tr>
<tr>
<td><strong>FRC, L</strong></td>
<td>4.05 ± 0.71 (121)</td>
<td>3.90 ± 0.82 (115)*</td>
</tr>
<tr>
<td>Δ FRC, L</td>
<td>-0.07 ± 0.17 (-2)</td>
<td>-0.27 ± 0.29 (-9)§</td>
</tr>
<tr>
<td><strong>IC, L</strong></td>
<td>3.10 ± 1.01 (106)</td>
<td>3.15 ± 0.86 (109)</td>
</tr>
<tr>
<td>Δ IC, L</td>
<td>0.04 ± 0.19 (1)</td>
<td>0.12 ± 0.32 (4)</td>
</tr>
<tr>
<td><strong>sRaw, cmH₂O·s</strong></td>
<td>12.7 ± 4.3 (301)</td>
<td>9.34 ± 4.63 (220)*</td>
</tr>
<tr>
<td>Δ sRaw, cmH₂O·s</td>
<td>-0.6 ± 1.7 (-15)</td>
<td>-4.7 ± 3.5 (-111)§</td>
</tr>
</tbody>
</table>

Values are described as means ± SD. * p<0.05 post-IB vs post-PL value within group; ‡ p<0.05 pre vs post treatment value (IB or PL). §p<0.05 difference between within-treatment post-predose differences. Abbreviations: Δ, post-dose minus pre-dose difference; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; PEF, peak expiratory flow; FEF₂₅₋₇₅%, force expiratory flow between 25 and 75% of FVC; DLCO, diffusing capacity of the lung for carbon monoxide; VA, alveolar ventilation; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; SVC, slow vital capacity; RV, residual volume; IC, inspiratory capacity; sRaw, specific airway resistance.
Table 4.3. Postdose “peak” of symptom-limited constant-load exercise at 80-85 % Wmax (99±32 W)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ipratropium bromide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise time, min</td>
<td>8.2 ± 5.3</td>
<td>8.2 ± 4.8</td>
</tr>
<tr>
<td>Dyspnea, Borg scale</td>
<td>7.8 ± 2.9</td>
<td>7.7 ± 2.5</td>
</tr>
<tr>
<td>Leg discomfort, Borg scale</td>
<td>8.6 ± 1.9</td>
<td>8.4 ± 2.2</td>
</tr>
<tr>
<td>Reason for stopping, n (%):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breathing</td>
<td>3 (19)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Legs</td>
<td>6 (37)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Both breathing and legs</td>
<td>7 (44)</td>
<td>5 (31)</td>
</tr>
<tr>
<td>$\dot{V}O_2$, L/min</td>
<td>1.88 ± 0.64</td>
<td>1.81 ± 0.56</td>
</tr>
<tr>
<td>$\dot{V}CO_2$, l/min</td>
<td>1.73 ± 0.55</td>
<td>1.75 ± 0.58</td>
</tr>
<tr>
<td>$V_E$, l/min</td>
<td>69.4 ± 18.2</td>
<td>73.5 ± 23.9</td>
</tr>
<tr>
<td>$f$, breaths/min</td>
<td>39.6 ± 7.9</td>
<td>39.1 ± 7.3</td>
</tr>
<tr>
<td>$V_T$, liters</td>
<td>1.81 ± 0.56</td>
<td>1.91 ± 0.58 *</td>
</tr>
<tr>
<td>IC, liters</td>
<td>2.46 ± 0.70</td>
<td>2.59 ± 0.70 (p&lt;0.09)</td>
</tr>
<tr>
<td>IRV, liters</td>
<td>0.65 ± 0.26</td>
<td>0.67 ± 0.32</td>
</tr>
<tr>
<td>$V_T/T_E$, l/s</td>
<td>2.10 ± 0.59</td>
<td>2.24 ± 0.80</td>
</tr>
<tr>
<td>$V_T/T_I$, l/s</td>
<td>2.56 ± 0.63</td>
<td>2.68 ± 0.80</td>
</tr>
<tr>
<td>$T_I/T_{TOT}$</td>
<td>0.45 ± 0.03</td>
<td>0.45 ± 0.03</td>
</tr>
<tr>
<td>$P_{ET}CO_2$, mmHg</td>
<td>34.4 ± 4.7</td>
<td>33.0 ± 5.4 (p = 0.077)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>142 ± 16</td>
<td>140 ± 17</td>
</tr>
<tr>
<td>$SpO_2$, %</td>
<td>95 ± 3</td>
<td>95 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SD. *p<0.05 ipratropium bromide (IB) versus placebo (PL). $\dot{V}O_2$, oxygen uptake; $\dot{V}CO_2$, carbon dioxide production; $V_E$, minute ventilation; $f$, breathing frequency; $V_T$, tidal volume; IC, inspiratory capacity; IRV, inspiratory reserve volume; $V_T/T_E$ and $V_T/T_I$, mean inspiratory and expiratory tidal flows; $T_I/T_{TOT}$, inspiratory duty cycle, inspiratory time over total breath time; $P_{ET}CO_2$, partial pressure of end-tidal CO$_2$; $SpO_2$, oxygen saturation.
Exertional symptoms. After IB compared with PL, there was no change in peak Borg ratings of breathing or leg discomfort (Table 4.3); however, ratings of breathing and leg discomfort at the highest equivalent isotime (6.8±4.5 min) during exercise were lower after IB compared with PL by 0.88±1.83 (p=0.073) and 0.81±1.28 (p<0.05) Borg units, respectively (Table 4.4, Figure 4.1). Ten of sixteen patients decreased the intensity of their breathing discomfort at isotime by at least 1 Borg units, while the remaining subjects increased (n=4) or did not change (n=2) ratings of breathing discomfort after IB compared with PL. Ratings of breathing discomfort expressed relative to $\dot{V}_E$ were significantly lower (p<0.05) at isotime after IB compared with PL (Table 4.4). The selection frequency of dyspnea descriptor phrases at end-exercise was similar after IB compared with PL, except “expiratory difficulty” was chosen as one of the three most important descriptors of breathing discomfort in four subjects (25%) after PL but by no subjects after IB (p<0.05).

Ventilatory responses. Ventilatory responses to constant-load exercise after IB and PL are shown in Figure 4.1. $V_T$ was greater after IB compared with PL from minute 4 in exercise to peak exercise by between 0.10 and 0.16 L (p<0.05); increases in $V_T$ were accommodated by concurrent increases in IC of between 0.12 and 0.15 L (p<0.05). Inspiratory reserve volume (IRV) was not different at rest or throughout exercise across treatments. The extent of expiratory flow limitation measured by the $V_T$ overlap method (see methods) was reduced at isotime and at peak exercise by 10 and 17% (p<0.05), respectively, after IB compared with PL.
Table 4.4. Postdose values at isotime (6.8 ± 4.5 min) during constant-load exercise

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ipratropium bromide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea, Borg</td>
<td>7.4 ± 2.4</td>
<td>6.6 ± 2.4 (p=0.07)</td>
</tr>
<tr>
<td>Dyspnea/(\dot{V}_E), Borg/L/min</td>
<td>0.12 ± 0.05</td>
<td>0.10 ± 0.05 *</td>
</tr>
<tr>
<td>Leg discomfort, Borg</td>
<td>8.3 ± 1.7</td>
<td>7.5 ± 2.1 *</td>
</tr>
<tr>
<td>(\dot{V}O_2), L/min</td>
<td>1.72 ± 0.54</td>
<td>1.82 ± 0.66 (p=0.097)</td>
</tr>
<tr>
<td>(\dot{V}CO_2), L/min</td>
<td>1.67 ± 0.56</td>
<td>1.71 ± 0.62</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>137 ± 19</td>
<td>136 ± 19</td>
</tr>
<tr>
<td>SpO(_2), %</td>
<td>96 ± 3</td>
<td>96 ± 2</td>
</tr>
<tr>
<td>(\dot{V}_E), L/min</td>
<td>65.7 ± 19.6</td>
<td>69.0 ± 24.9</td>
</tr>
<tr>
<td>(V_T), L</td>
<td>1.83 ± 0.57</td>
<td>1.99 ± 0.65 *</td>
</tr>
<tr>
<td>(f), breaths/min</td>
<td>36.7 ± 8.3</td>
<td>35.3 ± 8.2</td>
</tr>
<tr>
<td>IC, L</td>
<td>2.51 ± 0.70</td>
<td>2.63 ± 0.66 *</td>
</tr>
<tr>
<td>(\Delta IC) isotime-rest, L</td>
<td>-0.55 ± 0.40</td>
<td>-0.49 ± 0.33</td>
</tr>
<tr>
<td>IRV, L</td>
<td>0.68 ± 0.31</td>
<td>0.64 ± 0.30</td>
</tr>
<tr>
<td>(T_i), s</td>
<td>0.77 ± 0.20</td>
<td>0.81 ± 0.21</td>
</tr>
<tr>
<td>(T_E), s</td>
<td>0.93 ± 0.20</td>
<td>0.98 ± 0.23 (p=0.06)</td>
</tr>
<tr>
<td>(T_i/T_{TOT})</td>
<td>0.45 ± 0.03</td>
<td>0.45 ± 0.03</td>
</tr>
<tr>
<td>(V_D/V_T) estimated, %</td>
<td>30 ± 7</td>
<td>29 ± 8 *</td>
</tr>
<tr>
<td>(P_{ETCO_2}), mmHg</td>
<td>35.4 ± 5.1</td>
<td>34.3 ± 5.5 (p=0.09)</td>
</tr>
</tbody>
</table>

Values are described as means ± SD. * Significant difference p<0.05 between ipratropium bromide and placebo. Abbreviations: \(\dot{V}O_2\), oxygen uptake; \(\dot{V}CO_2\), carbon dioxide production; HR, heart rate; SpO\(_2\), oxygen saturation; \(\dot{V}_E\), minute ventilation; \(V_T\), tidal volume; VC, vital capacity; \(f\), breathing frequency; \(V_D\), estimated dead space; IC, inspiratory capacity; IRV, inspiratory reserve volume; \(T_E\), expiratory time; \(T_i\), inspiratory time; \(T_i/T_{TOT}\), inspiratory duty cycle, inspiratory time over total breath time; \(P_{ETCO_2}\), partial pressure of end-tidal CO\(_2\). overlap method (see methods) was reduced at isotime and at peak exercise by 10 and 17% (p<0.05), respectively, after IB compared with PL.
Figure 4.1. Ventilatory responses to constant-load exercise. Ventilatory responses to constant-load exercise are shown against exercise time after ipratropium bromide compared with placebo (n=16). Tidal volume (VT), inspiratory capacity (IC), and abdominal (AB) but not rib cage (RC) volumes were significantly larger and expiratory flow limitation EFL were lower after ipratropium compared with placebo. Minute ventilation and inspiratory reserve volume (IRV) were not different between the two visits. * $P < 0.05$ ipratropium vs. placebo at a given time point or at peak exercise. Values are means ± SEM.
In the 12 subjects with LifeShirt® measurements, the 0.20±0.23 L (p=0.011) increase in \( V_T \) observed at isotime during exercise after IB was recruited from the abdominal compartment (Figure 4.1E): the abdominal contribution to \( V_T \) was larger (1.32±0.46 vs 1.15±0.52 L; p=0.034) with no difference in the ribcage contribution (0.88±0.28 vs 0.84±0.34 L; p=0.64) after IB vs PL, respectively. An improvement in breathing synchrony was also found during exercise, as measured by a lower phase angle at minute 4 (12±6 vs 17±10 °; p<0.05) and at isotime (15±10 vs 20±15 degrees; p=0.15) after IB and PL, respectively.

Ventilator mechanicsy (Figure 4.3). After IB compared to PL, airway resistance fell in the order of 0.7 to 0.8 cmH\(_2\)O/L/s at standardized timepoints throughout exercise, i.e., a reduction of ~20% (p<0.05). Total work of breathing expressed as J/L fell significantly (p<0.05) during exercise but not at rest after IB compared with PL; primarily due to significant (p<0.05) decreases in the inspiratory threshold load and the elastic work performed against this load. However, work of breathing measurements were not different when expressed as J/min; thus differences were directly related to differences in ventilation. The pressure-time integral and its surrogate, and the calculated tension-time index (Pes/P_{I\max} multiplied by TI/T_{TOT}), did not differ between IB and PL. After IB compared to PL, there was no significant difference in Pes/P_{I\max} or the Pes/P_{I\max}:V_T/predicted VC ratio at either a given time or \( \dot{V}_E \) during exercise.

Correlates of Dyspnea
At isotime during exercise, the difference in dyspnea after IB compared with PL correlated best with the concurrent difference in \( T_E \) (r=0.51, p=0.043). Using multiple
regression analysis, treatment differences in $T_E$ and EELV/TLC together accounted for 51% of the variance in the difference in Borg dyspnea ratings at isotime. When dyspnea was expressed as a ratio against $\dot{V}_E$ (Borg/(L/min)), the strongest correlate of this treatment difference at isotime was the concurrent difference in EELV/TLC ($r=0.58$, $p<0.05$).

Correlates of the IB-induced decrease in dyspnea ratings at isotime were the baseline pre-exercise resting IC expressed as %predicted ($r=0.64$, $p=0.008$), the EELV/TLC ratio ($r=-0.56$, $p=0.024$) and the IRV expressed as %predicted TLC ($r=0.541$, $p=0.030$), but no other baseline pulmonary function parameters. The best correlates of the IB-induced decrease in dyspnea/$\dot{V}_E$ ratios at isotime were also the pre-exercise resting IC expressed as % predicted ($r=0.71$, $p=0.002$), the EELV/TLC ratio ($r=-0.64$, $p=0.008$) and the IRV expressed as % predicted TLC ($r=0.55$, $p=0.028$).
Figure 4.2. The ratio of dyspnea intensity to ventilation and intensity ratings of leg discomfort at a given time points during constant-load exercise. The ratio of dyspnea intensity to ventilation and intensity ratings of leg discomfort are shown at a given time points during constant-load exercise. * $P < 0.05$ ipratropium vs. placebo at a given time point. Values are means ± SEM.
Figure 4.3. Respiratory mechanical measurements during exercise after ipratropium compared with placebo (n = 6). Airway resistance and inspiratory threshold load (ITL) decreased during exercise after ipratropium. While peak tidal inspiratory and expiratory esophageal pressure (Pes), tidal Pes swings as a fraction of maximal inspiratory esophageal pressure (Plmax), total work of breathing, and the ratio of respiratory effort (tidal Pes/Plmax) to thoracic displacement (tidal volume (VT expressed as a fraction of predicted vital capacity (VC)) were not different between the treatments. * P < 0.05 (one-tailed) ipratropium vs. placebo at a given time point or at peak exercise. Values are means ± SEM.
DISCUSSION

The novel findings of this study are as follows: first, treatment with IB was associated with consistent improvements in forced expiratory flows, specific airway resistance and static lung volumes in symptomatic patients with GOLD stage I COPD; second, during exercise, IB treatment was associated with significant increases in dynamic IC and $V_T$ which did not translate into an increased cycle exercise endurance time, and; third, improvement in dynamic EELV was linked to a reduction in ratings of exertional dyspnea intensity.

Changes in Resting Pulmonary Function

Our results confirm that release of cholinergic tone improved airway function both at rest and during exercise in current or ex-smokers with relatively mild airflow obstruction. In general, changes in resting spirometry were in the same direction but more modest than those previously reported following a similar dosage of IB in moderate to severe COPD (O’Donnell et al., 1998; Ayers et al., 2001; Oga et al., 2003). FEV$_1$, the traditional spirometric index of airflow reversibility, improved (p<0.05) by an average of 0.16 L (7%) after IB compared with placebo with no significant change in the FEV$_1$/FVC ratio (Table 4.2). Bronchodilator therapy facilitated lung emptying and lung volume recruitment as indicated by small but consistent improvements in RV and VC. However, changes in lung volumes were ~50% of the magnitude reported during anticholinergic therapy in advanced COPD (Ayers et al., 2001). Airway resistance, corrected for the lower resting operating volume, decreased after IB by 33% of baseline values while isovolume maximal flow rates in the effort-independent range also improved.
In contrast to previous studies of the acute effects of IB in more advanced disease, resting IC did not increase significantly in our milder COPD cohort. Thus, FRC and TLC fell in tandem and to a similar extent such that change in IC underestimated the extent of IB-induced lung deflation. The lack of increase in resting IC in our patients is not surprising considering their preserved IC. Based on the study of Tantucci et al. (1998), bronchodilator-induced increases in IC are only expected in patients with COPD who have more extensive expiratory flow-limitation and lung hyperinflation (i.e., IC<80 % predicted) at rest. Indeed, the largest improvement in exertional dyspnea within our study sample occurred in those with the greatest degree of lung hyperinflation at baseline (smallest IC).

**Altered Ventilatory Responses to Exercise after Bronchodilator**

Exercise endurance time did not increase after bronchodilator compared with placebo. Possible explanations for this may include: 1) the study was powered to detect an improvement in dyspnea at a standardized work rate and not a change in exercise endurance time; 2) intolerable leg discomfort and not dyspnea was the dominant exercise-limiting symptom in the majority of this group, and; 3) increase ventilatory constraints did not contribute sufficiently to exercise limitation, partial reversal of mechanical abnormalities by IB would not be expected to improve performance. Among our patients there was significant variability in the baseline endurance time at a constant work rate of 80-85 % maximum (placebo visit: range 4-24 min; average: 8.1±5.0 min). It is possible that for some individuals with relatively preserved exercise capacity, the work rate selected was substantially higher than their maximal sustainable aerobic capacity (or
critical power). This would make the detection of change in exercise performance after a therapeutic intervention more difficult. It follows that cycle exercise endurance protocols that have been shown to be sufficiently responsive for the purpose of evaluation of bronchodilator efficacy in more advanced COPD may not be appropriate for patient populations with mild COPD (O'Donnell et al., 2006c; Ayers et al., 2001; Oga et al., 2003).

From rest to peak exercise, IC diminished by 0.55 L confirming the presence of air trapping due to expiratory flow limitation and high ventilatory demand in patients with mild COPD. IB treatment was associated with an increased IC (decreased EELV) throughout exercise compared with placebo (Figure 4.1), although acute changes in IC during exercise remained similar. Dynamic IC was consistently greater by ~0.12 to 0.15 L throughout exercise despite slightly greater levels of ventilation (~3 L/min). We also found consistent reductions in the degree of expiratory flow limitation after IB, crudely shown as a reduction in the extent of overlap of tidal expiratory flow-volume loop on the maximal curve (Figure 4.1). Moreover, pulmonary resistance was significantly reduced at time points during exercise in the smaller sample of patients (6) who consented to esophageal pressure measurements (Figure 4.3). Therefore, the likeliest explanation for lung deflation is improvement in the time constant for lung emptying as a result of reduced airway resistance. Our results indicate that expiratory time prolongation and altered static lung recoil pressure were unlikely to account for the reduced dynamic EELV in response to IB treatment.

The improved dynamic IC allowed greater V_{T} expansion throughout exercise without further encroachment on the dynamic IRV. Unlike the situation in more
advanced COPD, bronchodilator therapy was not associated with a delay in reaching a critically reduced IRV where there is a discernible plateau in the $V_T$ response to exercise. Expansion of $V_T$ occurred in association with changes in the thoraco-abdominal contribution to ventilation. Thus, while ribcage volumes remained unaltered, abdominal volumes increased (by 0.16 L; $p<0.05$) suggesting a reduction in abdominal muscle activation in association with mechanical unloading during IB therapy (Figure 4.1). This altered recruitment pattern has been reported following bronchodilator therapy in advanced COPD but the precise mechanisms remain obscure. Reduced requirement for expiratory pressure generation might occur, for example, in the presence of reduced expiratory airway resistance following bronchodilator administration.

**Mechanisms of Dyspnea Relief**

Our patients had clinically significant chronic activity-related dyspnea (measured by validated questionnaires) and exercise intolerance. After IB compared with placebo, dyspnea intensity was reduced at a standardized time during exercise by almost 1 Borg unit ($p=0.07$) while dyspnea/$\dot{V}_E$ ratios also decreased ($p<0.05$). The magnitude of this effect was similar or greater than that seen previously in studies on the effects of anticholinergics in more advanced COPD where benefits occurred at a relatively lower $\dot{V}_E$ and $\dot{V}O_2$ than in our study group. Fifty-one percent of the variance in improved dyspnea intensity was explained by decreased dynamic EELV and increased expiratory time. This correlation between EELV and dyspnea intensity supports our previous
postulation that dynamic pulmonary hyperinflation contributes to dyspnea in symptomatic mild COPD.

**Reduced Leg Discomfort**

We were surprised to find that, in contrast to several previous studies on the effects of bronchodilators in more advanced COPD, perceived leg discomfort was consistently reduced during IB compared to placebo in mild COPD. However, this subjective benefit was not sufficient to improve exercise endurance even in patients who reported leg discomfort as the primary exercise limiting symptom. The mechanisms for this benefit, in so far as it pertains to acutely improved peripheral muscle function, are unknown. Thus, we were unable to demonstrate consistent improvements in indirect indices of cardiac function (heart rate, blood pressure, or ventilatory threshold) or in pulmonary gas exchange (arterial oxygen saturation, $P_{ET CO_2}$ or $V'_E/VCO_2$) which might have improved perfusion or oxygen delivery to the active locomotor muscles. Similarly, indirect assessment of the oxygen cost of breathing was not reduced during IB treatment in our small subgroup. Our results do not support the concept that reduced competition (i.e., vascular steal effect) between the ventilatory muscles and the active peripheral muscles explains the reduced leg discomfort (Aliverti *et al.*, 2008).

In summary, traditional spirometric measurements reliably detected modest but consistent improvements in airway function after bronchodilator treatment in symptomatic patients with mild COPD. The most responsive physiological parameters of airflow reversibility were specific airway resistance and residual volume. Bronchodilator administration was associated with improved dynamic IC and a deeper breathing pattern throughout exercise. Dyspnea intensity ratings fell only at the higher levels of ventilation.
with IB treatment, in association with reduced dynamic EELV. Mechanical and perceptual improvements during exercise after IB treatment were most pronounced in those with the smallest resting IC and therefore the greatest resting mechanical constraints on tidal volume expansion. Our results provide a physiological rationale for a trial of bronchodilator therapy in selected patients with GOLD stage I COPD who have troublesome activity-related dyspnea and who wish to engage in sustained physical activity.
Chapter 5: Ventilatory and Perceptual Responses to Cycle Exercise in Obese Females

Dror Ofir, Pierantonio Laveneziana, Katherine A. Webb, Denis E. O’Donnell

ABSTRACT

The main purpose of this study was to examine the relative contribution of respiratory mechanical factors and the increased metabolic cost of locomotion to exertional breathlessness in obese women. We examined the relationship of intensity of breathlessness to ventilation ($\dot{V}_E$) when exertional oxygen uptake ($\dot{V}O_2$) of obesity was minimized by cycle exercise. Eighteen middle-aged (54±8 years, mean±SD) obese (body mass index [BMI] 40.2 ± 7.8 kg/m$^2$) and 13 age-matched normal-weight (BMI 23.3 ± 1.7 kg/m$^2$) females were studied. Breathlessness at higher submaximal cycle work-rates was significantly increased (by ≥1 Borg unit) in obese compared to normal-weight females, in association with a 35-45% increase in $\dot{V}_E$ and a higher metabolic cost of exercise. Obese females demonstrated greater resting expiratory flow limitation, reduced resting end-expiratory lung volume (EELV) (by 20%) and progressive increases in dynamic EELV during exercise: peak inspiratory capacity (IC) decreased by 16% (0.39 L) of the resting value. $\dot{V}_E/\dot{V}O_2$ slopes were unchanged in obesity. Breathlessness ratings at any given $\dot{V}_E$ or $\dot{V}O_2$ were not increased in obesity, suggesting that respiratory mechanical factors were not contributory. Our results indicate that in obese females, recruitment of resting IC and dynamic increases in EELV with exercise served to optimize operating lung volumes and to attenuate expiratory flow limitation so as to accommodate the increased ventilatory demand without increased breathlessness.
INTRODUCTION

In health, it is generally assumed that ventilatory capacity exceeds demand even during exhaustive exercise and that the respiratory system is rarely the proximate limit to exercise performance, at least in non-athletic individuals (Aaron et al., 1992; Johnson et al., 1992). However, it is increasingly recognized, that even in people with otherwise normal lungs, the normal ventilatory responses to exercise can become constrained, under conditions such as obesity (Babb et al., 1989; Babb et al., 1991; Babb et al., 2002). Moreover, it is suggested that the ventilatory constraints to exercise may be more pronounced in females compared with males at a standardized power output due to a comparatively reduced anatomical size of the lungs and airways, together with the reduced mass of the respiratory musculature (Killian et al., 1992). This can lead to higher rates of exertional breathlessness in women compared with men for any standardized physical task reflecting the relatively high ventilation demand: capacity ratio in the former. When the effects of obesity are compounded by the co-existent physiological influences of gender, ventilatory constraints to exercise may reach a critical level with attendant exertional symptoms (Johnson et al., 1991).

Activity-related breathlessness is a common symptom in obesity and the question arises whether this is due to: (1) abnormal respiratory mechanical factors related to chest wall loading, (2) the increased metabolic demand of locomotion in obesity or (3) both of these together. Babb et al. (2002) showed that in younger females (mean age 35 years) with mild obesity (mean body mass index [BMI] 34 kg/m²) measurements of work of breathing and ratings of breathlessness during incremental cycle exercise were similar to those of normal weight controls. However, an explanation for these findings was not
pursued in that study. The current study was undertaken to extend our knowledge of the physiological derangements of obesity and specifically to determine whether abnormalities of dynamic ventilatory mechanics peculiar to obesity (chest wall elastic loading combined with expiratory flow limitation), contributes to the quality and intensity of exertional breathlessness in female participants. In this study the increased metabolic cost of locomotion in obesity was minimized by using weight-supported cycle exercise. We postulated that if the intensity of breathlessness at any given ventilation (\( \dot{V}_E \)) and oxygen uptake (\( \dot{V}O_2 \)) did not increase in obesity compared with normal-weight control subjects, then respiratory mechanical factors were unlikely to be contributory. Alternatively, an increase in breathlessness/\( \dot{V}_E \) and breathlessness/\( \dot{V}O_2 \) slopes during weight-supported cycle exercise in obese compared with normal-weight participants would indicate that restrictive ventilatory mechanics as a result of obesity contributed to increased breathing discomfort. We therefore compared ventilatory (operating lung volumes, airway function, gas exchange, and breathing pattern) and perceptual responses (quality and intensity of breathlessness and leg discomfort) to incremental cycle exercise in 18 middle-aged, obese females (OB) and 13 age-matched females with normal body mass index (NW).

**METHODS**

**Subjects**

Eighteen middle aged (40 - 80 yrs) obese females with a body mass index (BMI) > 30 kg/m\(^2\) completed the study. In accordance with criteria established by the American
Thoracic Society (American Thoracic Society, 1995), there was no evidence that any subjects suffered from chronic obstructive pulmonary disease (COPD) or bronchial asthma. Obese subjects were also excluded if they had: (1) other medical conditions which could cause or contribute to breathlessness, i.e., metabolic, cardiovascular or other respiratory diseases, or (2) other disorders which could interfere with exercise testing, i.e., neuromuscular diseases, musculoskeletal problems, etc.

Thirteen older females were included as control subjects showing: (1) normal body weight (BMI = 20-25 kg/m$^2$), (2) normal baseline spirometry (forced expiratory volume in 1 s (FEV$_1$) $\geq$ 80% predicted, ratio of FEV$_1$ to forced vital capacity (FVC) $\geq$ 70%), and (3) absence of any health problems, including cardiovascular, neuromuscular, musculoskeletal or respiratory diseases which may contribute to breathlessness or exercise limitation. Healthy subjects were recruited from the local community using word-of-mouth, notices posted in community health care facilities and newspaper advertisements.

**Study Design**

This was a controlled, cross-sectional study in which informed consent was obtained from all subjects and ethical approval was received from the University and Hospital Health Sciences Human Research Ethics Board. The subjects were tested on two separate days over the course of approximately one week. On the first day, after informed consent and appropriate screening of medical history, all subjects (OB and NW) underwent anthropometric and Dual Energy X-ray Absorptiometry (DEXA) measurements, and were familiarized with the various questionnaires and scales for rating the intensity and quality of breathlessness. On the second day, all subjects completed
pulmonary function testing and cardiopulmonary exercise testing. Prior to testing at each visit, subjects were asked to avoid the ingestion of alcohol, caffeine-containing products and a heavy meal for at least four hours and to refrain from strenuous activity (e.g. cycling, running) for at least 12 hours. Subjects were also required to eat a normal mixed diet prior to laboratory visits to provide valid experimental/metabolic results during exercise. Experimental visits were conducted at the same time of day for each subject.

**Anthropometric and DEXA Measurements**

Standard girth (including waist and hip circumference measurements) and skinfold measurements (triceps, biceps, subscapular, iliac crest, and medial calf) were assessed. A full body DEXA scan was performed to measure fat, bone and lean muscle mass.

**Evaluation of Dyspnea**

Assessments of chronic activity-related dyspnea were made on the first visit using the Baseline Dyspnea Index (BDI) (Mahler et al., 1984) and the Oxygen Cost Diagram (OCD) (McGavin et al., 1978). Exertional breathlessness was evaluated using the ten-point Borg Scale (Borg, 1982) during exercise testing (see below).

**Pulmonary Function Testing**

Lung function testing was conducted in accordance with recommended techniques (Lazarus et al., 1997; Wasserman et al., 1999; American Thoracic Society; American College of Chest Physicians, 2003, Miller et al., 2005a; Miller et al., 2005b). Routine spirometry, constant-volume body plethysmography, single-breath diffusing capacity for carbon monoxide (D\textsubscript{L}CO), and maximum inspiratory and expiratory mouth pressures
(Pi\textsubscript{max} and Pe\textsubscript{max}; measured at FRC and TLC, respectively) were performed while sitting at rest using an automated pulmonary function testing system (6200 Autobox DL or Vmax229d; SensorMedics, Yorba Linda, CA). Predicted normal values for spirometry, lung volumes, diffusing capacity, airway resistance, Pe\textsubscript{max} and Pi\textsubscript{max} and were those of Morris \textit{et al.} (1988), Crapo \textit{et al.} (1982), Burrows \textit{et al.} (1961), Briscoe & Dubois (1959), Black & Hyatt (1969), and Hamilton \textit{et al.} (1995), respectively. Predicted normal inspiratory capacity (IC) was calculated as predicted total lung capacity (TLC) minus predicted functional residual capacity (FRC).

**Cardiopulmonary Exercise Testing**

Incremental exercise testing was conducted on an electronically braked cycle ergometer (Ergometrics 800S; SensorMedics, Yorba Linda, CA) using the Vmax229d Cardiopulmonary Exercise Testing System (SensorMedics) according to recommended guidelines (American Thoracic Society; American College of Chest Physicians, 2003). Equipment was calibrated immediately before each test. All exercise tests consisted of a steady-state resting period (at least 6 minutes of quiet breathing through a mouthpiece) and a 1 minute warm-up of 10 watts load pedalling followed by an incremental test in which the work rate was increased in 2 minutes intervals by increments of 20 watts. Pedalling rate was maintained between 50 and 70 revolutions per minute. All exercise tests were terminated at the point of symptom-limitation (peak exercise).

Breath-by-breath data were collected at baseline and throughout exercise while subjects breathed through a mouthpiece with nasal passages occluded by a nose-clip. Oxygen saturation (SpO\textsubscript{2}) by pulse oximetry, electrocardiographic monitoring of heart rate (HR), rhythm and ST-segment changes, and blood pressure by indirect
sphygmomanometry were carried out at rest and throughout exercise testing.

Gas exchange measurements: Minute ventilation ($V_t$), oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and end-tidal carbon dioxide partial pressure ($P_{ET}CO_2$) were calculated using standard formulae (Jones, 1988). Exercise variables were measured and averaged over the last 30 seconds of each minute and at peak exercise. Peak $\dot{V}O_2$ was defined as the highest $\dot{V}O_2$ that could be sustained for at least 30 seconds during the last stage of exercise. $\dot{V}O_2$ was reported in absolute units (L/min), after correction of body weight (ml/kg/min) and fat-free mass (FFM) (mL/kg FFM/min), and as a percentage of predicted normal values accounting for gender, age, height, and ideal body weight (Wasserman et al., 1999). Exercise parameters were compared with the predicted normal values of Jones (1988).

The ventilatory threshold (VTh) was detected individually using the V-slope method (Wasserman et al., 1999) and verified against other points, i.e., the $\dot{V}O_2$ at which the ventilatory equivalent for oxygen ($V_t/\dot{V}O_2$) begins to increase systematically without an increase in the ventilatory equivalent for carbon dioxide ($V_t/\dot{V}CO_2$) and where end-tidal oxygen partial pressure ($P_{ET}O_2$) begins to increase without a decrease in $P_{ET}CO_2$ (Wasserman et al., 1999).

Symptom evaluation: Exertional dyspnea was defined as “the sensation of labored or difficult breathing” and leg discomfort as “the level of leg discomfort experienced during exercise.” Before exercise testing, subjects were familiarized with the Borg scale (Borg, 1982) and its endpoints were anchored such that zero represented “no
breathing (leg) discomfort” and 10 was “the most severe breathing (leg) discomfort that they had ever experienced or could imagine experiencing.” By pointing to the Borg scale, subjects rated the magnitude of their perceived breathing and leg discomfort at rest, every minute and at peak exercise. Upon exercise cessation, subjects were also asked to verbalize their main reason for stopping exercise (i.e., breathing discomfort, leg discomfort, both, or others) and this reason was documented. Qualitative aspects of perceived breathing discomfort at peak exercise were described by completion of a questionnaire of descriptors of breathlessness modified from Simon et al. (1990) (O’Donnell et al., 2000).

Operating lung volumes: Changes in end-expiratory lung volume (EELV) were estimated from IC measurements at rest, at the end of each 2-minutes increment of exercise and at peak exercise. Since TLC does not change during activity (Stubbing et al., 1980a), the change (reduction) in IC reflects the inverse change (increase) in dynamic EELV (EELV=TLC-IC), whereas changes in inspiratory reserve volume (IRV) reflect changes in end-inspiratory lung volume (EILV=TLC-IRV). This has been found to be a reliable method of tracking acute changes in lung volume (Yan et al., 1997; O’Donnell et al., 1998b). Techniques for performing and accepting IC measurements have been previously described (O’Donnell et al., 2001). Confirmation of satisfactory technique and reproducibility of IC maneuvers for each subject was established during an initial practice session at rest.

Tidal flow-volume loops: Flow and integrated volume were recorded continuously during exercise testing. Tidal flow-volume curves at rest, every 2 minutes during exercise and at peak exercise were constructed for each patient and placed within
their respective maximal flow-volume envelopes according to coinciding IC measurements. The presence or absence of expiratory flow-limitation was estimated by calculating the percent of tidal volume ($V_T$) that encroaches on the maximal flow envelope, the extent of encroachment of flow at the mid-range of $V_T$ on the maximal flow-volume envelope at isovolume (Johnson et al., 1991a; Johnson et al., 1999).

### Statistical Analysis

A sample size of 16 provides the power (80%) to detect a significant difference in dyspnea intensity (Borg Scale) measured at a standardized work-rate during incremental cycle exercise based on a relevant difference in Borg ratings of ±1, a SD of 1 for standardized Borg ratings found at our laboratory in a healthy older population (O’Donnell et al., 2001), $\alpha=0.05$, and a two-tailed test of significance. Results were expressed as means ± standard deviation from the mean (SEM). A $p<0.05$ level of statistical significance was used for all analyses. Between-group comparisons were made using unpaired $t$ tests with Bonferroni correction for multiple comparisons, i.e., measurements at rest, at peak exercise, at the ventilatory threshold and at a standardized work-rate were compared in addition to baseline comparisons of anthropometric measurements and pulmonary function. Qualitative dyspnea descriptors were analysed as frequency statistics and compared using the Fisher’s exact test.

### RESULTS

Subjects’ characteristics are listed in Table 5.1. Eighteen older females with mild-to-severe obesity (OB) and thirteen age-matched normal-weight females (NW) successfully completed the study protocol. The OB group included: five obese class I
(BMI 30-34.9 kg/m²), four obese class II (BMI 35-39.9 kg/m²), and nine obese class III (BMI >40 kg/m²) (Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults, 1998). Body weight, body surface area, sum of 5 skinfolds, waist circumference, trunk fat, body % fat, as well as total lean body mass were all significantly (p<0.05) greater in OB compared with NW. In all women of the OB group, the primary distribution of fat was central; waist circumference was greater than 88 cm in all obese subjects (Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults, 1998); waist-to-hip ratios were greater than 0.8 in all but two subjects, one with class III obesity (BMI 59 kg/m²) and the other with class I obesity (BMI 33 kg/m²) but a high percentage (45%) of trunk fat.

The BDI and OCD data revealed an important decrease in the ability to perform daily physical activities due to increased breathlessness (Table 5.1). OB scored ~ 3 units lower in the BDI questionnaire than NW (p<0.05), and perceived shortness of breath at a lower relative intensity of daily activities in the OCD (p<0.05). In the NW group, four subjects had a smoking history (13±8 pack-years). Of these four subjects, three had stopped smoking >20 years prior to study, and the one current smoker had a smoking history larger than 20 pack-years but no evidence of COPD or small airway disease as assessed by pulmonary function tests or previous thoracic computed tomography (CT) scan results performed as part of another study comparing potential prognostic indicators in COPD and age-matched healthy subjects. In the OB group, ten subjects had a smoking history (14±9 pack-years); eight of the subjects had stopped smoking between 12 and 29 years previously, and two were current smokers (20 and 29 pack-years) with no evidence of changes in pulmonary function. Habitual physical activity records were collected for
Table 5.1. Subjects characteristics

<table>
<thead>
<tr>
<th></th>
<th>Normal Weight (n = 13)</th>
<th>Obese (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>54.6 ± 2.0</td>
<td>54.2 ± 2.0</td>
</tr>
<tr>
<td>Height, cm</td>
<td>164.8 ± 1.1</td>
<td>161.5 ± 1.1 *</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>63.0 ± 1.2</td>
<td>104.4 ± 4.3 *</td>
</tr>
<tr>
<td>Weight, % ideal body weight †</td>
<td>98 ± 2</td>
<td>168 ± 8 *</td>
</tr>
<tr>
<td>Weight/height, kg/cm</td>
<td>0.38 ± 0.03</td>
<td>0.65 ± 0.12 *</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.3 ± 0.5 (20 – 25)</td>
<td>40.2 ± 1.8 * (30 – 59)</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.69 ± 0.02</td>
<td>2.17 ± 0.13 *</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>75.6 ± 1.5 (65 - 82)</td>
<td>112.1 ± 3.7 * (94 - 136)</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.78 ± 0.03</td>
<td>0.85 ± 0.01 *</td>
</tr>
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</table>

**DEXA measurements:**

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<table>
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<tbody>
<tr>
<td>Body fat, %</td>
<td>31.7 ± 1.8</td>
<td>45.2 ± 1.1 *</td>
</tr>
<tr>
<td>Lean body weight, kg</td>
<td>41.4 ± 0.7</td>
<td>52.6 ± 1.3 *</td>
</tr>
<tr>
<td>Trunk fat, % total body weight</td>
<td>26.8 ± 2.2</td>
<td>45.1 ± 1.4 *</td>
</tr>
</tbody>
</table>

**Chronic dyspnea questionnaires:**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Baseline Dyspnea Index, 1 - 12</td>
<td>11.5 ± 0.2 (10 -12)</td>
<td>8.9 ± 0.5 (5 – 12) *</td>
</tr>
<tr>
<td>Oxygen Cost Diagram, 0 -100 mm</td>
<td>86 ± 4 (69 – 100)</td>
<td>71 ± 4 (47 – 96) *</td>
</tr>
</tbody>
</table>

Values are means ± SEM (range). * p<0.05 Obese group versus Normal weight group. † Ideal body weight calculated from equation in reference (Wasserman et al., 1999).
13 NW and 12 OB subjects. All 13 NW subjects reported that they performed between three to five aerobic activities (i.e., walking, cycling, etc) per week for at least 30 minutes, while seven OB subjects performed aerobic activity between one and five times per week.

**Pulmonary Function**

Pulmonary function test results are summarized in Table 5.2. All subjects had normal FEV\(_1\), FVC, and FEV\(_1\)/FVC (Pellegrino et al. 2005), as well as normal D\(_{LCO}\) normalized to alveolar volume. In absolute and relative terms, OB had significantly (p<0.05) lower expiratory reserve volume (ERV) (0.62±0.22 vs. 1.29±0.09 L) and greater IC (2.98±0.41 vs. 2.44±0.17 L) compared with NW, respectively. Similarly, FRC described in relative terms (Table 5.2), as a percentage of predicted TLC (46±7 vs. 66±8 % predicted TLC) and in absolute terms (2.30±0.45 vs. 3.42±0.41 L) was significantly (p<0.05) lower in OB. Interestingly, plethysmographic FRC (or resting EELV) correlated with the percentage of trunk fat (r\(^2\) = 0.62, p<0.05). However, the decrease in FRC had no effect on maximal inspiratory pressures in the OB group, and both P\(_{imax}\) and P\(_{Emax}\) were similar to the NW group (Table 5.2).

**Cardiorespiratory Responses to Symptom-limited Cycle Exercise**

Respiratory responses (\(\dot{V}O_2\), \(\dot{V}E\), \(\dot{V}E/\dot{V}CO_2\) and Sp\(O_2\)) shown against work rate are provided in Figure 5.1. Breathing pattern and operating lung volume responses to exercise are shown in Figures 5.2 and 5.3, respectively. Compared with NW, OB had reduced \(V_T\) and an increased breathing frequency (F) (associated with decreases in both inspiratory and expiratory time (T\(_I\) and T\(_E\)) with no difference in the duty cycle (T\(_I\)/T\(_{TOT}\)) for a given \(\dot{V}E\) during exercise (Figure 5.2). Results at VTh and at peak exercise are
<table>
<thead>
<tr>
<th></th>
<th>Normal Weight (n = 13)</th>
<th>Obese (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, % predicted</td>
<td>110 ± 3</td>
<td>107 ± 3</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>114 ± 3</td>
<td>108 ± 4</td>
</tr>
<tr>
<td>FEV₁/FVC, % predicted</td>
<td>103 ± 2</td>
<td>101 ± 2</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>112 ± 3</td>
<td>107 ± 2</td>
</tr>
<tr>
<td>IC, % predicted</td>
<td>108 ± 2</td>
<td>136 ± 4 *</td>
</tr>
<tr>
<td>FRC, % predicted</td>
<td>115 ± 6</td>
<td>83 ± 3 *</td>
</tr>
<tr>
<td>ERV, % predicted</td>
<td>132 ± 10</td>
<td>52 ± 8 *</td>
</tr>
<tr>
<td>RV, % predicted</td>
<td>107 ± 5</td>
<td>89 ± 3 *</td>
</tr>
<tr>
<td>DlCO/Vₐ, % predicted</td>
<td>111 ± 5</td>
<td>111 ± 4</td>
</tr>
<tr>
<td>sRaw, % predicted</td>
<td>166 ± 81</td>
<td>178 ± 75</td>
</tr>
<tr>
<td>P₁max, % predicted</td>
<td>114 ± 12</td>
<td>121 ± 10</td>
</tr>
<tr>
<td>Pₑmax, % predicted</td>
<td>80 ± 6</td>
<td>92 ± 6</td>
</tr>
</tbody>
</table>

Values are means ± SEM. * Statistically different from normal-weight control group (p<0.05). Abbreviations: DlCO, diffusing capacity of the lung for carbon monoxide; ERV, expiratory reserve volume; FEV₁, force expired volume in one second; FRC, functional residual capacity; FVC, force vital capacity; IC, inspiratory capacity; P₁max, maximal inspiratory pressure measured at FRC; Pₑmax, maximal expiratory pressure measured at TLC; RV, residual volume; sGaw, specific airways conductance; TLC, total lung capacity; Vₐ, alveolar volume.
summarized in Table 5.3.

**Steady-state rest:** At rest, OB had a higher $\dot{V}O_2$ (0.26±0.06 vs. 0.18±0.05 L/min, $p<0.05$) than NW. There was no difference between groups when $\dot{V}O_2$ was normalized for lean body mass. These results suggest that the higher metabolic rate measured in obese women at rest is a consequence of larger muscle mass.

**Ventilatory threshold:** OB compared with NW, reached their $V_{Th}$ at a lower (p<0.05) cycle work-rate, $\dot{V}O_2$ indexed to FFM, to actual body weight and as a percent of predicted maximum, but at a similar $\dot{V}O_2$ if expressed as ml/min, as well as at a similar $\dot{V}E$ (Table 5.3). During exercise from rest to $V_{Th}$, IC changed by 0.06±0.29 L and -0.17±0.27 L in NW and OB, respectively (p<0.05). Acute changes in IC from rest to $V_{Th}$ correlated with BMI ($r=0.65$, $p<0.01$) and with percentage trunk fat ($r=0.60$, $p<0.02$).

**Peak exercise:** Metabolic and ventilatory parameters measured during the last 30 seconds of exercise (peak) are shown in Table 5.3. Compared with NW, OB women stopped exercise at a lower $\dot{V}O_2$ normalized to body mass (p<0.05), and at a lower $\dot{V}O_2$ indexed to FFM (p<0.05), but at a similar absolute $\dot{V}O_2$ and $\dot{V}E$. OB achieved lower maximal HR and a similar oxygen pulse compared with NW. IRV at peak exercise was similar in both groups (Figure 5.3). At end-exercise, OB experienced significantly greater dynamic increases in EELV than NW: IC decreased by 0.38±0.34 vs. 0.01±0.25 L, respectively (p=0.001).
Figure 5.1. $\dot{V}O_2$, $\dot{V}E$, $O_2$ saturation, and the $\dot{V}E/\dot{V}CO_2$ responses to symptom-limited incremental cycle exercise in obese (OB) females (closed circles) and in normal-weight (NW) females (open circles). Higher $\dot{V}O_2$ and $\dot{V}E$ were found between rest and 80 watts but not at peak exercise in OB compared with NW females. $SpO_2$ was lower in OB compared with NW females at rest but not during exercise. Similar relationships in both OB and NW females were found between $\dot{V}E/\dot{V}CO_2$ and work-rate. Values are expressed as mean ± SEM. *p <0.05 OB versus NW.
Figure 5.2. Tidal volume, expiratory flow limitation, and breathing frequency responses to incremental exercise in obese and normal weight females. Extent of expiratory flow limitation (EFL), tidal volume ($V_T$) and breathing frequency ($F$) are expressed against ventilation ($V_E$), and breathing frequency expressed against tidal volume during exercise in obese (OB) females (close circles) and normal-weight (NW) females (open circles). Breathing pattern was relatively rapid and shallow in OB compared with NW females. Values are expressed as mean ± SEM. * p < 0.05 OB versus NW.
Figure 5.3. Lung volumes from rest to peak exercise in obese (OB) and normal-weight (NW) females. Significant increases in EELV by 0.38±0.08 L (p<0.05) were measured in OB while no significant change in EELV was found in the NW subjects. Inspiratory reserve volume (IRV) was significantly higher at rest and throughout the exercise in OB women but did not reach a statistical significant difference at the peak of exercise.
Table 5.3. Cardiorespiratory and perceived discomfort at the ventilatory threshold and at the peak of symptom-limited cycle exercise.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Ventilatory threshold</th>
<th>Peak exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NW</td>
<td>OB</td>
</tr>
<tr>
<td>Work rate, watt (%)</td>
<td>85 ± 5</td>
<td>59 ± 4*</td>
</tr>
<tr>
<td>(predicted max)</td>
<td>(79 ± 6)</td>
<td>(56 ± 4)*</td>
</tr>
<tr>
<td>VO2, L/min (%)</td>
<td>1.22 ± 0.06</td>
<td>1.16 ± 0.05</td>
</tr>
<tr>
<td>(% predicted max)*</td>
<td>(66 ± 3)</td>
<td>(69 ± 3)</td>
</tr>
<tr>
<td>VO2, ml/ FFM kg/min</td>
<td>29.0 ± 1.3</td>
<td>21.7 ± 0.9*</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>130 ± 5</td>
<td>117 ± 4*</td>
</tr>
<tr>
<td>O2 pulse, mlO2/beat</td>
<td>9.4 ± 0.4</td>
<td>10.3 ± 0.6</td>
</tr>
<tr>
<td>VE, L/min (%)</td>
<td>32.2 ± 1.4</td>
<td>31.5 ± 1.4</td>
</tr>
<tr>
<td>(%MBC) (predicted)</td>
<td>(33 ± 1)</td>
<td>(36 ± 2)</td>
</tr>
<tr>
<td>PETCO2, mmHg</td>
<td>47.3 ± 1.2</td>
<td>45.2 ± 0.8</td>
</tr>
<tr>
<td>IC, L (%)</td>
<td>2.47 ± 0.07</td>
<td>2.68 ± 0.12</td>
</tr>
<tr>
<td>(% predicted)</td>
<td>(110 ± 3)</td>
<td>(122 ± 5)</td>
</tr>
<tr>
<td>IRV, L (%)</td>
<td>1.07 ± 0.07</td>
<td>1.45 ± 0.12*</td>
</tr>
<tr>
<td>(%TLC predicted)</td>
<td>(21 ± 2)</td>
<td>(28 ± 2)*</td>
</tr>
</tbody>
</table>

Values are means ± SEM. * p<0.05 OB compared with NW group; † p<0.05 significant difference from concurrent dyspnea rating. Abbreviations: FFM, fat free mass; HR, heart rate; IC, inspiratory capacity; IRV, inspiratory reserve volume; max, maximum; MBC, estimated maximal breathing capacity; PETCO2, partial pressure of end-tidal CO2; TLC, total lung volume; VE, minute ventilation; VO2, oxygen consumption. † Predicted normal values for VO2 from Wasserman (Wasserman et al. 1999).
Breathing and Leg Discomfort during Cycle Exercise

At the end of exercise in the NW group, six women stopped primarily due to breathing discomfort, six due to leg discomfort, and one stopped due to the combination of leg and breathing discomfort. In the OB group, five women stopped due to breathing discomfort, eight due to leg discomfort, three due to the combination of breathing and leg discomfort, and two stopped exercise due to factors other than breathing or legs. No difference in the distribution of the reasons for stopping exercise was found between the two groups.

Ratings of intensity of breathing and leg discomfort relative to work-rate are shown in Figure 5.4. No differences were found for breathing or leg discomfort between NW and OB at the end of the symptom-limited cycle test. However in the OB group, leg discomfort was rated higher than breathing discomfort (5.0±2.7 vs. 4.1±2.4 Borg units, p<0.05) (Table 5.3). OB started perceiving significantly greater breathing discomfort from a workload of 60 watts (~55% predicted), that corresponded with VT\textsubscript{h}. Significantly (p<0.05) higher ratings of dyspnea intensity were found in OB compared with NW at 60 watts (0.7 Borg units) and at 80 watts (1.2 Borg units). Leg discomfort was greater in OB from exercise onset (20 watts) and throughout exercise; differences for leg discomfort ranged from 0.4 unit of Borg (p<0.05) at 20 watts to 1.6 unit of Borg at 80 watt (p<0.05). Dyspnea/\dot{V}_E and dyspnea/\dot{V}_O\textsubscript{2} curves were superimposed for OB and NW (Figure 5.4). At a standardized work-rate (80 watts) in OB, ratings of dyspnea intensity correlated significantly with \dot{V}_E/\dot{V}_O\textsubscript{2} (r=0.77, p<0.0005), \dot{V}_T/T_E (r=0.71, p=0.001), \dot{V}_T/T_I (r=0.67, p=0.002), \dot{V}_E expressed as a fraction of maximal breathing
capacity \( (r=0.60, p=0.008) \), and \( \dot{V}_E/\dot{V}CO_2 \) \( (r=0.54, p=0.021) \).

In comparison with NW, OB described their breathing discomfort at the end of exercise as more “shallow” and related to “expiratory difficulty” \( (p<0.05) \) (Figure 5.5). NW reported that breathing discomfort could be described as “increased work” \( (p<0.05) \).

**Expiratory Flow-Limitation at Rest and during Exercise**

Expiratory flow-limitation relative to \( \dot{V}_E \) is presented in Figure 5.2. Compared with NW, we found a significantly \( (p<0.05) \) greater extent of expiratory flow-limitation in OB at rest and during submaximal exercise. In 10 out of the 18 OB, resting \( V_T \) was under some degree of expiratory flow-limitation, i.e., 36 to 100% of \( V_T \) overlapped the maximal flow-volume envelope. In contrast, none of the NW females were flow-limited at rest. During exercise, the average extent of estimated expiratory flow-limitation in obese was maintained, but increased in NW. During exercise, OB were significantly more expiratory flow-limited than NW by an average of 42% at the 20 watt and by 27% at the 80 watt loads. Examples of tidal versus maximal flow-volume loops in an OB and an age-matched NW female are shown in Figure 5.6; these flow-volume loops are representative of the EELV behaviour in each group. While the majority \( (13/18) \) of the OB group increased EELV during exercise, the NW group had small inconsistent changes in EELV during exercise.
Figure 5.4. Relationship between intensity of breathing and leg discomfort (assessed by the modified Borg scale) and work-rate during symptom-limited incremental cycle exercise in obese (OB) females (closed circles) and in normal-weight (NW) females (open circles). Relationships between intensity of breathing discomfort and both minute ventilation ($V_E$) and oxygen uptake ($\dot{V}O_2$) during exercise were similar in OB and NW. Values are expressed as mean ± SEM. *p <0.05 OB versus NW at a standardized cycle work rate.
Figure 5.5. Selection frequency of qualitative descriptors of breathlessness in obese and normal weight females at the peak of cycle exercise. Selection frequency of qualitative descriptors of breathlessness are shown in OB and NW at the peak of cycle exercise. The descriptor cluster “increased work of breathing” was selected more frequently by NW females, while “shallow breathing” and “expiratory difficulty” were selected more frequently by OB females. * p<0.05 OB versus NW as tested by Fisher’s exact test.
Dynamic changes in EELV during exercise were similar in the 4 NW participants with a smoking history as those of the non-smokers. There was no significant difference between the OB smoking subgroups in resting pulmonary function (i.e., spirometry, plethysmographic lung volumes, and diffusing capacity) or in EELV changes during exercise; EELV increased similarly by 0.41±0.36 and 0.36±0.32 L from rest to peak exercise in subjects with and without a smoking history, respectively.

DISCUSSION

The main findings of this study were that: (1) symptom-limited peak \( \dot{V}O_2 \) when expressed as a percentage of predicted for ideal body weight was normal in OB, (2) breathlessness intensity was significantly higher at any given submaximal cycle work rate in OB, reflecting the higher ventilatory demand as a result of a higher metabolic cost of performing this task, and (3) quantitative flow-volume loop analysis demonstrated significant mechanical ventilatory constraints in OB compared with NW. Despite this, breathlessness ratings were not increased at any given \( \dot{V}E \) or \( \dot{VO}_2 \) throughout exercise in OB compared with NW.

It is well established that when peak \( \dot{V}O_2 \) is expressed as a fraction of actual body weight, peak aerobic capacity can be significantly underestimated in obesity, as was the case in this study. When peak \( \dot{V}O_2 \) was indexed to ideal body weight utilizing the formula of Wasserman et al. (1999), we determined that values were well within the normal range in the OB group. Peak \( \dot{V}O_2 \) corrected for the increased lean body mass was diminished by an average of 22% in OB compared with NW. In the absence of predicted
Figure 5.6. Resting, ventilatory threshold (VTh), and peak exercise tidal flow-volume loops are plotted within the respective maximal flow-volume loops in typical obese and normal-weight females. The lean participant increased tidal volume (from rest to VTh) by encroaching both on the inspiratory and expiratory reserve volume. In contrast, the obese female started with a significant tidal flow limitation at rest and experienced a significant increase in dynamic EELV from rest to peak exercise.
values for $\dot{V}O_2$ corrected for FFM, this finding is difficult to interpret.

Compromised cardiovascular function, which has previously been described in morbid obesity (Powell et al., 2006) may have been contributory in some of our participants but this remains conjectural.

Exercise limitation was multifactorial in OB and it was impossible to identify the proximate physiological limit in this group. Peak heart rates were significantly lower in OB versus NW, but this may simply reflect the lower peak $\dot{V}O_2$ achieved in the former. Both groups reached a similar peak $\dot{V}_E$ and reserves for $V_T$ expansion, as reflected by a high peak EILV/TLC ratio, were similarly reduced in both groups. Overt ventilatory insufficiency ($CO_2$ retention) at the peak of exercise was not evident in any participant, even in those with morbid obesity. The distribution pattern of exercise-limiting symptoms was similar in both groups. However, intensity ratings for leg discomfort were significantly higher than those for breathing discomfort at peak exercise within the OB group.

Obese females were, on average, almost twice the ideal body weight and reported mild-to-moderate activity-related breathlessness as measured by the BDI and the OCD. Ratings of breathlessness in OB were statistically higher at any given submaximal cycle work rate throughout cycle exercise compared with NW (Figure 5.4). However, the OB group was able to exercise to 80% of their predicted maximum work-rate while reporting only slight (Borg = 2 units) breathing discomfort. Thereafter, Borg ratings of breathlessness in OB rose more steeply by an average of ~2 units in the final phase of exercise as $\dot{V}_E$ increased from 44 L/min to a peak of 59 L/min. The rate of rise in
breathlessness in the final minutes of exercise was similar in both groups (Borg units increased by an average of 1 unit per 8.2 L/min increase in $V_E$).

Ventilation was consistently elevated at any given cycle work-rate throughout exercise; at 80 watts, $V_E$ was increased by approximately 11 L/min or 40% in OB versus NW (Figure 5.1). This excessive $V_E$, in part, reflected the high metabolic cost of lifting heavy limbs against gravity as well as an increase in the work of breathing. There was an upwards parallel shift of the $\dot{V}O_2$/work-rate relationship in OB but $V_E$/\dot{VO}_2 slopes were similar in OB and NW. $\dot{V}_E$/\dot{V}CO_2 slopes, estimates of physiological deadspace throughout exercise (Davis et al., 1980), and oxygen saturation measurements were similar in both groups. It is unlikely therefore that increased chemo-stimulation, as a result of critical arterial oxygen desaturation or inefficiency of CO_2 elimination, contributed to the amplified ventilatory response in OB. Regardless of the mechanism, the accelerated ventilatory response in OB likely contributed to increased intensity of breathing discomfort at a given power output in OB: not only were slopes of Borg dyspnea ratings over $\dot{V}_E$ superimposed (Figure 5.4), but Borg ratings at a standardized work-rate correlated well with $\dot{V}_E$/\dot{V}CO_2 and $\dot{V}_E$/\dot{VO}_2 within the OB group and in the total study sample. Given this scenario, increased contractile inspiratory muscle force generation (relative to maximum) and the concomitant increase in central motor command output in association with higher $\dot{V}_E$ may be an important source of breathing discomfort in OB (Davenport et al., 1986; Gandevia & Macefield, 1989; Chen et al., 1992; Moosavi et al., 2000).
To determine the effect of respiratory mechanical factors on exertional breathlessness in OB, we compared dyspnea/\( \dot{V}_E \) slopes and dyspnea/\( \dot{V}O_2 \) slopes with those of the NW group throughout cycle exercise (which would attenuate the increase in \( \dot{V}O_2 \) normally associated with weight-bearing exercise in OB). Previous studies have shown that external mechanical loading of the ventilatory muscles causes breathlessness to rise at any given \( \dot{V}_E \) during exercise, compared with unloaded control (Chonan et al., 1987; Xu et al., 1993; Harty et al., 1999; O’Donnell et al., 2000). Similarly, studies of mechanical unloading in patients with respiratory diseases demonstrated consistent reductions in dyspnea intensity at any given \( \dot{V}_E \) during cycle exercise (O’Donnell et al., 1988; Hernandez et al., 2001). Our results showed that breathlessness ratings at any given \( \dot{V}_E \) or \( \dot{V}O_2 \) throughout exercise were not increased in OB compared with NW (Figure 5.4). The explanation for this surprising finding becomes evident after detailed analysis of ventilatory mechanics at rest and during exercise in OB.

The nature and severity of the mechanical abnormalities encountered in OB will vary with the extent and anatomical distribution of adipose tissue (Collins et al., 1995; Lazarus et al., 1997). Our subjects had predominant central fat distribution; waist circumferences exceeded 88 cm in all subjects (range 95 to 136 cm) and waist-to-hip ratios exceeded 0.8. A reduced plethysmographic EELV in OB reflected decreased respiratory system compliance (Naimark & Cherniack, 1960) and the re-setting of the relaxation volume (Babb et al., 1989; Babb et al., 1991a; Babb et al., 2002). The finding that plethysmographic EELV correlated with the percentage of trunk fat (\( r^2 = 0.62 \)) supports this notion. As expected, ERV was reduced (by 52%) indicating that EELV was
positioned close to RV at the lower extreme of the respiratory system’s sigmoidal pressure-volume relationship. Previous studies have indicated increased respiratory resistance (Sharp et al., 1964; Zerah et al., 1993) and increased expiratory flow-limitation in obesity during resting breathing (Babb et al., 1989; Rubinstein et al., 1990; Ferretti et al., 2001; Babb et al., 2002). In the OB group, specific airway conductance was not different than NW, but maximal expiratory flow rates at 75% of the VC tended to be lower. Overlap of resting $V_T$ on the maximal expiratory flow-volume curve averaged 40% in OB compared with zero overlap in NW. We concede that the overlap method of assessment of expiratory flow limitation can lead to over-estimation because of volume history and gas compression effects (Johnson et al., 1991a; Johnson et al., 1992). Nevertheless, when flows throughout much of tidal expiration reach or exceed the maximal expiratory flow envelope at that operating volume, it strongly suggests the existence of expiratory flow limitation, particularly when considered in the context of attendant acute increases in EELV.

During incremental exercise in non-obese females, dynamic EELV declined slightly but tended to increase after exceeding the VTh. This behavior of EELV contrasts with previous reports in younger (often more athletic) participants, which showed more consistent reductions in EELV during both treadmill and cycle exercise (Babb et al., 1989; Henke et al., 1988; Babb et al., 2002). The different results may be explained by the increased age (range 44 – 65 years) of some of our participants. Thus, changes in the connective tissue matrix of the lung in older participants would increase the propensity for expiratory flow-limitation and dynamic hyperinflation during incremental exercise (Johnson et al., 1991b). Despite the lack of decline in EELV, $V_T$ expansion and alveolar
ventilation were not compromised in NW, and operating lung volumes were likely maintained in the compliant portion of the respiratory system’s pressure-volume relation (i.e., <80% of the vital capacity). In contrast, OB showed progressive dynamic hyperinflation throughout exercise (Figure 5.3); peak IC was reduced by 16% (0.39 L) of the resting value. Participants with marked obesity showed earlier dynamic hyperinflation than the remainder; changes in IC from rest to VTh correlated with BMI (r=0.65, p<0.01) and with percentage trunk fat (r=0.60, p<0.02). Dynamic hyperinflation likely arose during exercise because of the combination of slow mechanical time constants for lung emptying (because of the relatively low operating position of EELV) and increased breathing frequency with diminished $T_E$ as exercise progressed. Babb et al. (2002) showed that younger females (mean age 35 years) with mild obesity (mean BMI 34 kg/m²) retained the ability to reduce EELV in the early phase of incremental cycle exercise. This difference in the control of EELV early in exercise between the two studies might be explained by higher resting expiratory flow limitation in the obese group in the present study. This could be related to the greater age and severity of obesity, both of which have been reported to affect expiratory flow limitation.

Why did respiratory mechanical factors not contribute importantly to exertional breathlessness in obesity? We propose that, first, dynamic increases in EELV may have had salutatory effects on respiratory sensation by attenuating the expected rise in expiratory flow-limitation as $V_E$ increased during exercise. Dynamic increases in EELV in OB to a level that is closer to the predicted relaxation volume of the respiratory system would improve pressure-volume relations without any disadvantage to the inspiratory muscles. The increase in operating lung volumes in OB preserved their ability to
generate the required tidal expiratory flow rates: mean expiratory and inspiratory flow rates at any given $\dot{V}_E$ in OB were comparable to that of NW, supporting this idea.

Second, the recruitment of resting IC in OB, by an average of 0.54 L (28% predicted) higher than NW, is also likely mechanically advantageous. The increase in IC occurred in obesity because EELV declined to a greater extent than TLC. Inspiratory capacity (not vital capacity), represents the true operating limits for $V_T$ expansion during exercise in flow-limited participants. An increased resting IC meant that $V_T$ expansion (and the increased demand for $\dot{V}_E$) could be accommodated within the most compliant portion of the respiratory system’s pressure-volume relation in spite of progressive dynamic hyperinflation. We have previously presented similar arguments for the benefits of resting IC recruitment following bronchodilator therapy in patients with chronic obstructive pulmonary disease (O’Donnell et al., 2004; O’Donnell et al., 2006; Peters et al., 2006).

The third possible adaptation is the adoption of a relatively shallow breathing pattern throughout exercise in OB compared with NW. This could represent a behavioral compensatory adjustment which minimized the discomfort associated with increased elastic loading of the inspiratory muscles. True mechanical limitation is a less likely explanation for this shallow breathing pattern in OB because, on average, the minimal IRV was greater in OB than NW: at the VTh, IRV was significantly higher in OB by 0.37 L despite similar $\dot{V}_E$ (32 L/min).

Qualitative descriptor choices of breathlessness at peak exercise were remarkably similar across groups, but obese women were more likely to report “shallow” breathing
and “expiratory difficulty” at the end of exercise (Figure 5.5). These descriptor choices may reflect an awareness of reduced thoracic displacement and expiratory flow limitation but this remains conjectural. It is noteworthy that increased leg discomfort was a prominent exertional symptom in OB: Borg ratings of leg discomfort were significantly greater in OB throughout exercise and severe leg discomfort was reported at the peak of exercise. Moreover, 11 of the 18 obese participants listed leg discomfort as a primary or co-primary exercise-limiting symptom. Leg discomfort may simply reflect the higher contractile muscle effort and central motor command output required to mobilize the heavy limbs (Gandevia, 1982; Matthews et al., 1982).

In summary, although breathlessness was common in OB it was of mild to moderate severity and, on average, participants could reach their predicted maximal power output and VO₂. During weight-supported cycle exercise, intensity of breathlessness rose in all subjects as ventilation increased. In OB, breathlessness ratings were higher, at any submaximal cycle work-rate, reflecting relatively higher ventilation and metabolic cost. Since \( \dot{V}_E/\dot{V}O_2 \) slopes were not altered by obesity, we can reasonably predict that an increase in \( \dot{V}O_2 \) with weight-bearing exercise in OB would be associated with higher \( \dot{V}_E \) and intensity of breathlessness compared with cycle exercise. Ratings of breathlessness at any given exercise \( \dot{V}_E \) and \( \dot{V}O_2 \) were not increased in OB compared with NW, and strongly suggests that respiratory mechanical factors, per se, contributed little to exertional respiratory discomfort. Three potential ameliorating factors were discovered in OB. First, dynamic increases in EELV attenuated progressive expiratory flow limitation and preserved their ability to increase ventilation in tandem with the
increased metabolic demand. Second, despite the increased dynamic EELV, resting IC recruitment permitted expansion of tidal volume within the compliant portion of the respiratory system’s pressure-volume relation where neuromechanical coupling is enhanced. Third, the adoption of a relatively shallow breathing pattern likely further obviated the respiratory discomfort normally associated with excessive elastic loading of the inspiratory muscles.
CHAPTER 6: GENERAL DISCUSSION
Healthy young humans can undertake vigorous physical exertion requiring high levels of ventilation while experiencing little in the way of respiratory discomfort (O'Donnell et al., 2000). We believe that avoidance of exertional respiratory discomfort is, in part, attributable to a number of physiological adaptations which ensure preservation of the harmony between the increased drive to breathe and the mechanical/muscular response of the respiratory system under stress. As we have seen, these adaptations include control of airway calibre (Warren et al., 1984; England & Bartlett, Jr., 1982; Clanton et al., 1987) and operating lung volumes (Sharratt et al., 1987; Kagawa & Kerr, 1970; Henke et al., 1988), as well as avoidance of excessive chemostimulation via enhanced cardiopulmonary interactions (West & Dollery, 1960; West, 1985; Hakim et al., 1988). It follows that when these adaptations become undermined, there is the potential for increased perceived respiratory discomfort at any given exercise ventilation or oxygen consumption (\(\dot{V}O_2\)).

Our studies have documented several derangements in these normal “protective” adaptations to exercise that occur under conditions of aging, superimposed airway damage (from tobacco smoking), and restrictive constraints associated with excessive adipose tissue deposition. All of these conditions affect dynamic airway function during exercise. Thus, expiratory flow limitation, which accompanies natural aging, is markedly accelerated in smokers with early COPD (Anthonisen et al., 2002). In contrast to the above conditions, airway dysfunction in obesity mainly reflects the reduced resting end expiratory lung volume, which is potentially reversible with volume recruitment. It is clear that the existence of expiratory flow limitation during activity (in all of the above conditions) has profound sensory and mechanical implications for exercise performance.
Thus, flow limitation compromises lung function during exercise as occurs in youth. In fact, at higher ventilations, significant air trapping is precipitated, which can restrict tidal volume ($V_T$) expansion earlier in exercise, thereby introducing mechanical constraints on ventilation (Cotes, 1970; Muza et al., 1990; O'Donnell et al., 2001; O'Donnell et al., 2006b; Weiner et al., 2002).

The existence of expiratory flow limitation during exercise in all three of the above conditions means that dynamic inspiratory capacity (IC), not vital capacity, represents the true operating limit for $V_T$ expansion. The age-related diminution of resting IC is particularly important in women whose baseline IC (in absolute terms) is naturally reduced compared with age-matched men (Table 2.1). The inability to reduce dynamic EELV and the accelerated dynamic pulmonary hyperinflation (reflected as a reduced dynamic IC) becomes evident even earlier in exercise in elderly patients with mild COPD (Figure 3.5).

In sharp contrast to the elderly (with or without COPD), obese females consistently recruit resting IC (Table 5.2). This primarily reflects the reduced functional residual capacity (FRC) dictated by the decreased chest wall compliance. Reduced FRC in the setting of a relatively preserved TLC resulted in consistent increases in resting IC. We have described how volume-dependent expiratory flow limitation in obese females is partially reversed by increased air trapping during exercise (Figure 5.2). This actually resulted in “pseudo-normalization” of EELV towards its predicted relaxation volume. We have argued that this behaviour may, in fact, have salutary sensory consequences (see below).
The relatively diminished IC in the elderly and further dynamic reductions during exercise, particularly in women and in smokers, resulted in more restrictive dynamic ventilatory mechanics than in youth (Figure 2.3; 3.5). Breathing pattern was more shallow and rapid, and $V_T$ expansion became limited (i.e., reached a plateau) at a lower ventilation and $\dot{V}O_2$ than in youth. In other words, when faced with a diminished IC, end-inspiratory lung volume reached the minimal IRV (~0.5 L below TLC) at lower ventilations during exercise imposing significant mechanical constraints on increasing ventilation. Thus, the smaller the dynamic IC and IRV become at a given $\dot{V}O_2$ during exercise, the closer $V_T$ becomes positioned relative to TLC and the upper, less compliant reaches of the respiratory system’s pressure-volume relationship. We know from studies that, when breathing close to TLC, the inspiratory muscles are weakened and must cope with increased elastic loading (O'Donnell et al., 2000; O'Donnell et al., 2006b).

**Alterations in Chemical Drive and Exertional Breathlessness**

In tandem with the mechanical derangements outlined above, we have demonstrated that ventilatory drive for a given $\dot{V}O_2$ increased under all three conditions (aging, COPD, obesity). In the elderly, with and without COPD, the increased ventilatory requirements primarily reflected abnormalities in $\dot{V}/Q$ matching. Thus, the relatively increased wasted ventilation is the primary source of the increased chemostimulation of central respiratory drive during exercise. As expected, $\dot{V}/Q$ disequilibrium was amplified in heavy smokers with consequent increased ventilatory requirements compared with healthy age-matched non-smokers. It is evident from our
studies that the magnitude of the prevailing reflexly increased chemical drive dictates the
time course of changes in dynamic ventilatory mechanics. Thus, high physiological
deadspace (that fails to decline during exercise) is associated with higher ventilations,
which in turn accelerate the rate of dynamic hyperinflation and the onset of restrictive
ventilatory mechanics.

Another potential source of ventilatory stimulation that we considered was earlier
metabolic acidosis, reflecting skeletal muscle deconditioning and abnormalities in oxygen
transport to the locomotor muscles. Although anaerobic (ventilatory) thresholds tended
to be lower in the elderly COPD patients (versus healthy elderly), these differences were
not always consistent.

In obesity, the source of the increased ventilation at a given work rate was
metabolic rather than a result of a defect in pulmonary gas exchange. Higher ventilations
reflected a higher $\dot{V}_{CO_2}$ that, for the most part, reflected the increased metabolic cost of
locomotion in these individuals with heavy lower limbs. In obese females, higher
ventilatory requirements in the setting of volume-dependent expiratory flow limitation at
rest accelerated the rate of change in EELV early in exercise.

**Sensory-Mechanical Inter-Relationships in the Elderly, Mild COPD and Obesity**

Having clearly delineated the abnormalities in ventilatory control and in dynamic
ventilatory mechanics in all three conditions, the next challenge is to determine their
contribution to perceived breathing difficulties during exercise. Clearly, as mentioned
above, the altered chemical drive and altered mechanical/muscular responses are
inextricably linked to a degree that it becomes very difficult to estimate their relative
contribution to the intensity and quality of breathlessness. We confirmed the existence of a strong relationship (Chapter 3: \( r=0.61, p<0.05 \); Chapter 5: \( r=0.60, p=0.008 \)) between intensity of breathlessness and \( V_E \) (relative to the maximal possible ventilation) across all conditions. Regardless of the stimulus of the increased ventilation (i.e., V/Q abnormalities or metabolic acidosis), perceived exertional breathlessness rose as ventilatory demand approached capacity (Killian et al., 1992). If maximal breathing capacity is diminished, due to mechanical abnormalities or reduced strength of the respiratory muscles, breathlessness will manifest at relatively lower power outputs and \( V_O2 \) during cycle ergometry, particularly if ventilatory requirements are increased.

Evaluation of the dyspnea/\( V_E \) relationship was helpful in partitioning the relative contribution of increased drive and abnormal mechanics/muscular function to perceived respiratory difficulty. In aging and in COPD, the dyspnea/\( V_E \) slope was elevated compared to healthy non-smoking control subjects (Figure 2.1). Based on our previous work, the explanation for this increased slope is excessive loading or functional weakness of the respiratory muscles. In addition to the previously outlined mechanical derangements of aging and mild COPD, we also documented in our cross-sectional study, progressive age-related reduction in respiratory muscle strength. Both were likely instrumental in breathlessness causation and their presence would mean that greater electrical activation (and contractile effort) was required for a given force generation by the muscle.

To our surprise, obesity did not affect the breathlessness (Borg)/ \( V_E \) relationship, strongly suggesting that neither mechanical derangements nor inspiratory muscle dysfunction contributed (Figure 5.4). We argued that recruitment of resting IC, pseudo-
normalization of operating lung volumes during exercise and the adoption of a shallow breathing pattern (to minimize the effects of elastic loading) collectively attenuated the mechanical contribution to increased breathlessness in obese females. In this group, at least during weight-supported cycle exercise, increased metabolically induced respiratory drive appears to be the primary source of unpleasant respiratory sensation (Figure 5.1). Based on our knowledge of neurophysiology of breathlessness, the most plausible explanation is increased sense of contractile muscle effort (with increased central corollary discharge) in association with the increased $V_E$. By contrast, in the aging and mild COPD populations, mechanical/muscular factors were very likely associated with exertional breathlessness at the higher levels of $V_E$ during exercise.

**Mechanical Factors and Exertional Breathlessness**

The net effect of abnormalities in dynamic airway function in aging and in COPD was to force restrictive “high-end” mechanical constraints on ventilation during exercise. With correlative analysis, we were able to demonstrate consistent statistical associations between ratings of intensity of breathlessness and indices of mechanical restriction, such as the $V_T$/IC ratio (Table 2.4). In both aging and COPD participants, breathlessness/IRV relationships remained superimposed throughout exercise. However, at any given power output or metabolic work, breathlessness increased and IRV diminished in the elderly (versus the young) and in COPD (versus the healthy elderly), again supporting the notion that restriction in $V_T$ expansion at a critically reduced dynamic IRV contributes to breathing difficulty in the setting of increased ventilatory drive, i.e., neuromechanical dissociation.
To test this hypothesis, we manipulated mechanics with bronchodilator therapy to determine the effect on respiratory sensation. Anticholinergic administration increased dynamic IC throughout exercise and permitted release of $V_T$ restriction, thus enabling patients to increase their ventilatory output ($\dot{V}_E$) with no increase in breathlessness. In fact, at the higher ventilations near the limits of tolerance, breathlessness intensity fell significantly (Figure 4.2). More detailed mechanical measurements in a small subset of individuals showed consistent reductions in inspiratory threshold loading (auto-PEEP effect). In the context of our previous studies in both asthma and COPD, the inspiratory threshold load on the inspiratory muscles at the beginning of inspiration exemplifies the presence of neuromechanical dissociation. In other words, moments at the start of each breath, neural activation of motor units in the respiratory muscles is not associated (or rewarded) by the appropriate thoracic volume displacement. The corollary of this is that relief of dyspnea occurs when this threshold load is diminished by pharmacological lung volume reduction or counterbalanced by the application of external PEEP. Both interventions partially restore neuromechanical harmony.

Our knowledge of the neurophysiological underpinnings of neuromechanical dissociation continues to increase. Several previous experiments have indicated that when $V_T$ expansion is restricted, either voluntarily or through external loading, breathing difficulty quickly rises to intolerable levels. Moreover, release of $V_T$ restriction (for example by bronchodilatation that recruits IC) is associated with relief of dyspnea. We postulate that some degree of neuromechanical dissociation may be at play at higher exercise intensities in the elderly with and without COPD (who have sharp decreases in dynamic IC), particularly in elderly women who have a clinically reduced baseline IC.
Conscious awareness of inspiratory difficulty (more specifically, unsatisfied inspiration) likely derives from the integrated sensory information from the respiratory centres, and multiple sources of sensory feedback from the lungs, airways, chest wall and its musculature. It remains to be determined whether increased contractile muscle effort (associated with the increased ventilatory demand) and the increased neuromechanical dissociation (that arises from dynamic volume restriction) contribute distinct qualitative nuances to this multidimensional sensory experience of breathlessness.

LIMITATIONS OF THE STUDIES

General limitations

- Borg was measured at intervals of 1 to 3 minutes; this limited the number of data points that were compared between the groups. In fact, this could also limit the ability to examine the interaction between physiological measurements and perceived symptoms.

- Measurements of dyspnea quality were performed only at the end of exercise and not during the exercise; if the quality of dyspnea was different between early to late in the exercise due to mechanical factors, we could not detect this threshold.

- Measurements of ventilatory mechanics derived from esophageal and abdominal were not performed in all the studies. Without mechanical measurements of the pressures generated by the respiratory muscles during exercise, our interpretation of the results is to some extent limited. Measurements such as: 1) respiratory muscle effort, 2) effort-displacement ratio (described in Chapter 1), 3) work of
breathing, 4) indices of muscle fatigue could allow better understanding of
dyspnea in older subjects, obese females and mild COPD patients.

- We did not measure maximal ventilatory ventilation (MVV), but we estimated
MVC based on spirometry only. This estimation of MVC may limit our
evaluation of the ventilatory reserve as well as the maximal endurance and
maximal possible contractile effort expended by the ventilatory muscles.

Specific limitations of the Studies:

Chapter 2: Aging

- The main limitation of using a treadmill as the exercise modality (weight-bearing
treadmill walking) is that increments in metabolic and ventilatory demand for
most protocols are often larger than those selected for cycle exercise protocols.
This can limit the number of data points available for analysis and for
interpretation of normality of response. In addition, cardiorespiratory
measurements are usually harder to perform during intense treadmill walking:
untrained subjects may find it difficult to concentrate on exercise as well as
answer questions related to symptoms or perform maximal inspiratory capacity
maneuvers.

- Although we found a change in decline in spirometry above 60 year of age, our
arbitrary selection of age cut-offs (with the potential for overlap) in a cross-
sectional design may have underestimated true physiological differences between
the young and old. Group comparisons with wider age differences might provide
a truer reflection of the subjective and physiological differences between young and old individuals.

- Another limitation of this study is the inclusion of a remote smokers in the group. Although there was no measurable evidence of airway obstruction on spirometry between smokers and the non-smokers, minor changes in airway function may not have been measured which potentially may affect different components in the ventilatory and perceptual responses to exercise.

Chapter 3: Mild COPD

- The females with symptomatic mild COPD tended to report breathlessness as the predominant reason for stopping exercise, while the males reported leg discomfort as the main exercise-limiting symptom. A larger sample size with equal gender representation could allow us to further explore gender differences in exertional breathlessness in early COPD.

- Our criterion for COPD was based on symptoms and spirometry criteria (GOLD). More precise clinical phenotyping with CT scanning and biomarker evaluation might further clarify the heterogeneous pathophysiology in early COPD and might have implications for symptom perception and bronchodilator response.
Chapter 4: Mild COPD after ipratropium bromide

- Sample size was calculated based on dyspnea (clinical importance difference and SD in previous studies). However, we were under-powered for detecting changes in endurance time, which is an important outcome for these subjects.

- In this study we included all the volunteer patients that fit the criteria for a symptomatic mild COPD; we did not consider the symptom limitation to exercise. People who stop exercise due to breathing discomfort may be a better target for an improvement in exercise capacity and symptoms after bronchodilator.

Chapter 5: Obesity

- We included several remote smokers in the study (without evidence of airway obstruction), without knowing the implication for dyspnea and ventilatory adaptation during exercise.

- Our study sample included participants who spanned a wide age range and this may have potentially impacted the subjective and ventilatory responses to exercise.

- We did not evaluate menopause status which is known to impact ventilatory control. Blood gases and lactate were measured only in a few subjects, thus we were limited in our ability to elucidate the potential abnormalities of pulmonary gas exchange and metabolic loading in obesity.
FUTURE STUDIES

Aging and Gender

Chapter 2 demonstrates that aging, especially in females, is associated with increased ventilatory constraints that in many cases can contribute to increased symptoms of breathing discomfort during exercise. Future studies aimed at examining the relationship between aging, gender and ventilatory and perceptual responses to exercise would include the following: 1) chemical loading during exercise in males and females, 2) respiratory muscle training in females, and 3) the effect of decreased airway resistance and flow limitation using bronchodilator and Heliox administration.

Chemical loading during exercise in older males and females. In a previous study from the respiratory investigation unit, exercise during chemical loading (added dead space) in young healthy males did not increase dyspnea even with an increase in V˙E of ~10 L/min, suggesting sufficient ventilatory reserve (O’Donnell et al. 2000). However, females generally have compared to males, a reduced ventilatory capacity males, that is further affected by the age-related decline of pulmonary function (Chapter 2). We hypothesized that exercise with chemical loading would be associated with a higher rating of dyspnea at a given power in older females compared with older males. In fact, due to increased mechanical restriction in older females at lower ventilations, the quality of dyspnea will change earlier in exercise from a sense of increased effort to a sense of inspiratory difficulty or unsatisfied inspiration. In this study, older (>60 years) females and males will perform an exercise test with and without dead space loading (~600 ml will be added to the breathing circuit) in a blinded crossover design. We will evaluate the cardiorespiratory responses to exercise in both groups under the two conditions. In
addition, the intensity and the quality of breathlessness will be measured using the 10-point Borg scale at a given intervals (30 seconds). The intensity of dyspnea during exercise will be measured using Borg scale ratings of three different qualitative descriptors: increase in effort, inspiratory difficulty, or expiratory difficulty. The results of this study will have important implications with respect to our understanding of why women with various cardiopulmonary conditions suffer greater morbidity than age-matched males with similar disease severity.

**Respiratory muscle training in females.** Females have a lower respiratory muscle strength compared with males (Figure 2.2). These differences in muscle strength are further amplified by aging and may explain in part why the intensity of dyspnea in older females is higher compared with that in older males. In asthmatic patients, inspiratory muscle training in females results in a decrease in perceived breathing discomfort in females, similar to the rate of untrained males. We hypothesize that in older females, an improvement in $P_{\text{I}}^{\text{max}}$ in response to inspiratory muscle training (closer to the level in older males), will decrease the dyspnea rating difference between older females and older males. The ventilatory adaptations and respiratory symptoms during cycle exercise in older males and females will be compared pre- and post-inspiratory muscle training in females.

**Decreased airway resistance and flow limitation using bronchodilator administration.** The aging process of the respiratory system is associated with greater flow limitation during exercise with a dynamic EELV increase as a result of reduced lung emptying and increased air trapping (Johnson & Dempsey, 1991; Delorey & Babb, 1999) – referred to as dynamic pulmonary hyperinflation (DH). DH results in higher dynamic
end-inspiratory lung volume EILV relative to TLC than in youth at a given submaximal ventilation (Delorey & Babb, 1999). Although DH optimizes expiratory flows by avoiding expiratory flow limitation at lower volumes near RV, it increases the elastic work of the inspiratory muscles (Johnson et al. 1991). As a result, the pressures generated by the inspiratory muscles during tidal breathing represent a higher fraction of the maximal possible dynamic inspiratory force generating capacity in the elderly than in youth for a given $\dot{V}_E$ or $\dot{V}O_2$ (Johnson et al. 1991; LeBlanc et al. 1988). As reported in Chapter 2 aging was associated with leftward and upward shift in the dyspnea/$\dot{V}O_2$ relationship (Figure 2.1). An interesting observation was reported by Hopp et al. (1985), showing that elderly subjects, 55-65 years, tend to respond more to a metacholine challenge test. It suggested that changes in autonomic control at the level of the airways are evident with aging. It also suggests the potential for greater benefit with the proposed blockage of the cholinergic receptors. We can therefore propose to examine the effect of an anticholinergic bronchodilator on exercise capacity and exertional dyspnea in elderly healthy subjects. In this study we will examine the effect of an anticholinergic agent versus placebo on resting pulmonary function and on the ventilatory and perceptual responses to constant-load exercise.

**Obesity**

In chapter 3, I demonstrated that, compared with normal-weight females, obese females are more dyspneic during weight-supported exercise. However, this increase in dyspnea was not proven to be associated with greater respiratory mechanical restriction. We propose that the dynamic increases in EELV during the exercise, the recruitment of
resting IC, and the adoption of a relatively shallow breathing pattern throughout exercise protected these subjects from any increase in symptoms of breathing discomfort related to increased ventilatory mechanical constraints. Future studies will include incremental cycle exercise with and without dead space loading in obese and normal weight subjects. During exercise, subjects will undergo mechanical measurements of transdiaphragmatic and abdominal pressure in addition to the described cardiorespiratory and symptom measurements (Chapter 5). We hypothesize that the adaptations described above will allow obese subjects to increase $\dot{V}_E$ without an increase in mechanical ventilatory limitation or dyspnea. The quality of dyspnea will be mainly related to increase effort. Measurements of work of breathing based on pressures and volumes will allow an evaluation of the energy demand of the expiratory and inspiratory muscles and may explain why obese participants report greater expiratory difficulty than lean controls (figure 5.4).

**Mild COPD**

We first reported that exercise capacity is significantly reduced and exertional dyspnea ratings are higher at a given work rate in symptomatic patients with GOLD stage I COPD (post bronchodilator $\text{FEV}_1 \geq 80\%$ predicted, $\text{FEV}_1/\text{FVC} < 0.7$) compared with healthy age-matched control subjects (Chapter 3). In Chapter 4, we then showed a mild to moderate improvement in pulmonary function as well as improvements in the control of operating lung volumes (i.e. larger IC and larger $V_T$) and reductions in the intensity of exertional breathing and leg discomfort (Chapter 4). In contrast to these encouraging results, we were not able to demonstrate a clear increase in exercise endurance time.
Several reasons have been suggested for this apparent unresponsiveness (in terms of improved exercise endurance) of GOLD stage I COPD to anticholingeric agent (see discussion in Chapter 4). As a result of our findings, we suggest the following modifications to the original protocol to further increase our knowledge about how to improve exercise capacity and to decrease symptoms of breathing discomfort during exercise in mild COPD patients.

*Changes in the bronchodilator, combination of bronchodilator, and the duration of administration.* Further improvements in resting pulmonary function and the ventilatory and perceptual responses to exercise may result from: changing the anticholinergic bronchodilator from ipratropium to tiotropium bromide; evaluating a combination of bronchodilators ($\beta_2$-agonist with anticholinergic) to achieve maximal bronchodilation, or by testing over a longer treatment period (4-8 weeks).

Experimental Heliox administration to hastens the time constant for lung emptying in patients with expiratory flow limitation, thus reducing air trapping (Palange et al., 2004). Its use in early symptomatic COPD (in a short term placebo-controlled study) would further determine the role of abnormalities in dynamic ventilatory mechanics in dyspnea causation in mild COPD.

*Use of a lower exercise intensity (65-70%) as well as different modalities of exercise.* In some patients in the present study, an exercise intensity of 80-85% of maximal power was maintained for a limited time of 3 to 5 minutes. These subjects may therefore have been working at a higher relative work rate than we desired for (based on the power–time relationship). The use of a lower intensity may increase the sensitivity of the test to bronchodilator administration. We also think that treadmill exercise better
mimics daily activities that do not generally include weight-supported activity (like cycle exercise) and that have higher metabolic and ventilatory requirement, that may be associated with an increase in symptoms of breathing discomfort.
REFERENCES


APPENDIX A: MODIFIED MEDICAL RESEARCH COUNCIL DYSPNEA SCALE

MODIFIED MEDICAL RESEARCH COUNCIL DYSPNEA SCALE

GRADE

0  NOT TROUBLED WITH BREATHTLESSNESS EXCEPT WITH STRENUOUS EXERCISE

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

2  WALKS SLOWER THAN PEOPLE OF THE SAME AGE ON THE LEVEL BECAUSE OF BREATHTLESSNESS OR HAS TO STOP FOR BREATH WHEN WALKING AT OWN PACE ON THE LEVEL

3  STOPS FOR BREATH AFTER WALKING ABOUT 100 YARDS OR AFTER A FEW MINUTES ON THE LEVEL

4  TOO BREATHTLESS TO LEAVE THE HOUSE OR BREATHTLESS WHEN DRESSING OR UNDRESSING

APPENDIX C: MODIFIED BASELINE DYSPNEA INDEX

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
MODIFIED BASELINE DYSPNEA INDEX

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):
MODIFIED BASELINE DYSPNEA INDEX

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):
MODIFIED BASELINE DYSPNEA INDEX

FUNCTIONAL IMPAIRMENT AT WORK

GRADE 4: No Impairment: The patient is able to carry out usual job-related activities without SOB. To be classified as grade 4, the patient should:

(a) Not have changed jobs or job activities as a result of SOB.

(b) Not, for reasons of SOB, have decreased the number of hours/week of work or curtailed any job-related activities because they were too strenuous, either by eliminating certain tasks in the same job or by changing jobs to a less physically demanding one.

GRADE 3: Slight Impairment: The patient recognizes that SOB has caused alteration of job activities. Although no job responsibilities have been completely abandoned as a result of SOB, at least one job-related task is done more slowly due to SOB.

GRADE 2: Moderate Impairment: The patient has:

(a) Maintained the same job and same hours/week as before the onset of dyspnea but, because of SOB, has abandoned completely at least one of the tasks done as part of that job, or

(b) Changed jobs to a less strenuous position because SOB interfered with job activities, or

(c) Maintained previous job (ie. the job before dyspnea began) but decreased the number of hours/week worked at that job.

Categories (b) and (c) are not mutually exclusive, as when the patient decreases the number of hours on one job but adds a second, less strenuous job for financial reasons. This situation is also coded as grade 2.

GRADE 1: Severe Impairment: The patient no longer works because of SOB. This category would include:

(a) Patients who retired early from their job because of SOB and who, despite a desire to work, have not found a realistically limited job because of SOB.

(b) Patients who reached expected retirement age and stopped working and who also have dyspnea are graded according to how their SOB affected their job before retiring.
Functional Impairment at Work (cont'd)

W: Amount Uncertain: Patient is impaired due to SOB, but amount cannot be specified because details are not sufficient.

X: Unknown. Information unavailable.

Y: Impaired for Reasons Other than SOB. Grade Y is assigned if the patient has a main limitation due to a disability other than SOB.

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

Z: The patient has not had a job since before symptoms of SOB began and has not since sought work. Example: A non-breadwinner who had not intended to find a job even before SOB began.

For patients who were not working when their SOB began but who have since begun to work and found SOB to be a factor in determining their job, code as grade 2.
MODIFIED BASELINE DYSPNEA INDEX

Instructions for Assigning Composite Functional Grade

<table>
<thead>
<tr>
<th>Work Functional Grade</th>
<th>Home Functional Grade</th>
<th>Composite Function Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>2, 3 or 4</td>
<td>2, 3 or 4</td>
<td>The lower grade in either &quot;work&quot; or &quot;home&quot; category becomes the composite grade; for identical grades in &quot;work&quot; and &quot;home&quot; categories, the composite grade is that same grade.</td>
</tr>
<tr>
<td>1</td>
<td>2, 3 or 4</td>
<td>Assign composite grade as Grade 1 or severe impairment.</td>
</tr>
<tr>
<td>2, 3 or 4</td>
<td>1</td>
<td>Assign composite grade as Grade 1 or severe impairment. Recipients of Grade 0 will no longer be working due to shortness of breath (ie. function Grade 1 on work) and will be severely impaired in their usual home activities.</td>
</tr>
<tr>
<td>2, 3 or 4</td>
<td>W, X or Y</td>
<td>Assign the work functional grade as the composite grade.</td>
</tr>
<tr>
<td>W, X, Y or Z</td>
<td>1, 2, 3 or 4</td>
<td>Assign the home functional grade as the composite grade.</td>
</tr>
<tr>
<td>W, X, Y or Z</td>
<td>W, X or Y</td>
<td>Assign as a composite grade the two letter combination (in order with &quot;work&quot; grade first) of each of the individual grades; ie. &quot;work&quot; Grade W and &quot;home&quot; Grade X would be composite Grade WX.</td>
</tr>
</tbody>
</table>

APPENDIX D: BORG SCALE

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Nothing at all</td>
</tr>
<tr>
<td>0.5</td>
<td>Very, very slight (just noticeable)</td>
</tr>
<tr>
<td>1</td>
<td>Very slight</td>
</tr>
<tr>
<td>2</td>
<td>Slight</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>Somewhat severe</td>
</tr>
<tr>
<td>5</td>
<td>Severe</td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Very severe</td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Very, very severe (almost maximal)</td>
</tr>
<tr>
<td>10</td>
<td>Maximal</td>
</tr>
</tbody>
</table>

APPENDIX E: ONLINE DATA SUPPLEMENT FOR CHAPTER 4

Mechanisms of Dyspnea during Cycle Exercise in Symptomatic Patients with GOLD Stage I COPD

Dror Ofir, Pierantonio Laveneziana, Katherine A. Webb, Yuk-Miu Lam, Denis E. O’Donnell

METHODS

Pulmonary Function Testing

Pulmonary function testing was conducted in accordance with recommended techniques (American Thoracic Society/European Respiratory Society, 2002; Miller et al. 2005a; Miller et al. 2005b; Wanger et al., 2005; MacIntyre et al., 2005). Spirometry, body plethysmography, single-breath diffusing capacity for carbon monoxide (D\textsubscript{L}CO), and maximum inspiratory and expiratory mouth occlusion pressures (PIm\textsubscript{ax} and PE\textsubscript{max}, measured at FRC and TLC, respectively) were performed while sitting at rest using automated testing equipment (Vmax229d with Autobox 6200 D\textsubscript{L}; SensorMedics, Yorba Linda, CA). Closing volumes were measured using the single-breath nitrogen test as modified by Anthonisen et al. (1969). In all mild COPD patients and in 10 healthy control subjects, all measurements were repeated 30 minutes post-bronchodilator (400 µg salbutamol). Measurements were standardized as percentages of predicted normal values (Briscoe & Dubois, 1958; Burrows et al., 1961; Black & Hyatt, 1969; Crapo et al., 1982; Hamilton et al., 1995; Morris et al., 1998); predicted normal values for inspiratory capacity (IC) were calculated as predicted total lung capacity (TLC) minus predicted...
functional residual capacity (FRC). Predicted values for closing volumes were those of Buist & Ross (1973).

Exercise Testing

Incremental exercise testing was conducted on an electronically-braked cycle ergometer (Ergometrics 800S; SensorMedics, Yorba Linda, CA) using the Vmax229d Cardiopulmonary Exercise Testing System (SensorMedics) according to recommended guidelines (Roca et al., 1997; American Thoracic Society; American College of Chest Physicians, 2003). Equipment was calibrated immediately before each test. All exercise tests consisted of a steady-state resting period (at least 6 minutes of quiet breathing through a mouthpiece) and a 1 minute warm-up of unloaded pedalling followed by a stepwise protocol in which the work rate was increased in 2-minute intervals by increments of 20 watts. Pedalling rates were maintained between 50 and 70 revolutions per minute. All exercise tests were terminated at the point of symptom-limitation (peak exercise). Subjects were encouraged to cycle to the point of symptom limitation by being instructed to “cycle for as long as you can”. During exercise, standardized and continuous verbal encouragement to subjects was provided by a member of the study team who was blinded to the results of the lung function testing.

Subjects breathed through a mouthpiece and a low resistance flow transducer. Breath-by-breath measurements [minute ventilation ($\dot{V}_E$), tidal volume ($V_T$), breathing frequency ($F$), inspiratory and expiratory time ($T_I$ and $T_E$, respectively), duty cycle ($T_I/T_{TOT}$), and mean inspiratory and expiratory flow ($V_T/T_I$ and $V_T/T_E$, respectively), oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and end-tidal carbon
dioxide partial pressure ($P_{ET\text{CO}_2}$) were collected using a cardiopulmonary exercise testing system (Vmax229d; SensorMedics, Yorba Linda, CA). Pulse oximetry and electrocardiographic monitoring were carried out throughout exercise, while blood pressure was determined by indirect sphygmomanometry before, every 2 minutes during exercise, at the end of exercise and five minutes post-exercise. At rest, every minute during exercise, and at the end of exercise, subjects rated the intensity of their breathing and leg discomfort using the modified 10-point Borg category-ratio scale (Borg, 1982). IC maneuvers were performed after Borg ratings pre-exercise, every second minute during exercise, and at end-exercise.

Exercise parameters were compared with the predicted normal values of Blackie et al (1989) and Jones et al. (1985). Peak $\dot{V}O_2$ was reported in absolute units (L/min), after correction of body weight (ml/kg/min) and as a percentage of predicted normal values accounting for age, height, and sex (Blackie et al., 1989). Ventilation was compared with the maximal ventilatory capacity (MVC) that was estimated by multiplying the measured FEV$_1$ by 35 (Gandevia & Hugh-Jones, 1957). The ventilatory threshold (VTh) was detected individually using the V-slope method (Wasserman et al. 1999). Breathing pattern was evaluated by examining individual Hey plots (Hey et al., 1966).

**Exertional Symptoms**

Prior to exercise testing, subjects were informed that they would be asked to rate the intensity of their “breathing discomfort” and “leg discomfort” during exercise. Subjects were given no further information about these sensations. Subjects were first familiarized with the modified Borg category-ratio scale (Borg, 1982) and its endpoints
were anchored such that zero represented “no breathing (leg) discomfort” and 10 was “the most severe breathing (leg) discomfort that they had ever experienced or could imagine experiencing”. By pointing to the Borg Scale, subjects rated the intensity of their breathing and leg discomfort at rest, every minute during exercise, and at end-exercise. Symptom ratings preceded IC maneuvers by at least 5 breaths to avoid interference with pre-IC breathing patterns, and to avoid the possible influence that the performance of an IC maneuver might have on dyspnea intensity. At end-exercise, subjects also specified their reason for stopping exercise (see below). Qualitative aspects of perceived breathing discomfort at peak exercise were described by completion of a questionnaire of descriptors of breathlessness that we modified (O’Donnell et al., 2008) from that of Simon and coworkers (Simon et al., 1990).

Inspiratory Capacity Measurements

IC measurements were collected as previously described (O’Donnell et al., 2001). At each visit, the correct conduct of IC maneuvers was fully explained to the patient and then practiced at rest until consistently reproducible efforts were made (i.e., within ± 5% or ±100 mL, whichever was larger). Subjects were given a few breaths warning before an IC maneuver, a prompt for the maneuver (i.e., “At the end of the next normal breath out, take a deep breath all the way IN” or “at the end of this breath out, take a big breath all the IN”), and then strong verbal encouragement to make a maximal effort (i.e., “in…, in…, in…”) before returning to their regular breathing.

The resting IC was recorded as the mean of the two best reproducible efforts. Satisfactory technique and repeatability of maneuvers was ensured before proceeding
with exercise testing. During the constant-load exercise tests, IC maneuvers were performed at 2-minute intervals during the last 30-second period of each work rate. When subjects indicated the desire to terminate exercise, an “end-exercise” IC maneuver was performed within 15 seconds and the subjects were permitted to cool down; or if an acceptable IC had been performed within the preceding 30 seconds and the breathing pattern had not restabilized, then the value for that IC was used as the end-exercise value. If an exercise IC maneuver was found to be unacceptable (i.e., submaximal effort or anticipatory changes in breathing pattern immediately preceding the IC maneuver), it was not repeated and was excluded from the analysis.

End-expiratory lung volume (EELV) was calculated as total lung capacity (TLC) minus IC, on the assumption that TLC remains constant during exercise (Stubbing et al. 1980; Stubbing et al. 1980). Inspiratory reserve volume (IRV) was calculated as IC minus $V_T$. The change (decrease) in IC reflects the inverse change (increase) in dynamic EELV, or the extent of dynamic hyperinflation (EELV=TLC-IC); likewise, changes in inspiratory reserve volume (IRV=IC-$V_T$) reflect changes in end-inspiratory lung volume (EILV=TLC-IRV). This has been found to be a reliable method of tracking acute changes in lung volume (O'Donnell et al., 1998; Yan et al., 1997). Techniques for performing and accepting IC measurements have been previously described (O'Donnell et al., 2001). Confirmation of satisfactory technique and reproducibility of IC maneuvers for each subject was established during an initial practice session at rest.

**Tidal Flow-Volume Loops**

Flow and integrated volume were recorded continuously during exercise testing. Tidal flow-volume curves at rest, every 2 minutes during exercise and at peak exercise
were constructed for each patient and placed within their respective maximal flow-volume envelopes according to coinciding IC measurements. Maximal flow-volume loops were performed at rest and immediately after exercise for this analysis. The presence or absence of expiratory flow-limitation was assessed by calculating the percent of $V_T$ that encroaches on the maximal flow envelope, and the extent of encroachment of flow at the mid-range of $V_T$ on the maximal flow-volume envelope at iso-volume (Johnson et al., 1999).

**Locus of Symptom Limitation**

To determine the locus of symptom limitation, subjects answered the following question immediately after reaching the point of symptom limitation:

Did you stop exercising because of:

- Breathing discomfort?
- Leg discomfort?
- A combination of breathing and leg discomfort?
- Some other reason? If so, please describe this reason.

**Exercise Endpoints for Analysis**

Cardiopulmonary measurements were averaged over 30-second intervals. Three main time points were used for evaluation of exercise parameters, i.e., pre-exercise rest, a standardized work rate (*iso-work rate*), and peak exercise. *Rest* was defined as the steady-state period after at least 3 minutes of breathing on the mouthpiece while seated at rest on the cycle ergometer before exercise was started: cardiopulmonary parameters
were averaged over the last 30 seconds of this period, IC measurements for this period were collected while breathing on the same circuit immediately after completion of the quiet breathing period. Peak was defined as the last 30 seconds of loaded pedalling: cardiopulmonary parameters were taken as the average over this time period, IC measurements and Borg ratings were collected immediately at the end of this period. Iso-work rate measurements represent the data averaged over the first 30 seconds of the last minute of each work rate, while Borg ratings and IC measurements were captured within the second 30 seconds of this minute.

RESULTS

Subject Characteristics

Two patients in the mild COPD groups had coronary artery disease with a remote history of ischemia. Their exercise tests of these stable asymptomatic patients were examined carefully for any abnormality related to their coronary artery disease. The ventilatory threshold for these subjects was within the normal range (42 and 52% of predicted maximum $\dot{V}O_2$), and was similar to the average of the COPD group. Similarly, their maximal exercise was reduced but was within the range of the COPD group. There was no electrocardiographic evidence of active ischemia and no chest pain or any evidence of left ventricular decompensation. Based on these results, these patients were not excluded from the study sample.