THE EFFECT OF EXERCISE TEST MODALITY ON DYSPNEA PERCEPTION IN OBESE PATIENTS WITH COPD

by

Casey Ellis Ciavaglia

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Abstract

**Background:** Obesity is becoming increasingly prevalent in patients with chronic obstructive pulmonary disease (COPD) but the physiological and clinical consequences of their combination remain poorly understood. In particular, the impact of obesity on dyspnea and exercise intolerance in COPD is clinically pertinent but little studied and is the main focus of this thesis. Previous studies utilizing cycle ergometry have concluded that obesity does not convey either mechanical or sensory disadvantages during physical activity in COPD. However, it remains to be seen whether such advantages persist in COPD during weight-bearing walking when metabolic requirements are greater than during cycling.

**Aim:** To examine contributors to dyspnea in obese COPD by comparing physiological and perceptual responses at similar work rates during the two exercise conditions where metabolic loading and respiratory muscle activity are distinctly different.

**Methods:** Obese (body mass index >30 kg/m²) patients were recruited with moderate to severe airflow obstruction (post-bronchodilator FEV₁ 30-79% predicted). We compared metabolic, ventilatory (breathing pattern, operating lung volumes, respiratory muscle function and electromyography of the diaphragm) and dyspnea (intensity and quality) during symptom-limited cycle and treadmill exercise protocols using a matched linearized incremental 10 W step rise in work rate.

**Results:** Cycle exercise was associated with reduced oxygen uptake, greater arterial oxygen saturation, earlier ventilatory threshold, greater neuromuscular efficiency and activity of the diaphragm, and less expiratory muscle activity compared to treadmill walking (p<0.01). However, ventilation, breathing pattern, operating lung volumes, global respiratory effort and
electrical activation of the diaphragm were similar at comparable work rates across modalities.

Accordingly, dyspnea intensity and quality were not different.

**Conclusions:** Our results indicate that, when the rise in work rate is standardized, dyspnea intensity and quality are independent of small inter-modality difference in metabolic acidosis and arterial oxygen saturation that could potentially influence efferent output from the central respiratory controller. Moreover, altered afferent inputs associated with inter-modality differences in diaphragmatic function and expiratory muscle activity do not directly influence dyspnea at least when respiratory neural drive, breathing pattern and operating lung volumes are similar.
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## List of Abbreviations

- **BMI** – body mass index
- **COPD** – chronic obstructive pulmonary disease
- **CT** – computed tomography
- **DEXA** - dual-energy X-ray absorptiometry
- **DLCO** – diffusing capacity of the lung for carbon monoxide
- **EELV** – end-expiratory lung volume
- **EILV** – end-inspiratory lung volume
- **ERV** – expiratory reserve volume
- **F_{b}** – breathing frequency
- **FEV_{1}** – forced expiratory volume in one second
- **FFM** – fat free mass
- **FRC** – functional residual volume
- **FVC** – forced vital capacity
- **HR** – heart rate
- **IC** – inspiratory capacity
- **IRV** – inspiratory reserve volume
- **MRC** – medical research council
- **MVV** – maximal voluntary ventilation
- **O_{2}** - oxygen
- **P_{a}CO_{2}** – partial pressure of arterial carbon dioxide
- **P_{ET}CO_{2}** – partial pressure of end-tidal carbon dioxide
- **P-V** – pressure-volume
- **RER** – respiratory exchange ratio
- **sRAW** – specific airway resistance
- **SpO_{2}** – arterial oxygen saturation measured by pulse oximetry
- **SVC** – slow vital capacity
- **T_{I}/T_{TOT}** – inspiratory duty cycle (inspiratory time over total respiratory time)
- **TLC** – total lung capacity
- **RV** – residual volume
- **V_{A}** – alveolar ventilation
- **VCO_{2}** – carbon dioxide output
- **V_{E}** - minute ventilation
- **VO_{2}** – oxygen uptake
- **V/Q** – ventilation/perfusion
- **V_{T}** – tidal volume
- **VTh** – ventilatory threshold
Chapter 1

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a progressive and debilitating respiratory disease that is characterized by airflow limitation that is not fully reversible (Rodriguez-Roisin & Vestbo, 2011). In 1990, COPD was ranked as the sixth leading cause of death and is currently the third leading cause of death worldwide (Lozano et al. 2012). The true prevalence of COPD has been reported to be under-estimated in Canada (O’Donnell et al. 2008) and worldwide and significant under-diagnosis is a constant concern (van den Boom et al. 1998). The international Burden of Obstructive Lung Disease (BOLD) prevalence study found that 10.1% of a general population sample fulfilled spirometric criteria for COPD, with the majority fitting GOLD stage I and II severity classification (Buist et al. 2007). With increasing age, COPD can also be complicated with other comorbidities including cardiovascular disease, cancer, diabetes, osteoporosis and obesity (Barnes, 2009; Decramer, 2008).

Obesity, defined as a body mass index (BMI) greater than or equal to 30 kg/m$^2$, is a well recognized global epidemic (WHO 2012) that continues to rise worldwide (Finucane et al. 2011). Although it is the most common index of obesity, BMI is a relatively crude measure and other measures need be considered to differentiate between fat mass and fat free mass (FFM). For example, Janssen et al. (2004) have shown that an increased BMI and higher waist circumference is associated with higher risk of mortality
compared to increased BMI and lower waist circumference, suggesting that high central adipose tissue deposition poses a greater health risk. Interestingly, obese individuals who exhibit an active lifestyle have reduced mortality risk compared to normal weight sedentary individuals (Blair & Brodney, 1999). However, obese individuals are at a 3.6 fold greater risk of dyspnea on exertion (Zutler et al. 2012) which may deter these individuals from pursuing active lifestyles.

Although obesity and COPD are each independently becoming more prevalent in the population, some studies have shown that obesity is more prevalent in COPD patients compared to individuals without COPD (Guerra et al. 2002; Steuten et al. 2006; Eisner et al. 2007; Vozoris & O’Donnell, 2012). Estimates of obesity in COPD reached approximately 25% in Canada (Vozoris & O’Donnell, 2012), which was similar to a South American study at 23% (Montes de Oca et al. 2008) but higher than the Netherlands at 18% (Steuten et al. 2006) and lower compared to northern California at 54% (Eisner MD et al. 2007). Surprisingly, combining mild-moderate obesity and COPD appears to have a survival advantage (Chailleux et al. 2003; Landbo et al. 1999; Wilson et al. 1989), although this putative advantage is negated in morbid obesity (Jordan et al. 2010). Despite this survival advantage, obese COPD patients require more health care resources, including hospitalization, compared to non-obese COPD patients (Vozoris & O’Donnell, 2012). Surprisingly obese COPD patients may have improved in-hospital mortality and reduced readmission rates from COPD exacerbations compared to their normal weight counterparts (Zapatero et al. 2013; Lainscak et al. 2011).
In this thesis, I will briefly review the known respiratory physiological derangements associated with obesity in subjects without respiratory disease and with COPD during rest and exercise. My thesis project is divided into two parts which I will first set up by outlining their respective objectives and hypotheses: **Study 1** “Does exercise test modality influence dyspnea perception in obese patients with COPD?”; **Study 2** “Do differences in respiratory muscle activity during cycling and walking influence dyspnea perception in obese patients with COPD?” Next, a peer-reviewed, author submitted (version) manuscript will be presented as part of study 1 that addresses the previously unknown physiological effects of obesity on dyspnea in patients with COPD during weight-supported cycle and weight-bearing treadmill exercise where the rise in work rate was carefully matched. Study 2, the second submitted manuscript, evaluates respiratory muscle activity differences between exercise modalities in obese COPD patients and the potential afferent feedback pathways related to dyspnea intensity and quality using a diaphragmatic electromyogram catheter with esophageal and gastric pressure measurements. Finally, I will discuss novel findings and briefly summarize my thesis project and consider future directions.
Chapter 2

Literature Review

2.1 Physiological effects of obesity during resting

2.1.1 Respiratory Mechanics

Lung function derangements in obesity are the result of increased thoracic and abdominal adipose deposition and have been proposed to act collectively (compared to in isolation) to reduce respiratory system compliance (Sutherland et al. 2008; Babb et al. 2008). Studies have shown that obesity results in both reduced chest wall compliance in relaxed subjects (Naimark & Cherniack, 1960) and reduced lung compliance in supine anesthetized subjects (Pelosi et al. 1996; Pelosi et al. 1998). In addition, increased intrathoracic blood volume (Alexander et al. 1962), bi-basal airway closure followed by pulmonary gas trapping (Milic-Emili et al. 2007) and diffuse microatelectasis further increases static lung recoil pressure (Figure 1) (Hedenstierna & Santesson, 1976). The consequence of reduced compliance of the respiratory system results in tidal volume positioned on the lower alinear portion of the sigmoid-shaped pressure-volume relationship of the relaxed respiratory system. Basically, there is a “re-setting” of the end expiratory lung volume (EELV) to a lower value compared to that predicted for normal weight individuals (Pelosi et al. 1988; DeLorey et al. 2005; Jones & Nzekwu, 2006). EELV and expiratory reserve volume (ERV) decreases with increasing BMI across obesity categories following an inverse exponential relationship (Jones & Nzekwu,
FIGURE 1: The impact of obesity on the pressure-volume (P-V) relationship. Obesity (solid lines) shifts both the chest wall (left) and the lung P-V relationship (right) to the right relative to normal weight (dashed lines). For obesity, this rightward shift creates a lower relaxation point or ‘re-sets’ FRC. Abbreviations: FRC=functional residual capacity.
Lowering of EELV allows for an increase in inspiratory capacity (IC) (Jones & Nzekwu, 2006; Guenette et al. 2010) given that the total lung capacity (TLC) is reportedly normal or slightly reduced in mild-to-moderate obesity (Jones & Nzekwu, 2006; Watson & Pride, 2005; Babb et al. 2002; Ray et al. 1983). However, in morbid obesity (BMI >40 kg/m²), TLC and IC tend to diminish with further increases in BMI (Jones & Nzekwu, 2006).

Of clinical importance, obese individuals may present with expiratory airflow limitation at rest due to a reduced EELV (Figure 2). The combination of early airway closure from increased dynamic airway compression during a forced maneuver means that slow vital capacity (SVC) can exceed forced vital capacity (Hyatt et al. 2009). The consequences of obesity are further amplified when assuming a supine posture: here, greater expiratory flow limitation and elevated intrinsic positive end expiratory pressure, contribute to an increase in respiratory neural drive and diaphragm force production in order to maintain ventilation (Steier et al. 2009). This may also explain why some subjects are more dyspneic while supine compared to seated position (Ferretti et al. 2001). The excessive mechanical loads on the respiratory muscles at rest and the inability to maintain the increased work of breathing in the setting of increased ventilatory demand may predispose these patients to respiratory failure (Kress et al. 1999; Verbraecken & McNicholas, 2013).
FIGURE 2: Flow-volume loops of normal weight (left) and obese (right) subjects. The reduced EELV in obesity at rest results in the tidal loop impinging on the maximal flow-volume loop, i.e., flow limitation. Abbreviations: TLC=total lung capacity; RV=residual volume; EELV= end-expiratory lung volume.
2.1.2 Respiratory Muscles

The static strength of the respiratory muscles in mild-moderate obesity is relatively preserved (Kelly et al. 1988; Magnani et al. 2007). Some authors have shown normal inspiratory strength (Rochester & Arora, 1980; Kelly et al. 1988; Sahebjami, 1998) while others show a reduction (Sahebjami, 1998; Chilf et al. 2007; Casali et al. 2011). Given the increased elastic load and oxygen cost of breathing (Kress et al. 1999) from the imposed mass loading effect on the respiratory muscles, the maintenance of inspiratory strength/endurance within the normal range could be explained by chronic adaptation or a training effect from increased loading over time (Pelosi et al. 1996; Weiner et al. 1998).

2.1.3 Respiratory Gas Exchange

With increasing BMI, obese individuals may develop impaired pulmonary gas exchange as a result of ventilation/perfusion (\(\dot{V}/Q\)) mismatch due, in part, to microatelectasis (Zavorsky & Hoffman, 2008). A relative shunt may exist in these patients (widening alveolar-arterial partial pressure of oxygen) but only becomes physiologically relevant in the morbidly obese classification (Zavorsky & Hoffman, 2008). The effect of obesity on lung diffusing capacity for carbon monoxide (DL\(_{CO}\)) remains controversial where studies have indicated normal absolute DL\(_{CO}\) values or increased values when corrected for the prevailing alveolar lung volume (Ray et al. 1983; Biring et al. 1999). Other studies have shown increased absolute DL\(_{CO}\) in morbid obesity, possibly reflecting
an increase in intrathoracic blood volume (Jones & Nzekwu, 2006; Ray et al. 1983; Zavorsky & Hoffman, 2008; Saydain et al. 2004).

Adoption of the supine posture reduces arterial partial pressure of oxygen, which correlates strongly with reduction in ERV (Farebrother et al. 1974). In the supine posture, an increase in \( V/Q \) mismatch during sleep may have serious clinical implications that could be linked to obesity hypoventilation syndrome (Holley et al. 1967), classically referred to as “Pickwickian syndrome” (Burwell et al. 1956).

2.2 Physiological effects of obesity in patients with COPD during resting breathing

2.2.1 Respiratory Mechanics

The reduced compliance seen as a result of obesity in individuals without respiratory disease may be mechanically advantageous in COPD patients and most notably in those with severe airflow limitation. The increased static lung recoil pressure in obesity, compared to normal weight patients matched for airflow obstruction, would essentially reduce static hyperinflation in COPD patients (Ora et al. 2011). EELV and ERV decrease exponentially with increasing BMI, resulting in a linear increase in IC and IC/TLC (Figure 3) (O’Donnell et al. 2011). The increase in IC/TLC is not only mechanically advantageous in this COPD phenotype but may convey a survival advantage since reduced IC/TLC ratio is an independent risk factor for increased mortality (Casanova et al. 2005). However the survival advantages seen in COPD of
FIGURE 3: Relationship of BMI and lung volumes expressed as percent predicted for a sample size of 2,265. Regression equations and regression lines shown for each relationship. Abbreviations: FRC=functional residual capacity; IC=inspiratory capacity; RV=residual volume; TLC=total lung capacity. Modified with permission from O’Donnell DE et al. Chest 2011; 140(2):461-468.
coexistent mild-moderate obesity are negated in morbid obesity where the IC/TLC ratio sharply diminishes (O’Donnell et al. 2011).

Volume-corrected (specific) airway resistance decreases with increasing BMI in COPD (O’Donnell et al. 2011). Interestingly, a recent study by Boiselle et al. (2012) provides evidence of expiratory tracheal collapse in COPD patients with mild obesity. It is postulated that collapse may be even more pronounced in moderate-morbid obesity with increased neck mass (Boiselle et al. 2013). However, the effect of tracheal collapse on respiratory symptoms remains unclear.

2.2.2 Respiratory Muscles

Much is known about respiratory muscle function in COPD patients (McKenzie et al. 2009). However, in obese COPD patients, detailed studies of respiratory muscle structure and function are lacking. A study performed in obese COPD patients by Ora and colleagues (2011) showed inspiratory muscle strength (maximal inspiratory pressure) was similar to that in their normal weight counterparts who were matched for airflow obstruction (FEV$_1$). Obese subjects in this study had reduced lung hyperinflation and greater intra-abdominal pressure, suggesting a cephaloid shift of the diaphragm placing it in a more mechanical advantageous position during resting breathing.

2.2.3 Respiratory Gas Exchange

Gas exchange in obese COPD patients varies based upon the background V/Q mismatch and the extent of emphysematous destruction (Malhotra & Hillman, 2008). Airway closure from reduced compliance may be counterbalanced by an increased EELV
and may improve pulmonary gas exchange, although this is difficult to predict. The arterial partial pressure for carbon dioxide (PaCO\textsubscript{2}) has been reported to be in the normal range or slightly elevated in mild-moderate obesity (Chailleux et al. 2003), but hypercapnia can occur in morbidly obese patients with advanced COPD.

2.3 Physiological effects of obesity during exercise

Contrary to popular opinion, obese individuals without respiratory disease do not have an impairment in exercise capacity during cycle ergometry compared to their normal weight counterparts. In fact, in mild-moderate obesity, cardiorespiratory fitness is within normal range when expressed in absolute terms (L/min) or as a percentage of predicted normal (DeLorey et al. 2005; Babb et al. 2002; Ofir et al. 2007; Lorenzo & Babb, 2012; Buskirk & Taylor, 1957). Peak oxygen uptake (\textit{VO}_2) presented in relative terms (mL/kg/min) is underestimated due to the elevated denominator in obesity compared to normal weight (Lorenzo & Babb, 2012). Peak work rate in obesity falls within the normal range or lower range of normal (Ofir et al. 2007; Wasserman et al. 2005; Jones, 1988).

With the increase in total body adipose deposition, cycle exercise increases both oxygen uptake and carbon dioxide production that results in an increase in the ventilatory requirements for a given external work (Babb et al. 2002; Ofir et al. 2007; Jones, 1988; Neder et al. 2000; Lafortuna et al. 2008; Dempsey et al. 1966; Lafortuna et al. 2006; Whipp & Davis, 1984; Babb et al. 1991; Hulens et al. 2001; Seres et al. 2006; Chilf et al. 2007). The \textit{VO}_2/work rate relationship shows an upward parallel shift due an increased
peripheral muscle metabolic demand from lifting heavy limbs during cycle compared to normal weight subjects (Laforluna et al. 2008; Dempsey et al. 1966). During exercise, obese subjects increase EELV above its low resting value and this allows lung volumes to operate on the more linear portion of the pressure-volume curve, establishing a “pseudo-normalization” (Figure 4) (Ofir et al. 2007). This behavior of EELV reduces the elastic (Tobin, 1997) and inertial (Mead, 1956) forces that contribute to total work of breathing which is further reduced by concurrently adopting a shallow and rapid breathing pattern (Babb et al. 2002; Ofir et al. 2007; Chilf et al. 2007).

2.4 Physiological effects of obesity in patients with COPD during exercise

A detailed physiological study by Ora and colleagues (2009) comparing obese and normal weight COPD patients matched for FEV₁ during cycle exercise, found that absolute \(\dot{V}O_2\) and \(\dot{V}CO_2\) were increased in obesity throughout exercise to symptom-limited peak. Peak \(\dot{V}O_2\) corrected for ideal body weight was greater than normal weight. Also, obese patients had relatively reduced static and dynamic lung hyperinflation (in absolute terms), resulting in a greater cycling exercise tolerance (work rate) than normal weight. The elevated metabolic demand in obesity corresponded with the rise in ventilation. Collectively, differences in metabolic demand and ventilation did not influence dyspnea perception (Ora et al. 2009). The increased resting IC in obese COPD allowed patients to accommodate the increasing ventilatory demand (increased \(V_T\)) thus delaying the mechanical limitation to exercise. A subsequent mechanistic study from the same laboratory has identified potential mechanisms that mitigate the expected increase
FIGURE 4: Comparison of the pressure-volume (P-V) relationship of normal weight (top panel) and obesity (bottom panel). Tidal breathing (closed loops) in normal weight subjects is positioned on the linear portion of the P-V curve and during exercise (open loops) EELV is recruited to increase tidal volume in order to maintain operating lung volumes on the linear portion of the P-V curve. Tidal breathing in obesity is positioned on the lower alinear portion of the P-V curve and recruits lung volume and shifts toward the linear portion of the P-V curve during exercise. Abbreviations: EELV=end expiratory lung volume; IC=inspiratory capacity; IRV=inspiratory reserve volume; TLC=total lung capacity; RV=residual volume.
in dyspnea in obese COPD: 1) increased expiratory flow rate from increased static recoil pressure; 2) lower operating lung volumes, increased IC and IRV create a mechanical advantage for the respiratory muscles; 3) the diaphragm’s length-force relationship is optimized from increased intra-abdominal pressure pushing the diaphragm in a more cephalic position; 4) regional lung volume recruitment (increased EELV) increases respiratory flow rates; and 5) increased dynamic EELV improves gas exchange measured by the lower $\dot{V}_E/\dot{V}CO_2$ ratio, a measure of improved ventilatory efficiency (Ora et al. 2011). It has yet to be determined if these factors also convey advantages during weight-bearing exercise such as walking where metabolic requirements are known to be different than during cycling and this question is a major focus of my thesis.

2.5 Rationale

2.5.1 Research Question 1

It is widely believed that obese COPD patients have greater dyspnea and activity restriction than normal weight COPD patients (matched for airway obstruction) but the mechanisms are debated. Physiological studies using cycle ergometry have found that endurance time and peak oxygen uptake are comparable in mildly obese and normal weight COPD patients, matched for severity of airway obstruction (Ora et al. 2009; Laviolette et al. 2010). However, field walking tests indicate reduced distance to tolerance in obese versus normal-weight COPD patients (Sava et al. 2010). These disparities may reflect the well-described differences in skeletal muscle recruitment patterns and in metabolic and acid-base status between weight-supported cycling and
weight-bearing walking tests. These differences are likely exaggerated in obese COPD and may have implications for the clinical interpretation of laboratory exercise testing in this group.

**Pivotal questions are:** does the intensity and quality of dyspnea differ at a given work rate during treadmill and cycle exercise? Is perceived dyspnea intensity influenced by modality-specific factors that can affect the intensity of central neural drive which include: earlier metabolic acidosis (Mathur et al. 1995; Palange et al. 2000; Mahler et al. 2011) and greater mechanoreceptor stimulation in the quadriceps (Gagnon et al. 2012) during cycling, or greater \( \dot{V}CO_2 \) and \( \dot{V}O_2 \) (Hsia et al. 2009) and greater arterial \( O_2 \) desaturation during treadmill walking (Palange et al. 2000; Murray et al. 2009; Hsia et al. 2009; Zhang et al. 2010; Mahler et al. 2011).

**2.5.2 Research Question 2**

With increasing respiratory drive throughout exercise, respiratory muscle mechanoreceptors (i.e. sensing muscle force and length) are considered to provide feedback information to the somatosensory cortex on the adequacy of ventilation (Figure 5) (Parshall et al. 2012). Insightful mechanistic studies performed in normal weight, hyperinflated COPD patients at rest showed dyspnea relief upon assuming a seated leaning forward posture compared to standing erect posture where diaphragm neuromuscular efficiency was impaired (Sharp et al. 1980; Druz & Sharp, 1982), suggesting that diaphragm mechanoreceptor afferent feedback influenced dyspnea perception. However, two independent studies in health found diaphragm function
FIGURE 5: A schematic of a neurophysiological model of dyspnea. The somatosensory cortex evaluates the appropriateness of the ventilatory drive and the resulting mechanical response. In the situation of increasing ventilatory drive and the inadequate mechanical response, the consequential sensation is “unsatisfied inspiration” or respiratory discomfort. Respiratory muscles (muscle spindles, Golgi tendon organs and type III & IV afferents), lung (pulmonary stretch receptors, C-fibers, J-receptors), afferent information from receptors in the airways (pulmonary stretch receptors, C-fibers), central and peripheral chemoreceptors and central corollary discharge from brainstem and cortical motor centers all rely to somatosensory cortex on breathing appropriateness and are contributors of dyspnea. Abbreviations: PaCO$_2$, partial pressure of arterial carbon dioxide; [H$^+$], hydrogen ion concentration; PaO$_2$, partial pressure of arterial oxygen. Modified with permission from: O’Donnell DE, et al. Respir Physiol Neurobiol 2009;167:116-32.
to be similar during cycling (Aliverti et al. 1997) and during treadmill walking (Sanna et al. 1999).

Based on our own preliminary studies and the work of Abraham et al. (2002), we postulated that during walking, when the lower limb hip flexion is no longer available to support the obese abdomen as it is during cycling, intra-abdominal pressure would be lower and consequently this would lead to impairment in diaphragm force production.

Therefore, important questions to address include: (1) what is the impact of cycling and treadmill walking (where body position is different) on respiratory muscle function in COPD patients with elevated abdominal adiposity?; (2) if differences in muscle function are present during these two exercise modalities, does this influence dyspnea intensity and quality?

To answer these research questions, we conducted two separate studies which focused on: (1) the investigation of metabolic differences between cycle and treadmill exercise that could influence dyspnea; and (2) different respiratory muscle activity patterns that could alter afferent inputs and thus respiratory sensation during cycle and treadmill exercise in obese COPD patients.

2.5.3 Study 1: Does exercise test modality influence dyspnoea perception in obese patients with COPD?

Objective
• To compare metabolic, ventilatory and perceptual responses to exercise in obese COPD patients during incremental treadmill and cycle protocols where the rise in work rate is matched.

_Hypothesis_

• The dyspnea/ventilation relationship during incremental symptom-limited exercise will be unaltered by inter-modality differences in metabolic loading, arterial oxygen desaturation or peripheral muscle loading in obese COPD.

2.5.4 **Study 2:** _Do differences in respiratory muscle activity during cycling and walking influence dyspnea perception in obese patients with COPD?_

**Objective**

• To assess dyspnea intensity and quality in relation to diaphragm electrical activation, diaphragm force generation (i.e., diaphragm efficiency) and ventilatory muscle recruitment pattern between cycle and treadmill exercise in obese COPD.

**Hypothesis**

• Reduced diaphragm efficiency during walking exercise will not modulate dyspnea intensity or quality compared to cycle exercise in obese COPD patients.
Chapter 3

Does exercise test modality influence dyspnoea perception in obese patients with COPD?
3.1 ABSTRACT

The purpose of this study was to investigate whether differences in physiological responses to weight-bearing (walking) and weight-supported (cycle) exercise influence dyspnoea perception in obese COPD patients where such discrepancies are likely exaggerated.

We compared metabolic, ventilatory and perceptual responses during incremental treadmill and cycle exercise using a matched linearized rise in work rate in 18 (10 men, 8 women) obese (body mass index 36.4±5.0 kg/m²; mean±SD) patients with COPD (FEV₁ 60±11 % predicted).

Compared with cycle testing, treadmill testing was associated with a significantly higher oxygen uptake, lower ventilatory equivalent for oxygen, and greater oxyhemoglobin desaturation at a given work rate (p<0.01). Cycle testing was associated with a higher respiratory exchange ratio (p<0.01), earlier ventilatory threshold (p<0.01) and greater peak leg discomfort ratings (p=0.01). Ventilation, breathing pattern and operating lung volumes were similar between tests, as were dyspnoea/work rate and dyspnoea/ventilation relations.

Despite significant between-test differences in physiological responses, ventilation, operating lung volumes and dyspnoea intensity were similar at any given external power output during incremental walking and cycling exercise in obese COPD patients. These data provide evidence that either exercise modality can be selected for
reliable evaluation of exertional dyspnoea in this population in research and clinical settings.
3.2 INTRODUCTION

The prevalence of both obesity and COPD is increasing steadily throughout the world [1]. The combination of these common conditions is associated with increased activity restriction and health care burden [2]. The effective management of exercise intolerance in obese COPD patients remains a major challenge and awaits a better understanding of the underlying mechanisms.

It is widely believed that obese COPD patients experience greater dyspnoea than normal weight COPD during daily activities. However, while field tests indicate reduced walking distance in obese versus normal weight COPD patients [3,4], physiological studies using cycle ergometry have found that dyspnoea intensity, endurance time and peak oxygen uptake (\(\dot{V}O_2\)) are similar in the two groups when severity of airway obstruction is matched [5,6]. The question therefore arises: does measurement of perceived dyspnoea intensity and exercise performance in obese COPD during cycle ergometry (where leg muscles are selectively stressed [7,8]), accurately reflect the situation during daily activities such as walking? In this regard, no studies have compared the relationship between dyspnoea and physiological responses during carefully matched walking and cycling exercise protocols in obese patients with COPD.

It has previously been demonstrated that the dynamic respiratory mechanical derangements, and the associated dyspnoea, during exercise in COPD rise in direct proportion to the prevailing ventilatory requirement of the task [9]. It follows that differences in dyspnoea intensity between cycling and walking could occur at a given
power output if the metabolic and ventilatory responses to these tasks are different. In the obese COPD patient, the relative importance of the higher metabolic cost of external work during treadmill exercise or the earlier metabolic acidosis of cycle exercise in driving ventilation (and consequent dyspnoea intensity) is difficult to predict [10-12]. It is also conceivable that differences in dynamic respiratory mechanics or in the source of the ventilatory stimulation (i.e. metabolic loading, skeletal muscle recruitment, arterial oxygen saturation and hemodynamic responses) between the two exercise modalities could influence the dyspnoea/ventilation relation.

Accordingly, the main objective of this study was to better understand the influence of the physiological peculiarities of each exercise modality on dyspnoea perception in patients with combined obesity and COPD. We compared physiological responses, dyspnoea/work rate and dyspnoea/ventilation relations during symptom-limited incremental cycle and treadmill exercise tests, using matched linearized work rate protocols.
3.3 METHODS

3.3.1 Subjects

Eighteen clinically stable obese (body mass index (BMI) >30 kg/m$^2$) COPD (FEV$_1$/FVC <70%) patients between the ages of 40-80 with a post-bronchodilator FEV$_1$ <80% predicted were recruited. Patients were excluded if they had significant disease which affected breathlessness or exercise capacity (i.e. metabolic, cardiovascular, neuromuscular and/or musculoskeletal), received daytime oxygen therapy, had significant respiratory disease other than COPD, were too breathless to leave the house or too fit (Medical Research Council (MRC) dyspnoea scale 5 or 1, respectively) and had any contraindications to clinical exercise testing.

3.3.2 Study design

This cross-sectional study received University and Hospital Research Ethics Board approval (DMED-1187-09). After obtaining informed consent, subjects attended 3 visits each separated by at least 48 hours. Visit 1, all subjects underwent medical screening, detailed pulmonary function tests, and familiarization with all exercise testing procedures. Visits 2 and 3 included pulmonary function tests and either a cycle or treadmill test (randomized visit order). Before each visit, subjects withheld short-acting $\beta_2$-agonist and anticholinergic bronchodilators for at least 4 and 6 hours, respectively, and long-acting bronchodilators at least 12 hours. Subjects were instructed to avoid caffeine, heavy meals, alcohol, and major physical exertion prior to each visit. Subjects underwent a dual-energy X-ray absorptiometry (DEXA) scan within the study period to quantify
body composition. When available, prior clinical chest computed tomography (CT) scan results were used to provide qualitative assessments of emphysema.

3.3.3 Procedures

Pulmonary function testing included routine spirometry, body plethysmography, single-breath diffusing capacity (D\textsubscript{LCO}) and maximum voluntary ventilation (MVV) using automated testing equipment (Vs62j body plethysmograph with Vmax229d; SensorMedics, Yorba Linda, CA). Cardiopulmonary exercise tests were performed on an electronically braked cycle ergometer (Ergometrics 800S; SensorMedics, Yorba Linda, CA) and on a treadmill (Medtrack ST55; Quinton Instrument, Bothell, WA) using a Vmax229d Cardiopulmonary Exercise Testing System (SensorMedics). Cycle and treadmill exercise tests were both performed with 10-watt increments which increased every two minutes to a symptom-limited endpoint. The incremental treadmill protocol was individualized based on body weight: there was a linear increase in speed and a curvilinear rise in grade (see online supplement for more detail). Subjects rated “breathing discomfort” and “leg discomfort” on a modified 10-point Borg scale [13]. Inspiratory capacity (IC) maneuvers were performed during a steady-state resting period, during each stage of exercise and at peak exercise. Operating lung volumes were derived from IC measurements as previously described [14]. Immediately after exercise, subjects were asked why they stopped exercising. Breath-by-breath data from the last 30-s of loaded pedaling were averaged for each individual and analysed as “peak” exercise. Three independent observers, who were blinded to exercise modality, identified the
ventilatory threshold (VTh) by the “V-slope” plot which was then double-checked with
the inflection points suggested by the ventilatory equivalent and end-tidal pressure
methods [15].

3.3.4 Statistical analysis

A sample size of 18 provided 80% power to detect a minimal clinically important
difference in dyspnoea of ±1 Borg scale unit measured at a standardized work rate [16],
assuming an α of 0.05 and a within-patient standard deviation of 1 unit. Comparisons of
exercise modalities were made at rest, at standardized work rates (i.e., 10, 20, 30 and 40
watts) and at peak exercise using paired two-tailed t-tests. Results are reported as means
± SD.
3.4 RESULTS

3.4.1 Subjects

Subject characteristics and DEXA scan results are presented in Tables 1 and 2, respectively. Subjects had moderate airflow obstruction and lung volumes were within the predicted normal ranges with the exception of residual volume (RV) (124% predicted) and expiratory reserve volume (ERV) (66% predicted). Evidence of emphysema was shown on all available chest CT scans (13/18 subjects). DEXA scans from 15 subjects (equipment was unavailable for the last 3 subjects) revealed that total body mass was elevated by 15.5 kg (17.5%) in males and 16.1 kg (21.7%) in females compared to the population means for age-matched individuals [17]: this resulted from a greater total fat mass (males 11.0, females 7.1 kg) and lean mass (males 4.5, females 8.8 kg) compared to the population means.

3.4.2 Responses to cycle and treadmill exercise

Subjects reached a similar peak work rate during cycle and exercise tests (Table 3). Although exercise duration was longer by a mean difference of 52 seconds in the treadmill versus cycle test, this was not statistically significant (p=0.11). The distribution of main reasons for stopping exercise was also not different between tests (p=0.56): breathing discomfort (treadmill n=10; cycle 8), leg discomfort (treadmill 2; cycle 5) and a combination of breathing and leg discomfort (treadmill 6; cycle 5). Rest and peak exercise data are presented in Table 3.
TABLE 1. Subject characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>66 ± 8</td>
</tr>
<tr>
<td>Male : Female, n</td>
<td>10 : 8</td>
</tr>
<tr>
<td>Height, cm</td>
<td>167.2 ± 2.0</td>
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<tr>
<td>Weight, kg</td>
<td>102.1 ± 20.1</td>
</tr>
<tr>
<td>Ideal body weight, kg</td>
<td>69.3 ± 2.0</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>36.4 ± 5.0</td>
</tr>
<tr>
<td>Waist circumference, cm:</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>129 ± 10</td>
</tr>
<tr>
<td>Female</td>
<td>115 ± 7</td>
</tr>
<tr>
<td>Smoking history, pack-years</td>
<td>50 ± 32</td>
</tr>
<tr>
<td>COPD duration, years</td>
<td>8.8 ± 4.4</td>
</tr>
<tr>
<td>Baseline Dyspnoea Index, 0-12</td>
<td>6.6 ± 1.8</td>
</tr>
<tr>
<td>MRC dyspnoea scale, 0-5</td>
<td>2.4 ± 0.7</td>
</tr>
<tr>
<td>Pulmonary function:</td>
<td></td>
</tr>
<tr>
<td>FEV₁, L (% predicted)</td>
<td>1.40 ± 0.40 (60 ± 11)</td>
</tr>
<tr>
<td>FVC, L (% predicted)</td>
<td>3.08 ± 0.82 (88 ± 14)</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>48 ± 9</td>
</tr>
<tr>
<td>IC, L (% predicted)</td>
<td>2.41 ± 0.76 (90 ± 23)</td>
</tr>
<tr>
<td>FRC, L</td>
<td>3.31 ± 0.71 (105 ± 19)</td>
</tr>
<tr>
<td>RV, L</td>
<td>2.67 ± 0.68 (124 ± 33)</td>
</tr>
<tr>
<td>TLC, L</td>
<td>5.73 ± 1.07 (98 ± 13)</td>
</tr>
<tr>
<td>RV/TLC, %</td>
<td>47 ± 8</td>
</tr>
<tr>
<td>sRₐW, % predicted</td>
<td>385 ± 151</td>
</tr>
<tr>
<td>DₗCO, mL/mmHg/min (% predicted)</td>
<td>12.2 ± 4.4 (50 ± 12)</td>
</tr>
<tr>
<td>DₗCO/Vₐ, % predicted</td>
<td>76 ± 16</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD.
MRC: Medical Research Council; FEV₁: forced expired volume in 1 second; FVC: forced vital capacity; IC: inspiratory capacity; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity; sRₐW: specific airway resistance; DₗCO: diffusing capacity of the lung for carbon monoxide; Vₐ: alveolar volume.
<table>
<thead>
<tr>
<th></th>
<th>Obese COPD</th>
<th>Population Averages *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male and Female (n=15)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body:</td>
<td></td>
<td></td>
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<tr>
<td>Mass, kg</td>
<td>97.7 ± 12.2</td>
<td></td>
</tr>
<tr>
<td>Lean mass, kg</td>
<td>56.0 ± 8.1</td>
<td></td>
</tr>
<tr>
<td>Fat mass, % total body mass</td>
<td>40.2 ± 4.9</td>
<td></td>
</tr>
<tr>
<td>Trunk:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mass, kg</td>
<td>51.3 ± 8.1</td>
<td></td>
</tr>
<tr>
<td>Fat, % total trunk mass</td>
<td>42.4 ± 5.1</td>
<td></td>
</tr>
<tr>
<td>Both legs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mass, kg</td>
<td>29.9 ± 3.6</td>
<td></td>
</tr>
<tr>
<td>Lean mass, kg</td>
<td>17.4 ± 2.5</td>
<td></td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>11.5 ± 2.9</td>
<td></td>
</tr>
<tr>
<td>Fat, % total leg mass</td>
<td>38.5 ± 6.9</td>
<td></td>
</tr>
<tr>
<td><strong>Male (n=8)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mass, kg</td>
<td>104.2 ± 11.0</td>
<td>88.7</td>
</tr>
<tr>
<td>Lean mass, kg</td>
<td>62.3 ± 5.4</td>
<td>57.8</td>
</tr>
<tr>
<td>Fat mass, % total body mass</td>
<td>37.5 ± 4.4</td>
<td>31.2</td>
</tr>
<tr>
<td>Trunk:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mass, kg</td>
<td>55.8 ± 7.6</td>
<td>45.8</td>
</tr>
<tr>
<td>Fat mass, % total trunk mass</td>
<td>41.1 ± 5.8</td>
<td>33.1</td>
</tr>
<tr>
<td>Both legs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mass, kg</td>
<td>30.3 ± 3.3</td>
<td>27.0</td>
</tr>
<tr>
<td></td>
<td>Lean mass, kg</td>
<td>Fat mass, kg</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td></td>
<td>19.1 ± 2.9</td>
<td>17.7</td>
</tr>
</tbody>
</table>

Female (n=7)

<table>
<thead>
<tr>
<th></th>
<th>Mass, kg</th>
<th>Lean mass, kg</th>
<th>Fat mass, % total body mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body:</td>
<td>90.2 ± 9.1</td>
<td>48.9 ± 3.1</td>
<td>43.2 ± 4.0</td>
</tr>
<tr>
<td></td>
<td>74.1</td>
<td>40.1</td>
<td>42.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Mass, kg</th>
<th>Fat mass, % total trunk mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trunk:</td>
<td>46.2 ± 5.3</td>
<td>43.5 ± 4.6</td>
</tr>
<tr>
<td></td>
<td>37.1</td>
<td>41.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Mass, kg</th>
<th>Lean mass, kg</th>
<th>Fat mass, kg</th>
<th>Fat, % total leg mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both legs:</td>
<td>29.3 ± 4.0</td>
<td>15.4 ± 1.2</td>
<td>13.1 ± 3.3</td>
<td>44.3 ± 4.6</td>
</tr>
<tr>
<td></td>
<td>24.5</td>
<td>12.3</td>
<td>11.3</td>
<td>45.5</td>
</tr>
</tbody>
</table>

Values are means ± SD.
*Population averages are means for non-hispanic white people between the ages of 60 and 79 [17].
**Metabolic and gas exchange responses.** Peak $\dot{V}O_2$ expressed as a percentage of predicted was higher during treadmill compared to cycle ($91 \pm 30$ versus $78 \pm 26\%$ predicted, respectively, $p<0.05$) using the recommended gender-specific predictive equations for obese men [18] and obese women [19] described by Lorenzo et al. [20]. There was a significant upward displacement of $\dot{V}O_2$ relative to work rate during treadmill compared with cycle exercise; the $\dot{V}O_2$-work rate slope was $14.2\pm2.1$ and $12.5\pm3.7$ mL/min/watt during treadmill and cycle exercise, respectively ($p=0.07$) (Figure 1). Carbon dioxide production ($\dot{V}CO_2$) was higher at 30 and 40 watts and at the peak of treadmill exercise compared to cycling (Figure 1). The respiratory exchange ratio (RER) during cycle compared to treadmill tests showed an upward shift from the onset of exercise that was maintained through to peak exercise (Figure 1). Sixteen subjects had an identifiable VTh. Subjects reached an earlier VTh during cycle exercise at a $\dot{V}O_2$ of $1.01\pm0.23$ L/min compared to $1.17\pm0.27$ L/min during treadmill exercise ($p<0.05$). VTh relative to predicted peak $\dot{V}O_2$ was similar between modalities and above the lower limit of normal (cycle: 53%, treadmill: 58%) [18]. Subjects experienced greater arterial oxygen desaturation during treadmill compared to cycle exercise, with peak decreases of $-5.2\pm3.2\%$ and $-3.2\pm2.2\%$, respectively ($p=0.01$) (Figure 1).

**Cardiac responses.** Heart rate (HR) rose in a similar fashion between modalities throughout submaximal exercise but reached approximately 9 beats/min higher ($p<0.05$) at peak treadmill compared to peak cycle exercise (Table 3).
**TABLE 3. Measurements during symptom-limited incremental cycle and treadmill exercise**

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Peak</th>
<th>Cycle</th>
<th>Treadmill</th>
<th>Cycle</th>
<th>Treadmill</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Work rate, watts</td>
<td>0 ± 0</td>
<td>73 ± 20</td>
<td>78 ± 28</td>
<td>14:13 ± 01:15</td>
<td>15:05 ± 01:06</td>
</tr>
<tr>
<td></td>
<td>Exercise time, mm:ss</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
<td>14:13 ± 01:15</td>
<td>15:05 ± 01:06</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dyspnoea, Borg scale</td>
<td>0.1 ± 0.2</td>
<td>0.1 ± 0.2</td>
<td>6.6 ± 2.8</td>
<td>6.6 ± 2.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leg discomfort, Borg scale</td>
<td>0.1 ± 0.3</td>
<td>0.2 ± 0.3</td>
<td>6.6 ± 2.9</td>
<td>5.0 ± 2.7 ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VO₂, L/min</td>
<td>0.41 ± .14</td>
<td>0.42 ± .14</td>
<td>1.53 ± 0.40</td>
<td>1.79 ± 0.52</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VO₂, % predicted maximum</td>
<td>20.4 ± 6.7</td>
<td>20.5 ± 4.9</td>
<td>78.1 ± 25.7</td>
<td>90.7 ± 30.3 ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VCO₂, L/min</td>
<td>0.35 ± .12</td>
<td>0.34 ± .12</td>
<td>1.49 ± 0.39</td>
<td>1.65 ± 0.51 ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RER</td>
<td>0.84 ± .06</td>
<td>0.82 ± .09</td>
<td>0.98 ± .07</td>
<td>0.92 ± .10 ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VE, L/min</td>
<td>14.8 ± 4.2</td>
<td>15.1 ± 4.2</td>
<td>47 ± 10.8</td>
<td>49 ± 13.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VT, L</td>
<td>0.78 ± 0.21</td>
<td>0.85 ± 0.35</td>
<td>1.30 ± 0.34</td>
<td>1.34 ± 0.41</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fb, breaths/min</td>
<td>20 ± 5.3</td>
<td>20 ± 6.0</td>
<td>36 ± 6.1</td>
<td>37 ± 7.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T₁/TTOT</td>
<td>0.38 ± 0.05</td>
<td>0.38 ± 0.04</td>
<td>0.40 ± 0.04</td>
<td>0.41 ± 0.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IC, L</td>
<td>2.50 ± 0.75</td>
<td>2.44 ± 0.71</td>
<td>1.84 ± 0.37</td>
<td>1.79 ± 0.47</td>
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<tr>
<td></td>
<td>VT/IC, %</td>
<td>32.5 ± 9.9</td>
<td>34.6 ± 8.5</td>
<td>72.3 ± 11.1</td>
<td>74.6 ± 9.2</td>
<td></td>
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<tr>
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<td>IRV, L</td>
<td>1.73 ± .69</td>
<td>1.59 ± .48</td>
<td>0.51 ± .22</td>
<td>0.45 ± .18</td>
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<tr>
<td></td>
<td>EELV, L</td>
<td>3.31 ± 0.79</td>
<td>3.4 ± 0.79</td>
<td>3.97 ± 0.92</td>
<td>4.07 ± 0.94</td>
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<tr>
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<td>EILV, L</td>
<td>4.09 ± 0.82</td>
<td>4.30 ± 0.89</td>
<td>5.31 ± 1.12</td>
<td>5.42 ± 1.13 *</td>
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</tr>
<tr>
<td></td>
<td>EILV/TLC, %</td>
<td>70.7 ± 7.9</td>
<td>72.8 ± 6.1</td>
<td>91.1 ± 3.8</td>
<td>92.1 ± 3.5 *</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VE/MVV, %</td>
<td>29 ± 1</td>
<td>29 ± 1</td>
<td>90 ± 2</td>
<td>92 ± 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VE/VO₂</td>
<td>36.8 ± 5.0</td>
<td>37.1 ± 7.7</td>
<td>31.7 ± 6.1</td>
<td>28.0 ± 5.9 ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VE/VCO₂</td>
<td>43.9 ± 6.8</td>
<td>45.3 ± 7.7</td>
<td>32.4 ± 5.0</td>
<td>30.4 ± 4.8 ↓</td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>Cycle 1</td>
<td>Cycle 2</td>
<td>Cycle 3</td>
<td>Cycle 4</td>
<td></td>
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<tr>
<td>---------------------------</td>
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<td>---------</td>
<td>---------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P_{ET}CO_2, mmHg</td>
<td>34 ± 2.8</td>
<td>33 ± 3.8</td>
<td>37 ± 5.5</td>
<td>39 ± 6.0¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>77 ± 2.7</td>
<td>79 ± 10</td>
<td>119 ± 12.8</td>
<td>128 ± 14.6¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO_2, %</td>
<td>95 ± 1.8</td>
<td>95 ± 2</td>
<td>92 ± 2.7</td>
<td>90 ± 3.3¶</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD.

VO_2: oxygen uptake; VCO_2: carbon dioxide production; RER: respiratory exchange ratio; 
V_E: ventilation; V_T: tidal volume; F_b: breathing frequency; T_I/T_TOT: inspiratory duty cycle; IC: inspiratory capacity; IRV: inspiratory reserve volume; EELV: end-expiratory lung volume; EILV: end-inspiratory lung volume; V_E/VO_2: ventilatory equivalent for oxygen uptake; V_E/VCO_2: ventilatory equivalent for carbon dioxide production; P_{ET}CO_2: end-tidal partial pressure of carbon dioxide; HR: heart rate; SpO_2: arterial pulse oxygen saturation.

* p<0.05; # p=0.05; ¶ p< 0.01: cycle versus treadmill.
Figure 1. (a) Oxygen consumption ($\dot{V}O_2$), (b) carbon dioxide production ($\dot{V}CO_2$), (c) respiratory exchange ratio (RER), (d) minute ventilation ($\dot{V}E$), (e) the ventilatory equivalent for oxygen consumption ($\dot{V}E/\dot{V}O_2$), and (f) arterial oxygen saturation (SpO$_2$) are shown relative to work rate during cycle (closed circles) compared to treadmill (open squares). Values are means ± SEM. *p<0.05 cycle versus treadmill at a standardized work rate or at peak exercise.
**Ventilatory responses.** Ventilation ($\dot{V}_E$) was not different between test modalities at any given work rate (Figure 1). $\dot{V}_E/\dot{V}O_2$ was greater at all stages of cycle compared with treadmill exercise (Figure 1) but $\dot{V}_E/\dot{V}CO_2$ was only greater at 40 watts and at the peak of cycle exercise (Table 3) and $\dot{V}_E/\dot{V}CO_2$ slopes were similar (Figure 2). Breathing pattern and operating lung volumes were not statistically different at a given work rate or $\dot{V}_E$ (Figure 2) between modalities throughout exercise. Subjects reached critical respiratory-mechanical reserves at an EILV >90 %TLC and an inspiratory reserve volume (IRV) of approximately 0.5L during both exercise modalities at peak exercise (Table 3).

**Perceptual responses.** Dyspnoea intensity ratings at standardized work rates and at peak exercise were similar between modalities (Figure 3). Leg discomfort was also similar during exercise up to 40 watts but became significantly (p<0.05) greater at the peak of cycle compared with treadmill exercise (Figure 3). Relationships between dyspnoea intensity and both $\dot{V}_E$ and IRV were not different during cycle and treadmill exercise (Figure 3).
Figure 2. (a) The relationship between minute ventilation ($\dot{V}_E$) and carbon dioxide production ($\dot{V}CO_2$) was similar during cycle (closed circles) compared to treadmill (open squares). (b) tidal volume ($V_T$), (c) breathing frequency ($F_b$) and (d) operating lung volumes expressed relative to $V_E$ were also similar during cycle and treadmill exercise. TLC: total lung capacity; EELV: end-expiratory lung volume; EILV: end-inspiratory lung volume; IRV: inspiratory reserve volume. Values are means ± SEM.
Figure 3. Relationships between dyspnoea intensity and (a) work rate, (b) minute ventilation ($V_{E}$) and (d) inspiratory reserve volume (IRV) were similar during cycle (closed circles) compared to treadmill (open squares) exercise. (c) Intensity of leg discomfort relative to work rate was similar up to 40W then became significantly greater by peak exercise during cycle compared with treadmill exercise (*p<0.05). Values are means ± SEM.
3.5 DISCUSSION

The main findings of the study are as follows: 1) compared with cycle testing, treadmill testing was associated with a higher $\dot{V}O_2$, lower $\dot{V}E/\dot{V}O_2$, and greater oxyhemoglobin desaturation for a given work rate; 2) cycle testing was associated with a higher RER, earlier VTh and greater peak leg discomfort ratings; 3) ventilation, breathing pattern, operating lung volumes and dyspnoea intensity were similar at comparative work rates; and 4) despite physiological differences, exercise modality had no effect on the dyspnoea/work rate or dyspnoea/$\dot{V}E$ relations in obese patients with COPD.

Participants had mild to severe obesity with body weights in excess of ideal body weight by an average of 32.8 kg. DEXA scans confirmed increased adipose mass deposition compared to the average for age-matched individuals. The largely preserved IC and FRC likely reflects the known effects of increasing BMI on lung volume components in COPD [3,21]. Participants had moderate airway obstruction but surprisingly, average $D_LCO$ was diminished to 50% predicted (possibly reflecting underlying emphysema) in the absence of significant lung hyperinflation. Patients reported moderate chronic activity-related dyspnoea but had reasonably preserved cardiorespiratory fitness as assessed by peak $\dot{V}O_2$ relative to the predicted value based on ideal body weight.

The incremental exercise protocols were well matched for rate of increase in work rate and were of sufficient duration for accurate assessment of perceptual and physiological responses. Peak $\dot{V}O_2$ was significantly higher (by 17%) during treadmill
compared with cycle exercise (Figure 1), likely reflecting the larger skeletal muscle mass recruitment previously described in health [22]. Of note, patients had significant mechanical constraints on ventilation as evidenced by a low breathing reserve (high $\dot{V}_E$/MVV) and a high EILV/TLC ratio at relatively low peak work rates of 73 and 78 watts during cycle and treadmill, respectively. In contrast, participants had adequate cardiac reserve at peak exercise, reaching a mean heart rate of 72 and 77 % of the predicted maximum during cycle and treadmill tests, respectively.

3.5.1 The dyspnoea/work rate relation

A key finding of the present study was the similarity in dyspnoea/work rate relations during both exercise modalities. This indicates that differences in the metabolic cost of external work, $\dot{V}_E$/$\dot{V}$O$_2$, RER, VTh, oxyhemoglobin saturation, perceived leg discomfort and cardio-circulatory responses did not influence dyspnoea perception at a given power output during cycling and walking in obese COPD. The preserved dyspnoea/work rate relation ultimately reflected the between-test similarity in the $\dot{V}_E$, breathing pattern and operating lung volumes when the increase in work rate was carefully matched. It is remarkable that despite the differences in potential sources of ventilatory drive, $\dot{V}_E$ remained tightly coupled with “pulmonary” $\dot{V}$CO$_2$ regardless of the exercise modality. These findings are in line with those from on- and off-exercise kinetics studies where the time course of $\dot{V}_E$ has been found to closely follow the $\dot{V}$CO$_2$, and not $\dot{V}$O$_2$ or arterial partial pressure of oxygen [23].
3.5.2 The dyspnoea/ventilation relation

Our results show that the effective coupling of ventilation to the metabolic demand of comparable external work – expressed as \( \dot{V}CO_2 \) - is achieved by different mechanisms in cycling and treadmill tests. A higher RER (\( \dot{V}CO_2/\dot{VO}_2 \)) during cycling versus walking (or running) has been previously described in healthy individuals and may reflect preferential carbohydrate utilization with cycling [24]. We have previously shown that metabolic pathways in leg muscle are altered in COPD such that there is increased dependence on glycolysis and blood glucose utilization (rather than free fatty acid) compared with healthy individuals [25]. To what extent the higher RER in our obese COPD patients during cycling can be explained by preferential utilization of carbohydrate by the contracting leg muscles could not be determined in the current study. Regardless the mechanism(s), these muscle metabolic differences between cycling and walking are likely to have contributed to higher \( \dot{V}CO_2 \) (and \( \dot{V}E \)) for a given \( \dot{V}O_2 \) in the former modality.

The smaller locomotor muscle mass required to generate the same power output during cycling as walking means that the average metabolic rate per unit of contracting muscle mass is greater with cycling, which can force earlier metabolic acidosis [26]. Our findings of an earlier VT, increased \( \dot{V}E/\dot{VO}_2 \), preserved oxyhemoglobin saturation (at a given \( \dot{VO}_2 \)) and reduced peak \( P_{ET}CO_2 \) during cycling are consistent with the results of recent studies which additionally show relatively increased alveolar ventilation during cycling [10]. It remains possible (but unproven) that differential ventilatory stimulation
by mechanoreceptor/metaboreceptor activation (Type III and IV afferents) between active locomotor muscle groups (peculiar to the exercise test modality) may explain differences in $\dot{V}_E/\dot{V}O_2$ [27].

Despite the above-outlined differences in the sources of ventilatory stimulation during the two exercise modalities, perceived dyspnoea intensity was similar at comparable $\dot{V}_E$ in obese COPD. Based on previous studies, the dyspnoea/$\dot{V}_E$ relation during exercise in COPD is altered by change in dynamic respiratory mechanics but not by experimental manipulation of the central respiratory controller per se [28,29]. Thus, the preservation of the dyspnoea/$\dot{V}_E$ relation in the current study mainly reflects the similarities in operating lung volumes at a given $\dot{V}_E$ during cycling and walking, regardless of differences in metabolic loading and acid-base balance.

3.5.3 Limitations

Since dynamic respiratory mechanics and the extent of metabolic loading are different in normal weight COPD patients than in obese patients matched for airflow obstruction [3,30], the lack of effect of exercise modality on dyspnoea intensity seen in this study cannot be generalized to non-obese patients. The present study was performed in patients with moderate COPD and our results may not be generalized to more severe patients. However, we believe that given the close link of work to ventilation, dyspnoea/work rate and dyspnoea/ventilation relationships are likely to be similar across disease severity - if the work performed on different test modalities is closely matched, as in the current study. Measurements of blood lactate, arterial and mixed venous blood
gases would be required to better elucidate the observed between-test differences in RER and oxyhemoglobin saturation but this was not the main focus of the current study.

3.5.4 Conclusions/implications

Despite consistent task-specific differences in physiological derangements that can influence the central respiratory controller, perception of dyspnoea intensity was most closely linked to CO₂ output and the attendant ventilatory and dynamic respiratory mechanical response (Appendix 1). Dyspnoea/work rate and dyspnoea/$V_E$ relations were independent of exercise modality in obese COPD. Our results provide reassurance that either exercise modality can be selected for the reliable evaluation of dyspnoea in obese COPD patients, both in research and clinical settings. In obese COPD patients, the higher peak $VO_2$ and lower oxyhemoglobin saturation during treadmill exercise (compared with cycle) have potentially important implications for the individualized evaluation of cardiorespiratory fitness and pulmonary gas exchange abnormalities, respectively. Another important clinical implication of the results is that interventions that reduce CO₂ output (exercise training, energy substrate manipulation) during physical activity in obese COPD patients should effectively relieve exertional dyspnoea.

ACKNOWLEDGEMENTS: The authors wish to thank Daniel Langer and Amany Elbehairy for their assistance in determining ventilatory thresholds during exercise, and Ling Yang for her assistance with patient testing.
3.6 REFERENCES


3.7 ONLINE SUPPLEMENT

The influence of exercise modality on dyspnoea perception during cardiopulmonary exercise testing in obese patients with COPD

3.7.1 METHODS

Pulmonary function testing included routine spirometry, body plethysmography, single-breath diffusing capacity (Dl,CO) and maximum voluntary ventilation (MVV) using automated testing equipment (Vs62j body plethysmograph with Vmax229d; SensorMedics, Yorba Linda, CA) and was performed according to recommended techniques [1-3]. Cardiopulmonary exercise tests were performed according to recommended guidelines [4] on an electronically-braked cycle ergometer (Ergometrics 800S; SensorMedics, Yorba Linda, CA) and a treadmill (Medtrack ST55; Quinton Instrument, Bothell, WA) using a SensorMedics Vmax229d Cardiopulmonary Exercise Testing System.

Linearized incremental treadmill protocol

The rate of work (watts) done against gravity while walking up an incline depends on the subject’s absolute body weight, the walking speed and the grade [5]. Norman Jones [5] identified the following formula to quantify work done on the treadmill:

\[ WR(t) = m \times g \times v(t) \times \frac{AI}{100} \]
where $WR$ is the time course of work (watts) performed, $m$ is the absolute body mass in kilograms, $g$ is the acceleration due to gravity ($9.81 \text{ m/s}^2$), $v(t)$ is the time course of velocity in meters/sec, and $AI$ is the angle of inclination (or grade). Similarly, Cooper and Storer [6] estimate work performed on a treadmill as follows: watts = $0.1634 \times \text{speed (m/min)} \times (\% \text{ grade}/100) \times \text{body mass (kg)}$. This equation can then be rearranged to solve for $\%$ grade.

In this study, the external work performed during treadmill and cycle testing protocols was matched to allow accurate comparison of dyspnoea and physiological measurements at standardized work rates (and times): a linearized protocol with 10 watt increments increasing every 2 minutes in a stepwise fashion was used. Treadmill belt speed was selected to meet the subject’s functional abilities, limit biomechanical inefficiencies (with high treadmill belt speeds) [7] and create a linear rise over time. Similar to previous studies [8,9], treadmill belt speed was initiated at 0.8 miles per hour (mph) (0.36 m/s) during the first work rate (10 watts) and the subsequent linear rise in speed was kept constant for each subject (Figure 1). The belt speed increased progressively to 1.4 mph (0.63 m/s) at 40 watts and 2.2 mph (0.98 m/s) at 80 watts. Body weight varied between subjects; therefore, the inter-subject curvilinear rise in percent grade was different for each subject.
Figure 1. (a) Schematic diagram of the stepwise incremental treadmill protocol. (b) A linear rise in treadmill speed (open diamonds) and a curvilinear rise in grade (open squares) was individualized for each subject to match the protocol used during cycle testing, i.e., 2-min increments of 10 watts. (c) Each subject achieved a matched rise in work rate during cycle (closed circles) and treadmill (open squares) exercise.
The following table is a sample calculation of a representative male subject weighing 102 kg.

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Conversion factor: 0.1634 * 26.8224 (26.8224 m/min = 1 mph) = 0.043827801
3.7.2 RESULTS

Subjects

Subjects reported the following comorbidities: hypertension (n=5), diabetes mellitus (n=5), hypercholesterolemia (n=3), obstructive sleep apnea (n=3), arthritis (n=3), anxiety (n=4) and depression (n=2). Three subjects reported past myocardial infarction, although five had reported coronary intervention (coronary bypass graft: n=3; stents: n=2). The degree of obesity ranged from mild to severe (BMI 30-51 kg/m$^2$) [10]: there were eight class I (30-34.9 kg/m$^2$), seven class II (35-39.9 kg/m$^2$) and three class III (>40 kg/m$^2$) obese subjects.

Responses to cycle and treadmill exercise

Selected exercise responses are shown relative to oxygen consumption ($\dot{V}O_2$) during treadmill and cycle testing (Figure 2).
Figure 2. Selected exercise responses are shown relative to $\dot{V}O_2$ during treadmill (open squares) compared to cycle testing (closed circles). There was no difference between test modalities for: (a) heart rate, (b) arterial oxygen saturation measured by pulse oximetry ($\text{SpO}_2$), (c) ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}\text{CO}_2$) (d) partial pressure of end-tidal CO$_2$ ($P_{ETCO_2}$), but significant differences (*p<0.01) in cycle versus treadmill at a standardized $\dot{V}O_2$ of 1 L/min for: (e) carbon dioxide output ($\dot{V}\text{CO}_2$) and (f) respiratory exchange ratio (RER). Data are shown as means ± SEM.
3.7.3 REFERENCES


3.8 Appendix 1

In clinical practice, dyspnea assessments are based on estimating the magnitude of the physical task (e.g., stair climbing) the patient can undertake before having to stop because of dyspnea. Most validated dyspnea questionnaires incorporate “magnitude of task” evaluations (e.g., Medical Research Council dyspnea scale and Baseline Dyspnea Index). However, when studying mechanisms of dyspnea in the laboratory, it is important to additionally consider the inter-relationships between external power output, $\dot{V}O_2$ and $\dot{V}CO_2$ and how these can vary during different exercise modalities. It is also important to understand these relationships in order to be able to standardize the stimulus for comparative or interventional studies evaluating dyspnea responses. Our results indicate that inter-modality differences may exist in relationships between internal power output of the various muscles of locomotion (which is impossible to measure), net external power output, and the concomitant metabolic/chemical stimuli of the central respiratory controller (arguably the most relevant dyspneogenic stimulus) and this potentially has implications for understanding the origins of dyspnea. This is especially true in obese subjects where the metabolic consequences of weight-bearing versus weight-supported exercise are likely to be exaggerated compared with lean individuals.

By standardizing external power output between cycling and walking, we observed the expected upward parallel shift in the $\dot{V}O_2$/work rate relation during treadmill exercise (Figure 1a, pg 35). This likely reflects recruitment of a larger muscle mass during weight-bearing walking where the skeletal muscles are involved in both locomotor and body stabilization functions. During cycling, the quadriceps muscles are the dominant locomotor muscles engaged in the task.

A between-test comparison of $\dot{V}CO_2$/$\dot{V}O_2$ slopes (Figure 2e, pg 52) reveals that during cycling $\dot{V}CO_2$ production is relatively higher compared with walking. As already mentioned, the
disparity in $\dot{V}O_2$ and $\dot{V}CO_2$ (and RER) during cycling versus treadmill may be explained, at least in part, by differences in energy substrate utilization when the quadriceps muscles are selectively stressed in this manner. Changes in glycolytic pathways and fiber-type composition have been shown in leg muscle biopsies of COPD patients and, collectively, may lead to preferential carbohydrate utilization as an energy substrate during cycling (Green HJ et al. 2008). Additionally, the earlier anaerobic threshold during cycling was likely associated with increased bicarbonate buffering and increased $\dot{V}CO_2$ in the later stages of exercise.

To the extent that the proximate stimulus of ventilation (and therefore dyspnea) during exercise is the change in the metabolic and acid base status (rather than external power output, *per se*), it can be argued that comparisons of physiological and sensory parameters in mechanistic studies of dyspnea are best conducted at standardized metabolic loads rather than external power output. Our results showed that when comparisons were conducted at a given $\dot{V}O_2$, dyspnea intensity was increased to a greater extent during cycling than during walking (Figure 1c). Thus, at a standardized $\dot{V}O_2$ of 1 L/min during cycling, dyspnea ratings were significantly higher (by one Borg unit) in association with a concomitant increases in $\dot{V}CO_2$ by 0.13 L/min and $V_E$ by 4 L/min, and reduction in IRV by 0.15 L (Figure 1). It must be emphasized that, in absolute terms, Borg dyspnea ratings (1-2 units) at a submaximal $\dot{V}O_2$ during cycling represent only “very weak/slight/light” or “weak/slight/light” respiratory discomfort that is of questionable clinical significance (Figure 1c). Nevertheless, increases in dyspnea with cycling (compared with treadmill) at the highest exercise intensities are worthy of explanation.

It is noteworthy that when such sensory and physiological comparisons are made at a standardized $\dot{V}CO_2$ - the true proximate determinant of ventilatory output - differences in dyspnea intensity are much less and $V_E/\dot{V}CO_2$ and IRV/$\dot{V}CO_2$ are superimposed during cycling and
walking (Figure 1 d&e). Thus, \( \dot{V}CO_2 \) and not \( \dot{V}O_2 \) is the primary metabolic perturbation that determines the level of dyspnea, regardless of the exercise modality. Collectively, this analysis supports our contention that dyspnea/\( \dot{V}_E \) and dyspnea/IRV relations are independent of the oxygen uptake associated with the task but closely track \( \dot{V}CO_2 \). A major clinical implication is that interventions that reduce \( \dot{V}CO_2 \) production for a given work rate, such as manipulation of energy substrate utilization or exercise training (which reduces metabolic acidosis), should successfully relieve exertional dyspnea in obese COPD.
Figure 1. a) Ventilation (\(\dot{V}_E\)), b) inspiratory reserve volume (IRV) and c) dyspnea are expressed relative to oxygen uptake (\(\dot{V}O_2\)) during cycle and treadmill exercise. During cycle exercise, \(\dot{V}_E\) and dyspnea was higher at an iso-\(\dot{V}O_2\) of 1 L/min and IRV was reduced compared to treadmill. d) \(\dot{V}_E\), e) IRV and f) dyspnea were similar when expressed relative carbon dioxide output (\(\dot{V}CO_2\)). Data are shown as means ± SEM.

REFERENCES

Chapter 4

Do differences in respiratory muscle activity during cycling and walking influence dyspnea perception in obese patients with COPD?
4.1 ABSTRACT

In patients with combined obesity and chronic obstructive pulmonary disease (COPD), dyspnea intensity at matched work rates during weight-supported cycling and weight-bearing walking is similar, despite consistent metabolic differences between test modalities. The current study examined the influence of differences in activity of the diaphragm and abdominal muscles during cycling and walking on intensity and quality of dyspnea at matched ventilation in obese patients with COPD.

We compared respiratory muscle activity patterns and dyspnea ratings during incremental cycle and treadmill exercise tests, where work rate was matched, in twelve obese (body mass index 36.6±5.4kg/m²; mean±SD) patients with moderate COPD. We used a multi-pair electrode-balloon catheter to compare electromyography of the diaphragm and esophageal, gastric and trans-diaphragmatic pressures during the two exercise tests.

Ventilation, breathing pattern, operating lung volumes, global respiratory effort and electrical activation of the diaphragm were similar across exercise modalities for a given work rate. The cycling position was associated with greater neuromuscular efficiency of the diaphragm (p<0.01), greater diaphragm use (p<0.01) measured by the ventilatory muscle recruitment index and less expiratory muscle activity compared (p<0.01) to treadmill walking. However, intensity and quality of dyspnea were similar between exercise modalities.
In obese patients with COPD, altered respiratory muscle activity due to body position differences between cycling and walking did not modulate perceived dyspnea when indirect measures of respiratory neural drive were unchanged.
4.2 INTRODUCTION

The prevalence of both COPD and obesity is increasing at an alarming rate throughout the world (10). In patients with combined COPD and obesity, activity-related dyspnea is a major symptom and likely contributes to poor health-related quality of life. Dyspnea in obese patients with COPD is multifactorial and we have argued that increased metabolic requirements related to excessive body weight, which drive increased ventilation during physical activity, are more important than respiratory mechanical factors, per se, in contributing to exertional dyspnea (25,33). This is true regardless of exercise test modality (cycling versus walking) where the sources and magnitude of ventilatory stimulation (metabolic and acid-base abnormalities) are known to be different at matched work rates (6).

Several studies have established that dyspnea intensity ratings during standardized exercise tests in COPD correlate strongly with increasing respiratory neural drive, as indirectly assessed by increasing ventilation ($\dot{V}_E$), tidal esophageal pressures (Pes) and electrical activation of the diaphragm (EMGdi), when each is expressed as a fraction of its respective maximum (11,14,22,35). It is also believed that dyspnea intensity, or its dominant qualitative dimensions, is modulated by altered afferent inputs from peripheral sensory receptors in the lungs, respiratory muscles and chest wall (27,29,32). The current study further explores the potential impact of differences in afferent sensory inputs, which may arise from differences in respiratory muscle activity during cycling versus walking, on the intensity and quality of dyspnea in patients with COPD and obesity.
We reasoned that in patients with COPD with abdominal obesity, diaphragmatic function would be compromised by standing (and walking) despite compensatory adjustments in expiratory muscle activity to maintain abdominal compliance compared with weight-supported sitting (and cycling)\(^{(7,18,19,21)}\). Furthermore, we postulated that the attendant alterations in afferent activity from respiratory muscle mechanoreceptors during walking would influence the intensity and quality of dyspnea at a given ventilation. To test these hypotheses, we compared ventilation, breathing pattern, operating lung volumes, esophageal and transdiaphragmatic pressures, diaphragmatic efficiency and intensity and quality of dyspnea during incremental treadmill and cycle exercise when work rate was carefully matched.
4.3 METHODS

4.3.1 Subjects

Twelve clinically stable obese (body mass index (BMI) >30 kg/m²) patients with COPD (FEV₁/FVC <70%) and a post-bronchodilator FEV₁ <80% predicted were included. Exclusion criteria included: a significant disease (i.e. metabolic, cardiovascular, neuromuscular and/or musculoskeletal) which could affect breathlessness or exercise capacity, daytime oxygen therapy, a respiratory disease other than COPD, too breathless to leave the house or not breathless (Medical Research Council (MRC) dyspnea scale 5 or 1, respectively), and any contraindications to clinical exercise testing (3).

4.3.2 Study Design

This cross-sectional study received ethical approval from Queen’s University and Affiliated Hospitals Research Ethics Board (DMED-1187-09). Patients attended 3 visits separated by at least 48 hours. Visit 1 included medical screening, detailed pulmonary function tests, and familiarization with all exercise testing procedures. At visits 2 and 3, patients were randomized to perform either a cycle or treadmill test with detailed EMGdi and pressure-derived respiratory mechanical measurements. Before each visit, patients were instructed to withhold inhaler medication at least 4 hours for short-acting β₂-agonists, 6 hours for anticholinergics and 12 hours for long-acting bronchodilators. Patients were asked to refrain from the intake of caffeine, heavy meals, alcohol and from major physical exertion prior to each visit. At a separate visit, patients underwent dual-energy x-ray absorptiometry (DEXA) scans to quantify body composition.
4.3.3 Procedures

Pulmonary function testing included routine spirometry, body plethysmography, single-breath diffusing capacity for carbon monoxide (DL\textsubscript{CO}), maximum inspiratory and expiratory mouth pressures, static lung compliance (C\textsubscript{Lst}) and static lung recoil pressure (P\textsubscript{Lst}) using automated testing equipment (Vs62j body plethysmograph with Vmax229d; SensorMedics, Yorba Linda, CA). Cardiopulmonary exercise tests were performed on an electronically braked cycle ergometer (Ergometrics 800S; SensorMedics, Yorba Linda, CA) and on a treadmill (MedTrack ST55; Quinton Instrument, Bothell, WA) using a Vmax229d Cardiopulmonary Exercise Testing System (SensorMedics). Cycle and treadmill exercise tests were both performed with 10-watt increments, which increased every two minutes to a symptom-limited peak. The work rate was matched between cycle and treadmill exercise as previously described in detail (6). Breath-by-breath data (cardiopulmonary, EMGdi and respiratory-mechanical measurements) were analyzed using 30-s averages from each individual at steady-state rest, the first 30-s interval of the last minute from each exercise work rate and the last 30-s of loaded pedaling (peak). Inspiratory capacity (IC) maneuvers were performed during the steady-state resting period, during the last 30-s of each exercise work rate and at peak exercise. Operating lung volumes were derived from IC measurements as previously described (31). Subjects rated “breathing discomfort,” “leg discomfort,” “work or effort of breathing,” “difficulty breathing in” and “how unpleasant or bad is your breathing” on a modified 10-point
Borg scale at rest, every two minutes of exercise and at peak exercise (4). Immediately after exercise, subjects were asked why they stopped exercising.

4.3.4 Diaphragm EMG and Respiratory Pressures

A combined EMGdi electrode catheter with esophageal and gastric balloons was inserted nasally and positioned as previously described (17). The raw EMGdi signal was sampled at 2000 Hz (PowerLab, model ML880; ADInstruments, CastleHill, NSW, Australia) then amplified and band-pass filtered between 20-1000 Hz (Bioamplifier model RA-8; Guangzhou Yinghui Medical Equipment Co. Ltd, Guangzhou, China). This signal was converted to a root mean square and averaged during inspiration between cardiac QRS complexes using a 100ms time constant and a moving window. The largest value from the five electrode pairs was representative of each inspiration. The highest EMGdi value from either resting/peak sniff maneuvers or resting and exercise IC measurements was used as the maximum EMGdi (EMGdi,max).

The esophageal and gastric balloons were inflated with 1.0 mL and 1.2 mL of air, respectively, and connected to differential pressure transducers (model DP15-34; Validyne Engineering, Northridge, CA, USA); two-point calibration of pressures was performed. Esophageal (Pes) and gastric pressures (Pga) were continuously recorded at a rate of 200 Hz (PowerLab). Transdiaphragmatic pressure (Pdi) was recorded as the difference between Pga and Pes signals. The PowerLab system received continuous flow signal input from the Vmax229d cardiopulmonary testing system for offline analysis.
Pre- and post-exercise inspiratory sniffs (sn) were performed to obtain maximum Pes (Pes,sn) and Pdi (Pdi,sn). IC maneuvers at rest and throughout exercise were used to obtain dynamic peak inspiratory Pes (Pes,IC) and Pdi (Pdi,IC). Pre- and post-exercise FVC maneuvers were also performed to obtain dynamic peak expiratory Pes (Pes,FVC). Tidal Pes swings (Pes,tidal) were defined as the amplitude between the maximum expiratory value (Pes,exp) and minimum inspiratory value (Pes,insp) for each respiratory cycle, and expressed relative to maximum Pes (Pes,max: difference between Pes,IC and Pes,FVC). Similarly, tidal Pdi swings (Pdi,tidal) were defined as the excursion between maximum inspiratory (Pdi,insp) and minimum Pdi during expiration. The inspiratory rise in Pdi (Pdi,insp.rise) was defined as the increase in Pdi from the onset of inspiratory flow to peak Pdi during inspiration. The peak tidal expiratory Pga (Pga,exp) and expiratory rise in Pga (Pga,exp.rise), which is the increase in Pga from the lowest point after onset of expiratory flow to its peak value during expiration, were used to estimate expiratory muscle activation (40). End-inspiratory (EI) and end-expiratory (EE) data points of zero flow for Pes and Pga were collected. The ventilatory muscle recruitment (VMR) index was calculated as the difference between Pga,EI and Pga,EE divided by the difference between Pes,EI and Pes,EE (24): a negative value represents greater diaphragm contribution and a positive value represents a greater ribcage muscle contribution to inspiration. Finally, neuromuscular efficiency of the diaphragm was defined as the relation between inspiratory rise Pdi (Pdi,insp.rise) and EMGdi/EMGdi,max.
4.3.5 **Statistical Analysis**

A sample size of less than 12 (i.e., n=11) previously provided sufficient power to detect a within-group difference in dyspnea under two conditions (18). Comparisons of exercise modalities were made at rest, at standardized work rates (i.e., 10, 20, 30 and 40 watts) and at peak exercise using paired two-tailed t-tests. Linear interpolation was used to calculate Pdi,insp.rise for both tests at common levels of EMGdi/EMGdi,max (i.e., 30, 40 and 50 %). A two-way ANOVA for repeated measures was used to analyze measurements of respiratory muscle strength pre- and post-exercise across test modalities. To evaluate the relationship between dyspnea intensity (dependent variable) and relevant independent variables during exercise, the following were included in a multivariable linear regression model: the independent variable of interest, exercise modality as a categorical effect, an interaction term to determine whether the relationship being tested was similar across test modality (independent variable*modality), and subjects were treated as random effects to account for serial measurements (subject nested within modality). Results are reported as means ± SD.
4.4 RESULTS

Subject characteristics and resting pulmonary function are presented in Table 1. The mean BMI fell within the Class II obesity classification which is associated with a “very high disease risk” when combined with a waist circumference >88cm in women and >102cm in men (39). Waist circumference was elevated by 22cm in males and 25cm in females relative to previously defined abdominal obesity criteria (12,39). DEXA scans were available in 9 subjects and revealed that males (n=4) and females (n=5) had a similar mean percentage of total body fat (40 and 42 %, respectively) and truncal fat (45 and 42 %, respectively) (Table 1).

4.4.1 Exercise Responses

Steady-state rest and peak exercise responses are reported in Table 2. Patients exercised to a peak work rate of 73±17 watts on the cycle ergometer and 78±22 watts on the treadmill (p=0.27). Exercise duration was longer on the treadmill compared with the cycle ergometer by a mean difference of 67 seconds but was not significantly different (p=0.17). Peak oxygen uptake (\(\dot{V}O_2\)) during treadmill exercise was significantly higher compared to cycle exercise. \(\dot{V}E\) was similar at a given work rate (Figure 1) and carbon dioxide production (\(\dot{V}CO_2\)), and reached a similar peak value (Table 2) for both exercise modalities. For any given ventilation during exercise, both exercise modalities had similar EMGdi/EMGdi,max, global respiratory muscle effort (Pes,tidal in absolute terms and relative to Pes,max), breathing pattern and operating lung volumes (Figure 1).
Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male : Female, n</td>
<td>6 : 6</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>67 ± 8</td>
</tr>
<tr>
<td>Height, cm</td>
<td>167 ± 9</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>103 ± 25</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>36.6 ± 5.4</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>134 ± 9</td>
</tr>
<tr>
<td>Female</td>
<td>113 ± 7</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.05 ± 0.07</td>
</tr>
<tr>
<td>Female</td>
<td>0.92 ± 0.07</td>
</tr>
<tr>
<td>Total body fat*, %</td>
<td>41 ± 2</td>
</tr>
<tr>
<td>Male (n=4)</td>
<td>40 ± 2</td>
</tr>
<tr>
<td>Female (n=5)</td>
<td>42 ± 3</td>
</tr>
<tr>
<td>Truncal fat mass*, % total trunk mass</td>
<td>43 ± 5</td>
</tr>
<tr>
<td>Male (n=4)</td>
<td>45 ± 5</td>
</tr>
<tr>
<td>Female (n=5)</td>
<td>42 ± 5</td>
</tr>
<tr>
<td>Smoking history, pack-years</td>
<td>49 ± 35</td>
</tr>
<tr>
<td>Baseline Dyspnea Index, 0-12</td>
<td>6.5 ± 2.0</td>
</tr>
<tr>
<td>MRC dyspnea scale, 0-5</td>
<td>2.5 ± 0.8</td>
</tr>
<tr>
<td><strong>Pulmonary Function:</strong></td>
<td></td>
</tr>
<tr>
<td>FEV₁, L (% predicted)</td>
<td>1.43 ± 0.44 (60 ± 13)</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>50 ± 11</td>
</tr>
<tr>
<td>TLC, L (% predicted)</td>
<td>5.67 ± 1.24 (98 ± 10)</td>
</tr>
<tr>
<td>IC, L (% predicted)</td>
<td>2.37 ± 0.85 (89 ± 22)</td>
</tr>
<tr>
<td>FRC, L (% predicted)</td>
<td>3.30 ± 0.83 (105 ± 20)</td>
</tr>
<tr>
<td>Measure</td>
<td>Value</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>RV, L (% predicted)</td>
<td>2.77 ± 0.73 (126 ± 29)</td>
</tr>
<tr>
<td>ERV, L (% predicted)</td>
<td>0.54 ± 0.28 (61 ± 35)</td>
</tr>
<tr>
<td>sRaw, cmH\textsubscript{2}O•s (% predicted)</td>
<td>16.7 ± 7.9 (397 ± 177)</td>
</tr>
<tr>
<td>D\textsubscript{L}CO, mL\textsuperscript{-1}•min\textsuperscript{-1}•mmHg\textsuperscript{-1} (% predicted)</td>
<td>11.4 ± 4.6 (46 ± 10)</td>
</tr>
<tr>
<td>MIP, cmH\textsubscript{2}O (% predicted)</td>
<td>68 ± 27 (89 ± 36)</td>
</tr>
<tr>
<td>MEP, cmH\textsubscript{2}O (% predicted)</td>
<td>138 ± 56 (81 ± 22)</td>
</tr>
<tr>
<td>C\textsubscript{Lst}, L/cmH\textsubscript{2}O</td>
<td>0.27 ± 19</td>
</tr>
<tr>
<td>P\textsubscript{Lst}, cmH\textsubscript{2}O</td>
<td>20 ± 6</td>
</tr>
</tbody>
</table>

Values are means ± SD unless otherwise noted. MRC: Medical Research Council; FEV\textsubscript{1}: forced expired volume in 1 second; FVC: forced vital capacity; TLC: total lung capacity; IC: inspiratory capacity; FRC: functional residual capacity; RV: residual volume; ERV: expiratory reserve volume; sRaw: specific airway resistance; D\textsubscript{L}CO: diffusing capacity of the lung for carbon monoxide; MIP: maximal inspiratory pressure measured at FRC; MEP: maximal expiratory pressure measured at TLC; C\textsubscript{Lst}: static lung compliance; P\textsubscript{Lst}: static lung recoil pressure.

* Measurements obtained by DEXA scan.
## Table 2. Cardiopulmonary measurements during rest and peak exercise

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cycle</td>
<td>Treadmill</td>
</tr>
<tr>
<td><strong>Work rate, watts</strong></td>
<td>0 ± 0</td>
<td>0 ± 0</td>
</tr>
<tr>
<td><strong>Exercise time, mm:ss</strong></td>
<td>0 ± 0</td>
<td>0 ± 0</td>
</tr>
<tr>
<td><strong>Dyspnea, Borg scale</strong></td>
<td>0.1 ± 0.2</td>
<td>0.2 ± 0.2</td>
</tr>
<tr>
<td><strong>Leg discomfort, Borg scale</strong></td>
<td>0.2 ± 0.3</td>
<td>0.2 ± 0.4</td>
</tr>
<tr>
<td><strong>VO₂, L/min</strong></td>
<td>0.44 ± 0.14</td>
<td>0.43 ± 0.17</td>
</tr>
<tr>
<td><strong>VO₂, % predicted</strong></td>
<td>23 ± 6</td>
<td>21 ± 10</td>
</tr>
<tr>
<td><strong>VCO₂, L/min</strong></td>
<td>0.37 ± 0.12</td>
<td>0.34 ± 0.13</td>
</tr>
<tr>
<td><strong>RER</strong></td>
<td>0.83 ± 0.05</td>
<td>0.81 ± 0.11</td>
</tr>
<tr>
<td><strong>VE, L/min</strong></td>
<td>15.6 ± 3.7</td>
<td>14.9 ± 4.5</td>
</tr>
<tr>
<td><strong>VE/VCO₂</strong></td>
<td>43.9 ±6.0</td>
<td>44.9 ± 8.1</td>
</tr>
<tr>
<td><strong>VT, L</strong></td>
<td>0.81 ± 0.24</td>
<td>0.81 ± 0.10</td>
</tr>
<tr>
<td><strong>Fb, breaths/min</strong></td>
<td>21 ± 5</td>
<td>20 ± 6</td>
</tr>
<tr>
<td><strong>Tᵢ/TTOT</strong></td>
<td>38 ± 5</td>
<td>37 ± 4</td>
</tr>
<tr>
<td><strong>IC, L</strong></td>
<td>2.38 ± 0.80</td>
<td>2.37 ± 0.79</td>
</tr>
<tr>
<td><strong>IRV, L</strong></td>
<td>1.57 ± 0.69</td>
<td>1.56 ± 0.55</td>
</tr>
<tr>
<td><strong>Heart rate, beats/min</strong></td>
<td>80 ± 8</td>
<td>80 ± 7</td>
</tr>
<tr>
<td><strong>SpO₂, %</strong></td>
<td>95 ± 2</td>
<td>95 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SD. VO₂: oxygen uptake; VCO₂: carbon dioxide production; RER: respiratory exchange ratio; VE: ventilation; VE/VCO₂: ventilatory equivalent for carbon dioxide production; VT: tidal volume; Fb: breathing frequency; TI/TTOT: inspiratory duty cycle; IC: inspiratory capacity; IRV: inspiratory reserve volume; HR: heart rate; SpO₂: arterial pulse oxygen saturation.

* p<0.05 treadmill versus cycle exercise at peak exercise.
Fig 1. For a given work rate, ventilation ($V_E$) was similar between cycle and treadmill exercise. Electrical activation of the diaphragm (EMGdi), esophageal pressure (Pes) swings (inspiration upward), tidal volume ($V_T$), breathing frequency ($f_b$) and operating lung volumes were similar between exercise modalities and are shown relative to $V_E$. IRV: inspiratory reserve volume; EILV: end-inspiratory lung volume; EELV: end-expiratory lung volume; TLC: total lung capacity; Pes,IC: maximum inspiratory Pes during an IC maneuver. Data presented are mean±SEM. *p<0.05 cycle vs treadmill at peak exercise.
4.4.2 **Inspiratory Muscles**

Raw data tracing of a representative patient is shown in Figure 2 at a work rate of 30 watts with similar $\dot{V}_E$ (cycle: 24 L/min; treadmill: 26 L/min) illustrating differences in Pga, Pdi and the VMR (two panels include the same scale). Indices of inspiratory muscle strength were not significantly different across modalities for pre- and post-exercise measurements when analyzed by two-way repeated measures ANOVA; however, post-exercise Pdi,IC and Pdi,sn decreased significantly from pre-exercise values with both modes of exercise (Table 3). Pes,insp in absolute terms or relative to Pes,IC was similar during exercise under both conditions (Figure 1, Table 3). Pdi,insp was greater throughout cycle exercise compared to treadmill exercise (Figure 3); however, inspiratory diaphragmatic effort (Pdi,insp/Pdi,IC) was similar between both exercise conditions due to a concurrent increase in Pdi,IC during cycle exercise. Pdi,insp.rise was also significantly greater during cycling compared with treadmill exercise (Figure 3). Furthermore, the downward displacement of the VMR index during cycling indicates greater use of the diaphragm at rest and at any given work rate compared with treadmill exercise (Figure 3). Interpolated values of Pdi,insp.rise at standardized EMGdi/EMGdi,max of 30, 40 and 50 % were greater during cycle compared to treadmill exercise, indicating increased diaphragm efficiency during cycling (Figure 4).

4.4.3 **Expiratory Muscles**

There was greater abdominal expiratory muscle activity during treadmill compared with cycle exercise as shown by a greater Pga,exp.rise throughout exercise and by a
Fig 2. Raw data tracings for a representative female patient show mechanical measurements at the 30 watt load of cycle and treadmill exercise. The tracing shows similar ventilations (cycle: 24 L/min treadmill: 26 L/min) but different ventilatory muscle recruitment index (cycle: -0.67; treadmill: 0.45). Black circles (●) represent points of zero flow and connecting bars represent Pga and Pes slopes for the ventilatory muscle recruitment index calculation. Pes: esophageal pressure; Pga: gastric pressure; Pdi: transdiaphragmatic pressure; Expir: expiration; Inspir: inspiration.
Table 3. Respiratory mechanical measurements during rest and peak exercise

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Peak</th>
<th>Rest</th>
<th>Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cycle</td>
<td>Treadmill</td>
<td>Cycle</td>
<td>Treadmill</td>
</tr>
<tr>
<td>Pdi,sn, cmH₂O</td>
<td>88.4 ± 19.6</td>
<td>89.5 ± 24.5</td>
<td>74.7 ± 22.6</td>
<td>65.0 ± 24.8</td>
</tr>
<tr>
<td>Pdi,IC, cmH₂O</td>
<td>68.3 ± 23.6</td>
<td>62.0 ± 18.8</td>
<td>49.7 ± 15.4</td>
<td>38.8 ± 10.2</td>
</tr>
<tr>
<td>Pes,tidal, cmH₂O</td>
<td>9.8 ± 3.6</td>
<td>10.4 ± 4.7</td>
<td>38.3 ± 17.8</td>
<td>37.9 ± 16.3</td>
</tr>
<tr>
<td>Pes,tidal, %Pes,max</td>
<td>9.8 ± 3.3</td>
<td>10.0 ± 4.4</td>
<td>37.9 ± 17.2</td>
<td>36.1 ± 15.8</td>
</tr>
<tr>
<td>VMR index</td>
<td>-0.6 ± 0.8</td>
<td>-0.1 ± 0.8*</td>
<td>0.5 ± 0.6</td>
<td>1.2 ± 0.4*</td>
</tr>
<tr>
<td>EMGdi/EMGdi,max, %</td>
<td>18 ± 10</td>
<td>19 ± 9</td>
<td>64 ± 14</td>
<td>72 ± 13 *</td>
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<td><strong>Inspiratory muscle activity:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pes,insp, cmH₂O</td>
<td>-7.5 ± 2.2</td>
<td>-6.4 ± 3.4</td>
<td>-16.1 ± 2.2</td>
<td>-15.1 ± 5.2</td>
</tr>
<tr>
<td>Pes,insp, %Pes,IC</td>
<td>28 ± 10</td>
<td>22 ± 8</td>
<td>60 ± 16</td>
<td>71 ± 15</td>
</tr>
<tr>
<td>Pdi,insp, cmH₂O</td>
<td>26.7 ± 5.6</td>
<td>24.5 ± 4.9</td>
<td>34.1 ± 7.1</td>
<td>28.9 ± 5.4*</td>
</tr>
<tr>
<td>Pdi,insp, %Pdi,IC</td>
<td>42 ± 15</td>
<td>43 ± 14</td>
<td>71 ± 13</td>
<td>74 ± 10</td>
</tr>
<tr>
<td>Pdi,insp.rise, cmH₂O</td>
<td>10.0 ± 3.9</td>
<td>8.0 ± 2.8*</td>
<td>11.5 ± 6.1</td>
<td>8.3 ± 3.9*</td>
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<tr>
<td><strong>Expiratory muscle activity:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pes,exp, cmH₂O</td>
<td>2.3 ± 2.8</td>
<td>4.0 ± 2.3*</td>
<td>22.2 ± 15.2</td>
<td>22.8 ± 13.1</td>
</tr>
<tr>
<td>Pga,exp, cmH₂O</td>
<td>20.2 ± 4.9</td>
<td>19.7 ± 4.3</td>
<td>37.0 ± 17.8</td>
<td>37.5 ± 13.7</td>
</tr>
<tr>
<td>Pga,exp rise, cmH₂O</td>
<td>2.3 ± 1.6</td>
<td>3.4 ± 2.5</td>
<td>22.3 ± 17.8</td>
<td>27.0 ± 16.6*</td>
</tr>
<tr>
<td>Pga,EE, cmH₂O</td>
<td>19.5 ± 5.0</td>
<td>18.2 ± 4.6</td>
<td>17.7 ± 6.2</td>
<td>10.1 ± 4.2*</td>
</tr>
<tr>
<td>Pga,EE, cmH₂O</td>
<td>16.6 ± 3.3</td>
<td>16.0 ± 6.8</td>
<td>26.8 ± 8.5</td>
<td>27.4 ± 6.9</td>
</tr>
</tbody>
</table>

Values are means ± SD. See text for abbreviations.
*p<0.05 treadmill versus cycle exercise at that measurement point.
Fig 3. Transdiaphragmatic pressure (Pdi), Pdi inspiratory rise (Pdi,insp.rise), ventilatory muscle recruitment (VMR) index, gastric pressure at zero flow (Pga,zero flow), expiratory gastric rise (Pga,exp.rise) and expiratory muscle activity are shown relative to work rate. Pdi,IC: maximum Pdi during an IC maneuver; Pga,EE: gastric pressure at end-expiratory; Pga, EI: gastric pressure at end-inspiration. Data presented are mean±SEM. *p<0.05 cycle vs treadmill at a given work rate or at peak exercise.
Fig 4. The inspiratory rise of transdiaphragmatic pressure (Pdi,insp.rise) is shown relative to electrical activation of the diaphragm (EMGdi/EMGdi,max). Pdi,insp.rise at 30, 40, 50 EMGdi/EMGdi,max and at peak exercise was significantly greater during cycle compared with treadmill exercise (*p<0.05). Data presented are mean±SEM.
greater proportion of subjects exhibiting a Pga,exp.rise at rest and early in exercise (Figure 2). Pga,EE was similar during both modes of exercise, while Pga,El fell to a significantly greater extent during treadmill walking compared to cycling (Figure 3).

4.4.4 Exertional Dyspnea

Subjects reported similar intensity of “breathing discomfort” (Figure 5), “work/effort of breathing,” “difficulty breathing in” and “unpleasantness of breathing” during submaximal and symptom-limited peak exercise for both modalities. Breathing discomfort, alone or in combination with leg discomfort, was reported as the main reason for stopping exercise in 58% of cycle tests and in 83% of treadmill tests. Qualitative descriptors of breathlessness at end-exercise were similar between modalities. Dyspnea increased similarly in both tests as a function of increasing $\dot{V}_E$, EMGdi/EMGdi,max, and Pes,tidal/Pes,max throughout exercise (Figure 5). Dyspnea intensity during exercise correlated strongly with $\dot{V}_E$/MVV, Pes,tidal/Pes,max and EMGdi/EMGdi,max (all $p<0.0005$); these relationships were similar across testing modality.
Fig 5. Relationship between dyspnea and ventilation ($\dot{V}_E$), percent maximum electrical activation of the diaphragm (EMGdi/EMGdi max), percent maximum tidal esophageal pressure was similar between cycle and treadmill exercise. Unpleasantness relative to $\dot{V}_E$ was also similar. Data presented are mean±SEM. *p<0.05.
4.5 DISCUSSION

The novel findings of this study were: 1) COPD patients with abdominal adiposity had greater diaphragmatic efficiency and less expiratory muscle activity when cycling compared with walking; and 2) differences in body position-related respiratory muscle recruitment between exercise modalities did not impact intensity, affective and qualitative domains of dyspnea. Our results indicate that in circumstances where ventilation, breathing pattern, operating lung volumes and indirect measures of respiratory neural drive are similar across exercise modalities, altered afferent inputs from respiratory muscles (due to body position differences) do not modulate perceived dyspnea.

Patients had moderate airway obstruction and a largely preserved IC reflecting the known effects of increasing BMI on lung volume compartments in COPD (26). Our patients had moderate chronic activity-related dyspnea despite optimal pharmacotherapy as recommended by current guidelines (28). Patients were moderately obese (BMI: 36.6 kg/m²) with elevated trunk obesity relative to population norms (5) combined with significant abdominal adiposity: average waist circumference exceeded 102 cm for men and 88 cm for women (Table 1) (12,39). Cardio-respiratory fitness expressed as peak \( \dot{VO}_2 \) relative to ideal body weight was only modestly reduced. Mechanical constraints on ventilation were similar at peak exercise, as was peak dyspnea intensity, and breathing discomfort was the main reason for stopping exercise during both modalities.
As expected, treadmill walking was associated with greater oxygen uptake and arterial O\textsubscript{2} desaturation at similar work rates, compared with cycle exercise (6). For a given increase in VCO\textsubscript{2}, the rise in ventilation, respiratory neural drive (EMGdi/EMGdi,max) and global respiratory effort was similar during both exercise modalities (Figure 1). Thus, breathing pattern and operating lung volumes were also similar during walking and cycling despite positional differences in respiratory muscle activity.

Maintaining effective diaphragmatic function in the upright posture in humans requires a number of compensatory actions that include: increased EMGdi activation, together with increased activation of abdominal and ribcage intercostal muscles (7,8,18,20,21,40). Gravitational displacement of the abdominal viscera (on standing) is believed to stretch the abdominal wall and to activate abdominal muscles to maintain intra-abdominal volume and pressure (compliance), thereby improving the geometric and length-tension relationships of the diaphragm (7). Increased tonic activation of the diaphragm and abdominal muscles has been described in healthy humans in the standing position during repetitive upper limb movement (15,16). The sensory consequences of this competition between the respiratory and trunk-stabilizing functions of the diaphragm and abdominal muscles during different lower limb exercises in patients with already compromised respiratory muscle function is unknown. In severely hyperinflated COPD a reflexive increase in diaphragmatic and accessory muscle activity has been described in response to moving from the supine to the standing position (9). Whether such
compensatory strategies exist in less hyperinflated patients such as ours with combined COPD and obesity (where IC is relatively preserved) has not been studied. Moreover, it is not known if the presence of abdominal obesity in COPD further undermines these posture-compensating strategies to maintain effective respiratory function of the diaphragm during exercise.

Resting comparisons prior to onset of exercise (cycling and treadmill) showed small increases in Pdi,insp.rise, less accessory and expiratory muscle activity (VMR) and modestly reduced expiratory effort while sitting prior to cycling. At rest, there were no differences in tidal EMGdi or in diaphragmatic efficiency during sitting or standing. During cycling, obese COPD patients had greater Pdi,insp and greater peak force generating capacity (Pdi,IC) compared to treadmill exercise, suggesting a distinct mechanical advantage (Figure 3). Since efferent respiratory neural output (EMGdi/EMGdi,max) to the crural diaphragm was similar during both modalities, the greater Pdi,insp.rise pressures during cycling suggest greater neuromuscular efficiency of this muscle (Figure 4). Improved diaphragmatic efficiency (change in Pdi relative to change in EMGdi) during cycling may reflect relatively improved (reduced) abdominal compliance in this posture allowing an enhanced fulcrum effect of increased abdominal impedance during diaphragmatic descent (8). A leaning forward position while seated with arms extended grasping the handlebars might improve length-tension relations of the diaphragm or permit the pectoral and scalene muscles to act as accessory muscles of inspiration (13,37), as has been previously proposed (8,9). However, our ergometer and
mouthpiece assembly ensured an almost vertical position of the thorax during cycling suggesting that such factors are not instrumental in improving diaphragmatic efficiency in this circumstance. It is also possible that with hip flexion during cycling, the proximal thighs supported the lower abdominal wall during the breathing cycle, thus helping to maintain positive intra-abdominal hydraulic pressure to assist the diaphragms inspiratory action (1).

During walking, neuromuscular efficiency of the diaphragm was significantly reduced compared with cycling. Prior to exercise and consistent with previous studies in health (21), most patients had phasic expiratory muscle activity (Pga,exp.rise) while standing compared to sitting (91% vs 50%, respectively). However, on average, the magnitude of expiratory muscle activity was similar in both cycle and treadmill positions at rest. During treadmill walking there was a fall in Pga,El (Figure 2 & 3) and a shift in the respiratory muscle recruitment pattern towards more activity of the inspiratory muscles of the ribcage and expiratory muscles as indicated by analysis of Macklem VMR plots (23). A reduction in Pga,El and increased abdominal volume has been reported during cycle and treadmill exercise in separate studies in healthy individuals, and is thought to indicate abdominal wall relaxation during inspiration (2,36). Whether similar mechanisms are at play during walking in obese COPD patients could not be determined in the absence of concomitant measures of thoraco-abdominal displacements. In contrast to the situation during treadmill exercise, Pga,EE and Pga,El were similar in absolute terms throughout submaximal cycle exercise in our patients suggesting improved
(decreased) abdominal compliance. In keeping with the results of a recent study (20), there was no difference in the behaviour of EELV despite the differences in expiratory muscle recruitment between modalities.

Current concepts of the neurophysiology of exertional dyspnea in COPD emphasize the key role of increased respiratory neural drive from cortical and medullary centers in the brain and the attendant increased central corollary discharge to the somatosensory cortex (30,34). The strong correlations (independent of exercise modality) between dyspnea intensity and the three indirect indices of increasing respiratory neural drive (i.e., $V_E/MVV$, EMGdi/EMGdi,max and effort and Pes/Pes,max) support this hypothesis. As previously reported, the relationship between indices of neural drive and dyspnea intensity was not affected by differences in metabolic loading between modalities (6). There is also evidence that alteration of peripheral afferent inputs from the respiratory system, such as occurs with increased tidal volume expansion following pharmacological lung deflation, or during changes in posture at rest, can affect (reduce) activity-related dyspnea intensity perception, presumably by partially reducing neuromechanical dissociation of the respiratory system (27). In this context, it is reasonable to assume that during exercise, alteration of afferent inputs from various active respiratory muscle groups (which sense tension and displacement) will modulate dyspnea perception. The current study design allowed us, for the first time, to evaluate the sensory consequences of body position-related changes in diaphragmatic efficiency and in expiratory muscle recruitment in relative isolation, in a setting where intensity of
respiratory neural drive was constant. The finding that intensity, affective and qualitative domains of dyspnea were unaffected by alterations in respiratory muscle activity argues against a specific dyspneogenic role for mechanoreceptors in respiratory muscles of the chest wall and abdomen, at least when breathing pattern, operating lung volumes, respiratory neural drive and effort are similar. The lack of a further increase in dyspnea as a result of greater diaphragmatic dysfunction during treadmill walking may reflect the relative paucity of spindles in this muscle, which provide sensory information about length and displacement (38). The lack of influence of increased expiratory muscle recruitment on dyspnea during treadmill walking is in keeping with the results of a recent study, which shows no association between increased expiratory effort and dyspnea during exercise in COPD (20).

4.5.1 Limitations

The focus of the current study was to evaluate sensory-mechanical relations in patients with combined COPD and obesity; therefore, the results may not be generalizable to non-obese patients who are more likely to have reduced resting IC. The lack of measurements of thoraco-abdominal excursions and tonic and phasic EMG recordings from respiratory muscles other than the diaphragm precludes definitive conclusions about variability in the complex respiratory muscle coordination strategies employed as a result of positional differences during exercise.

4.5.2 Conclusions
The current study shows, for the first time, that diaphragmatic and expiratory muscle activity is different during cycling and walking in obese individuals with COPD. However, despite the relatively reduced neuromuscular efficiency of the diaphragm during weight-bearing treadmill exercise compared with weight-supported cycling, perceived respiratory discomfort was not increased. Our results further indicate that exertional dyspnea intensity is ultimately dictated by the amplitude of respiratory neural drive. Moreover, under conditions where respiratory neural drive and the volume and timing components of breathing were constant, body position-related alterations in activity of major respiratory muscles during different exercise modalities had no measurable effects on the intensity and quality of dyspnea.
4.6 REFERENCES


Chapter 5

General Discussion

Novel findings of my thesis project include the following: 1) cycling resulted in a reduced oxygen uptake, greater arterial oxygen saturation and an earlier ventilatory threshold compared to walking; 2) ventilation, breathing pattern and operating lung volumes were similar at matched work rates between modalities; 3) different sources of respiratory neural drive between exercise modalities did not alter the efferent output (i.e., EMGdi) from the central respiratory controller for a given ventilation; 4) posture related effects of walking resulted in reduced diaphragm efficiency with an earlier compensatory ribcage muscle recruitment and greater expiratory abdominal muscle recruitment compared to cycling; 5) despite physiological and respiratory muscle recruitment pattern differences, exercise modality did not impact the intensity, affective and qualitative domains of dyspnea for a given ventilation; and 6) dyspnea was closely related to $\dot{V}_E$, $\dot{V}CO_2$, EMGdi, and the respiratory mechanical response to exercise in obese COPD patients and not the $VO_2$ (Appendix 1; pg 55).

5.1 Summary

My thesis project was an extension of previous work performed in the Respiratory Investigation Unit where the effect of obesity on dyspnea was examined in patients with COPD by comparing obese and normal weight COPD patients during cycle exercise. Although, cycle ergometry is more commonly used to investigate mechanisms of
dyspnea, it does not accurately reflect typical physiological responses of daily activities and neglects to account for the known increases in metabolic demand during weight-bearing exercise in obese patients compared to weight-supported exercise. Accordingly, this project investigated mechanisms of dyspnea during treadmill walking in order to better understand how exercise responses compare to previous work performed on cycle ergometry in obese COPD. The objective of the current project was to illuminate physiological differences between cardiopulmonary exercise testing modalities (i.e., cycling vs. treadmill walking) using matched protocols with a linearized rise in work rate in obese COPD patients where weight-bearing exercise may have exaggerated physiological responses compared to weight-supported cycle exercise. Despite differences in metabolic loading, diaphragm efficiency and respiratory muscle recruitment patterns between exercise modalities, this project validates the previous findings during cycle exercise. Thus, obese COPD patients are not more dyspneic (or disadvantaged) for a given ventilation during weight-bearing exercise. It follows that both exercise modalities are appropriate for evaluating dyspnea in clinical and research settings.

5.2 Future Directions

Since obese COPD patients were the main focus of this project, this work cannot be generalizable to all COPD patients. Further testing is required in normal weight COPD patients to understand if the observed differences (metabolic, diaphragm efficiency and respiratory muscle recruitment patterns) and similarities (respiratory mechanical
response, electrical activation of the diaphragm) are a function of obesity or are independent of BMI and specific to exercise modality. Future studies involving measurements of diaphragm, ribcage, accessory and abdominal muscle electromyogram, in conjunction with respiratory mechanical measurements and thoraco-abdominal excursions, would further improve our understanding of the respiratory muscle afferent feedback pathways related to dyspnea. Studies that examine the impact of interventions to reduce obesity (e.g., bariatric surgery) on mechanics, respiratory muscle function and dyspnea would be particularly enlightening. Since abdominal obesity conveys mechanical advantages in COPD, consideration should be given to the study of abdominal strapping/support in non-obese hyperinflated COPD patients to improve dynamic respiratory mechanics during activity, in the hope of reducing dyspnea as an adjunct to exercise training.
Chapter 6

References


Blair, SN, Brodney S (1999). Effects of physical inactivity and obesity on morbidity and...


Appendix A

Research Ethics Board (REB) Approval

QUEEN'S UNIVERSITY HEALTH SCIENCES AND AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD
ANNUAL RENEWAL

Queen's University, in accordance with the "Tri-Council Policy Statement 2, 2010" prepared by the Interagency Advisory Panel on Research Ethics for the Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada requires that research projects involving human participants be reviewed annually to determine their acceptability on ethical grounds.

A Research Ethics Board composed of:

Dr. A.F. Clark, Emeritus Professor, Department of Biomedical and Molecular Sciences, Queen's University (Chair)
Dr. H. Abdollah, Professor, Department of Medicine, Queen's University
Dr. C. Cline, Assistant Professor, Department of Medicine, Director, Office of Bioethics, Queen's University, Clinical Ethicist, Kingston General Hospital
Dr. R. Brison, Professor, Department of Emergency Medicine, Queen's University
Dr. M. Evans, Community Member
Ms. J. Hudacin, Community Member
Dr. J. MacKenzie, Pediatric Geneticist, Department of Pediatrics, Queen's University
Mr. D. McNaughton, Community Member
Ms. P. Newman, Pharmacist, Clinical Care Specialist and Clinical lead, Quality and Safety, Pharmacy Services, Kingston General Hospital
Ms. S. Rohland, Privacy Officer, ICES-Queen's Health Services Research Facility, Research Associate, Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute
Dr. B. Simchison, Assistant Professor, Department of Anaesthesiology and Perioperative Medicine, Queen's University
Dr. A. Singh, Professor, Department of Psychiatry, Queen's University
Dr. J. Tang, Medical Resident, Department of Emergency Medicine, Queen's University
Ms. K. Weisbaum, LL.B. and Adjunct Instructor, Department of Family Medicine (Bioethics)

has reviewed the request for renewal of Research Ethics Board approval for the project The Effect of Obesity on Dyspnea and Exercise Performance in COPD as proposed by Dr. Denis Eunan Mary O'Donnell of the Department of Medicine, at Queen's University. The approval is renewed for one year, effective March 30, 2013. If there are any further amendments or changes to the protocol affecting the participants in this study, it is the responsibility of the principal investigator to notify the Research Ethics Board. Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other adverse events must be reported within 15 days after becoming aware of the information.

Chair, Research Ethics Board

Date: March 20, 2013

Romeo file#: 6004381
Appendix B

List of Publications

6.1 Abstracts/Presentations

6.1.1 European Respiratory Society International Congress 2014

Ciavaglia CE, Guenette JA, Langer D, Webb KA, Neder JA, O’Donnell DE. Neuromuscular dissociation of the diaphragm is more pronounced during treadmill exercise compared with cycle exercise in obese COPD patients. (Accepted)


6.1.2 American Thoracic Society International Conference 2014


- Invitation to the 4th annual Canadian Thoracic Society poster competition held at the American Thoracic Society International Conference 2014.


6.1.3 American Thoracic Society International Conference 2013


6.2 Peer Reviewed Publications


