Differences in respiratory muscle activity during cycling and walking do not influence dyspnea perception in obese patients with COPD

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Study's Main Message:

Dyspnea intensity and quality are not affected by differences in diaphragmatic efficiency or respiratory muscle recruitment patterns during walking and cycling in obese patients with COPD.

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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 $36.6 \pm 5.4 \text{ kg/m}^2$; mean $\pm$ 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.

Keywords: obesity, COPD, dyspnea, exercise modality, respiratory mechanics.

INTRODUCTION

It is believed that exertional dyspnea intensity in patients with chronic obstructive pulmonary disease (COPD) rises in association with increased central motor command output to the respiratory muscles (15,19,27,40) and can be further modulated by altered afferent inputs from peripheral sensory receptors in the lungs, respiratory muscles and chest wall (32,34,37). In patients with combined COPD and obesity, activity-related dyspnea is a major symptom and likely contributes to poor health-related quality of life (45). The prevalence of both COPD and obesity is increasing at an alarming rate throughout the world and improved symptom control in this sub-population with combined disorders awaits a better understanding of how excessive weight interacts with the basic pathophysiology of COPD (14,30). Studies have shown that dyspnea in obese patients with moderate-to-severe COPD is multifactorial and we have argued that increased metabolic requirements (increased carbon dioxide output) 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 (30,38).

In a recent non-invasive study in obese COPD patients, we established that dyspnea/work rate and dyspnea/ventilation slopes were not affected by exercise test modality (cycling versus walking when work rate was controlled) despite consistent inter-modality differences in some metabolic factors, e.g., oxygen uptake (VO_2) and arterial oxygen saturation (8). In the current study, we extend our previous work in obese COPD by examining, for the first time, the effect of potential differences in amplitude of central respiratory drive (measured indirectly by diaphragmatic electromyography) and

respiratory muscle activity (measured by esophageal and gastric balloons) between exercise modalities on dyspnea across its intensity, quality and affective dimensions.

A number of studies in non-obese healthy individuals have documented compensatory adjustments in abdominal muscle activity to preserve diaphragmatic function when adopting a standing body position (10,11,23,26,47). Such studies have, to our knowledge, not been conducted during rest or exercise in obese individuals with COPD. It is reasonable to assume that these normal compensatory adjustments to standing upright may be undermined by exaggerated gravitational effects of abdominal obesity. Thus, it is possible that diaphragmatic function may be more compromised during standing and walking (compared with weight-supported cycling) in obese patients and this may have negative sensory consequences. The corollary is that relatively improved diaphragmatic function during cycling would be associated with favourable effects on dimensions of dyspnea as has previously been shown in non-obese COPD patients after interventions that improve respiratory muscle function (e.g., leaning forward position, bronchodilators, non-invasive mechanical ventilation) (12,33,37). Accordingly, our objectives were to determine if: 1) diaphragmatic function, expiratory muscle activity and respiratory muscle recruitment pattern was different during walking and cycling in obese COPD patients, and 2) whether such inter-modality differences in respiratory muscle activity (and accompanying afferent inputs from muscle mechanoreceptors) had direct sensory consequences when external power output was standardized between tests. We therefore compared indirect indices of central respiratory drive, esophageal and transdiaphragmatic pressures, diaphragmatic efficiency and intensity, quality and affective

110 components of dyspnea during incremental treadmill and cycle exercise when work rate
111 was carefully matched.

112

METHODS

Subjects

Twelve clinically stable obese (body mass index (BMI) $>30 \text{ kg/m}^2$) patients with COPD ($\text{FEV}_1/\text{FVC} <70\%$) and a post-bronchodilator $\text{FEV}_1 <80\%$ 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).

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 β_2 -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.

Procedures

Pulmonary function testing included routine spirometry, body plethysmography, single-breath diffusing capacity for carbon monoxide (D_LCO), maximum inspiratory and expiratory mouth pressures, static lung compliance (C_{Lst}) and static lung recoil pressure (P_{Lst}) using automated testing equipment (Vmax229d; 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 treadmill work rate was adjusted as follows: speed began at 0.8 miles/hour (21.46 m/min) and thereafter increased linearly by 0.2 miles/hour (5.36 m/min) for every 10W increment for all subjects; a curvilinear rise in percent grade was calculated for each subject based on the equation by Cooper and Storer [$\text{watts} = 0.1634 \times \text{speed(m/min)} \times \text{\%grade}/100 \times \text{body mass(kg)}$] (9). 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 (36): end-expiratory lung volume (EELV)= total lung capacity (TLC) - IC, end-inspiratory lung volume (EILV)= EELV + tidal volume (V_T), and inspiratory reserve volume (IRV)= IC- V_T . 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 (4,39). Immediately after exercise, subjects were asked why they stopped exercising.

Diaphragm EMG and Respiratory Pressures

A combined EMGdi electrode catheter with esophageal and gastric balloons was inserted nasally and positioned according to the strength of inspiratory EMGdi recordings, i.e., position was optimal when the amplitude of the outer of the 5 electrode pairs was greatest and the middle electrode pair was lowest (22). The raw EMGdi signal was amplified and band-pass filtered between 20-1000 Hz (Bioamplifier model RA-8; Guanzhou Yinghui Medical Equipment Co. Ltd, Guangzhou, China) then sampled at 2000 Hz (PowerLab, model ML880; ADInstruments, CastleHill, NSW, Australia). 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). 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 were performed to obtain maximum P_{es} ($P_{es,sn}$) and P_{di} ($P_{di,sn}$). IC maneuvers at rest and throughout exercise were used to obtain dynamic peak inspiratory P_{es} ($P_{es,IC}$) and P_{di} ($P_{di,IC}$). Pre- and post-exercise FVC maneuvers were also performed to obtain dynamic peak expiratory P_{es} ($P_{es,FVC}$). Tidal P_{es} swings ($P_{es,tidal}$) were defined as the amplitude between the maximum expiratory value ($P_{es,exp}$) and minimum inspiratory value ($P_{es,insp}$) for each respiratory cycle, and expressed relative to maximum P_{es} ($P_{es,max}$: difference between $P_{es,IC}$ and $P_{es,FVC}$). Similarly, tidal P_{di} swings ($P_{di,tidal}$) were defined as the excursion between maximum inspiratory ($P_{di,insp}$) and minimum P_{di} during expiration. The inspiratory rise in P_{di} ($P_{di,insp.rise}$) was defined as the increase in P_{di} from the onset of inspiratory flow to peak P_{di} during inspiration. The peak tidal expiratory P_{ga} ($P_{ga,exp}$) and expiratory rise in P_{ga} ($P_{ga,exp.rise}$), which is the increase in P_{ga} 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 P_{es} and P_{ga} were collected. The ventilatory muscle recruitment (VMR) index was calculated as the difference between $P_{ga,EI}$ and $P_{ga,EE}$ divided by the difference between $P_{es,EI}$ and $P_{es,EE}$ (29): 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 P_{di} ($P_{di,insp.rise}$) and $EMG_{di}/EMG_{di,max}$.

Statistical Analysis

This study had a small sample size due to the complexity and invasiveness of the respiratory pressure/EMGdi measurements. However, in a previous study evaluating similar outcome measures, a sample size of 11 was sufficient to show significant within-subject differences in sensory and respiratory mechanical/EMGdi measurements at a standardized work rate across two conditions (22). 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 $\pm$ SD unless specified otherwise. A $p < 0.05$ was used for statistical significance.

RESULTS

Subject characteristics and resting pulmonary function are presented in Table 1. Subjects fit either GOLD 2 (n=9) or GOLD 3 (n=3) spirometric criteria for moderate or severe airflow obstruction, respectively (44). By GOLD recommendations, all subjects were symptomatic (category B or D) with either a modified MRC grade ≥ 2 or a COPD Assessment Test (CAT) score ≥ 10 (44). 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 $>88\text{cm}$ in women and $>102\text{cm}$ in men (46). Waist circumference was elevated by 22cm in males and 25cm in females relative to previously defined abdominal obesity criteria (16,46). 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**).

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 (VO_2) during treadmill exercise was significantly higher compared to cycle exercise. V_E (**Figure 1A**) and carbon dioxide production (VCO_2) were similar at a given work rate and reached similar peak values (**Table 2**) for both exercise modalities. Moreover, V_E/VCO_2 relationships were superimposed across exercise modalities. For any given V_E during exercise, both exercise modalities had similar $\text{EMGdi}/\text{EMGdi,max}$, global

respiratory muscle effort ($P_{es, tidal}$ in absolute terms and relative to $P_{es, max}$), breathing pattern and operating lung volumes (**Figure 1B and C**).

Inspiratory Muscles

Raw data tracings from a representative patient are shown in **Figure 2** to illustrate differences in P_{ga} , P_{di} and the VMR at a similar work rate (30W) and V_E (cycle: 24 L/min; treadmill: 26 L/min). 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 $P_{di, IC}$ and $P_{di, sn}$ decreased significantly from pre-exercise values with both modes of exercise (**Table 3**). $P_{es, insp}$ in absolute terms or relative to $P_{es, IC}$ was similar during exercise under both conditions (**Figure 1C, Table 3**). $P_{di, insp}$ was greater throughout cycle exercise compared to treadmill exercise (**Figure 3A**); however, inspiratory diaphragmatic effort ($P_{di, insp}/P_{di, IC}$) was similar between both exercise conditions due to a concurrent increase in $P_{di, IC}$ during cycle exercise. $P_{di, insp, rise}$ was also significantly greater during cycling compared with treadmill exercise (**Figure 3B**). 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 3C**). Interpolated values of $P_{di, insp, rise}$ at standardized $EMG_{di}/EMG_{di, max}$ of 30, 40 and 50 % were greater during cycle compared to treadmill exercise, indicating increased diaphragm efficiency during cycling (**Figure 4**).

Expiratory Muscles

There was greater abdominal expiratory muscle activity during treadmill compared with cycle exercise as shown by a greater $P_{ga, exp, rise}$ throughout exercise and by a greater

proportion of subjects exhibiting a $P_{ga,exp}$ rise at rest and early in exercise (**Figure 3E and F**). $P_{ga,EE}$ was similar during both modes of exercise, while $P_{ga,EI}$ fell to a significantly greater extent during treadmill walking compared to cycling (**Figure 3D**).

Exertional Dyspnea

Subjects reported similar intensity of “breathing discomfort” (**Figure 5A**), “work/effort of breathing,” “difficulty breathing in” and “unpleasantness of breathing” (**Figure 5B**) during submaximal and symptom-limited peak exercise for both test modalities. There were no significant differences between modalities for reasons for stopping exercise. 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. Conversely, leg discomfort, alone or in combination with breathing discomfort, was reported in 75% of cycle tests and in 58% 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 V_E , $EMG_{di}/EMG_{di,max}$, and $P_{es,tidal}/P_{es,max}$ throughout exercise (**Figure 5**). Dyspnea intensity during exercise correlated strongly with V_E/MVV , $P_{es,tidal}/P_{es,max}$ and $EMG_{di}/EMG_{di,max}$ (all $p < 0.0005$); these relationships were similar across testing modality.

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 respiratory muscle recruitment to achieve a given ventilation during different exercise modalities did not impact intensity, affective and qualitative domains of dyspnea. Our results do not support the hypothesis that differences in afferent inputs from the diaphragm and expiratory muscles during walking versus cycling modulate dyspnea perception in obese patients with COPD, at least in circumstances where ventilation, indirect measures of respiratory neural drive and dynamic respiratory mechanics are similar across exercise modalities.

Patients in this study had moderate airway obstruction and were moderately obese with significant abdominal adiposity (Table 1). Cardio-respiratory fitness expressed as peak 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 a predominant reason for stopping exercise during both modalities.

Respiratory Muscle Adjustments to Test Modality

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 (10,11,23,26,47). 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 (10). Increased tonic activation of the diaphragm and

abdominal muscles has been described in healthy humans in the standing position during repetitive upper limb movement (20,21). 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 (12). 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. To our knowledge, the current study is the first to determine 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 versus treadmill) showed small increases in $P_{di,insp}$, less accessory and expiratory muscle activity (more negative VMR) and modestly lower expiratory effort while sitting prior to cycling. At rest, there were no differences in tidal EMG_{di} or in diaphragmatic efficiency during sitting or standing. During cycling, obese COPD patients had greater $P_{di,insp}$ and greater peak force generating capacity ($P_{di,IC}$) compared to treadmill exercise, suggesting a distinct mechanical advantage (Figure 3). Since efferent respiratory neural output ($EMG_{di}/EMG_{di,max}$) to the crural diaphragm was similar during both modalities, the greater $P_{di,insp}$ pressures during cycling suggest greater neuromuscular efficiency of this muscle (Figure 4). Improved diaphragmatic efficiency (change in P_{di} relative to change in EMG_{di}) during cycling may reflect relatively improved (reduced) abdominal compliance

in this posture allowing an enhanced fulcrum effect of increased abdominal impedance during diaphragmatic descent (11). 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 (18,42), as has been previously proposed (11,12). 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 (26), most patients had phasic expiratory muscle activity ($P_{ga,exp.rise}$) 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 $P_{ga,EI}$ (Figure 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 (28). A reduction in $P_{ga,EI}$ 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 (2,41). 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, $P_{ga,EE}$ and $P_{ga,EI}$ 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 (25), there was no difference in the behaviour of EELV despite the differences in expiratory muscle recruitment between modalities.

Despite differences in respiratory muscle recruitment across tests, global measurements of respiratory muscle activity (tidal swings of P_{es}) were similar for a given ventilation. Individual respiratory muscle contributions to ventilation may vary such that reduced diaphragmatic contributions during treadmill is likely counterbalanced by increased contribution of other respiratory muscles to maintain the V_E dictated by the $\dot{V}CO_2$. Based on a previous study (25), we believe that the relatively increased expiratory muscle activity during treadmill testing in the current study is unlikely to translate into increased ventilatory output in the presence of expiratory flow limitation.

A related question is why relatively increased diaphragmatic activity during cycling compared with walking did not translate into increased V_E for a given work rate? In line with the argument above, one possibility is that increased diaphragmatic activity is linked to a corresponding reduction in activity of the other respiratory muscles (as suggested by our VMR analysis) such that V_E , as dictated by the prevailing $\dot{V}CO_2$, remains constant. A second possibility is that even in the face of increased inspiratory muscle activity during cycling, further increases in V_E are not possible, particularly at higher exercise intensities where significant restrictive respiratory mechanical constraints are present (Figure 1F).

The similarity in ventilatory response during the two exercise modalities, despite differences in the contribution of various respiratory muscles to support ventilation, is also explained by metabolic factors. Thus, the ventilatory response to exercise, regardless of the test modality, was ultimately determined by $\dot{V}CO_2$. As highlighted in our previous study (8), it is clear that net $\dot{V}CO_2$ /work rate responses and $\dot{V}_E/\dot{V}CO_2$ (and consequent $\dot{V}_E$ /work rate) slopes were similar across tests, notwithstanding differences in $\dot{V}O_2$ and RER.

Mechanisms of Exertional Dyspnea

Increased central neural drive. 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 (35,39). We extended the results of our previous study by demonstrating that not only ventilatory parameters but also respiratory neural drive ($EMG_{di}/EMG_{di,max}$) and global respiratory effort were similar during both exercise modalities and increased as a function of increasing $\dot{V}CO_2$. Thus we confirmed that the association between dyspnea intensity and measures of central respiratory drive was independent of the $\dot{V}O_2$ requirements at a standardized external power output during walking and cycling. The strong correlations (independent of exercise modality) between dyspnea intensity and the three indirect indices of increasing respiratory neural drive (i.e., $\dot{V}_E/MVV$, $EMG_{di}/EMG_{di,max}$ and effort and $P_{es,tidal}/P_{es,max}$) support the hypothesis that amplitude of central respiratory drive (and central corollary discharge) is an important determinant of dyspnea regardless of the nature of the physical task that provokes the symptom.

Altered afferent sensory inputs. The previously established relationship between

increase in dyspnea intensity and reduction of dynamic IRV towards its minimal value (33) has been shown to be independent of exercise modality (8). It is widely accepted that alteration of peripheral afferent inputs from the respiratory system (lung, chest wall and respiratory muscles), can influence dimensions of dyspnea during exercise. For example, increased V_T and IRV following pharmacological lung deflation, or changes in posture at rest, can affect (reduce) activity-related dyspnea intensity perception, presumably by altering peripheral afferent sensory inputs from the respiratory system and by partially reducing neuromechanical dissociation (32). It has long been postulated that afferent information from abundant sensory receptors in the respiratory muscles represents the proximate source of feedback regarding the status of the respiratory system and the appropriateness of its response to the prevailing central neural drive (7). 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 and global contractile respiratory muscle effort was constant. The finding that intensity, affective and qualitative domains of dyspnea were unaffected by test-specific alterations in respiratory muscle activity required to support a given ventilation argues against a specific dyspneogenic role for mechanoreceptors in respiratory muscles of the chest wall and abdomen, at least under the experimental conditions of our study. 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 (43). 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 (25).

To the extent that between-test differences in the respiratory muscle activity required to generate a given ventilation had no measurable effect on dimensions of dyspnea, it would seem that there is substantial redundancy in the peripheral sensory systems. "Sense of effort," as estimated by $P_{es,tidal}/P_{es,max}$, which was similar at a given V_E during both test modalities, may be more closely linked to amplitude of central corollary discharge than to the pattern of afferent inputs from contracting respiratory muscles, *per se* (6,13,17,24). Thus, afferent inputs from other sources such as pulmonary vagal receptors and chest wall mechanoreceptors, which are likely similar between tests (given the similarity of V_T and operating lung volumes), may represent the primary source of peripheral afferent feedback to the somatosensory cortex at least under the current experimental conditions.

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.

Conclusions and Implications

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 and concomitant dynamic restrictive mechanical constraints (decreasing IRV). 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 to achieve a similar ventilation during different exercise modalities had no measurable effects on the intensity and quality of dyspnea.

Clinicians involved in laboratory cardiopulmonary exercise testing should be aware of the fundamental physiological differences between cycling and treadmill in obese COPD patients. Either test modality is suitable for evaluation of dyspnea which, regardless of physical task, rises in association with increasing central neural drive. An important clinical implication is that interventions that reduce central respiratory drive (e.g., reduction of $\dot{V}CO_2$ by manipulation of energy substrate or exercise training) should successfully relieve exertional dyspnea in obese patients with COPD.

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605

FIGURE LEGENDS

Fig 1. (A) ventilation (V_E) for a given work rate was similar between cycle and treadmill exercise. **(B)** Electrical activation of the diaphragm as a percentage of maximum ($EMG_{di}/EMG_{di,max}$), **(C)** esophageal pressure (P_{es}) swings (inspiration upward), **(D)** tidal volume (V_T), **(E)** breathing frequency (f_b) and **(F)** operating lung volumes (inspiration upward) were similar between exercise modalities and are shown relative to V_E . **(C)** Maximum inspiratory P_{es} during an IC maneuver ($P_{es,IC}$) was not significantly different across modalities for pre- and post-exercise measurements when analyzed by two-way repeated measures ANOVA. EELV: end-expiratory lung volume; EILV: end-inspiratory lung volume; IRV: inspiratory reserve volume; TLC: total lung capacity. Data are means $\pm$ SEM.

Fig 2. Raw data tracings for a representative female patient show mechanical measurements at the 30 watt load of the cycle and treadmill exercise tests. Despite a similar ventilation (cycle: 24 L/min treadmill: 26 L/min), tracings show different respiratory muscle recruitment patterns: inspiratory P_{di} was greater during cycling, P_{ga} was shifted downwards during walking, and the ventilatory muscle recruitment (VMR) index was more negative during cycling (cycle: -0.67; treadmill: 0.45). Black circles (●) represent points of zero flow and connecting bars represent P_{ga} and P_{es} slopes for the VMR index calculation. P_{es} : esophageal pressure; P_{ga} : gastric pressure; P_{di} : transdiaphragmatic pressure; Expir: expiration; Inspir: inspiration.

Fig 3. (A) Transdiaphragmatic pressure (P_{di}), **(B)** P_{di} inspiratory rise ($P_{di,insp.rise}$), **(C)** ventilatory muscle recruitment (VMR) index, **(D)** gastric pressure at zero flow ($P_{ga,zero}$

flow), **(E)** expiratory gastric rise ($P_{ga,exp.rise}$) and **(F)** the frequency of expiratory muscle activity are shown relative to work rate. $P_{di,IC}$: maximum inspiratory P_{di} during an IC maneuver; $P_{ga,EE}$: end-expiratory gastric pressure; $P_{ga,El}$: end-inspiratory gastric pressure. Data are means $\pm$ SEM unless specified otherwise. * $p<0.05$ cycle vs treadmill at a given work rate or at peak exercise.

Fig 4. The inspiratory rise of transdiaphragmatic pressure ($P_{di,insp.rise}$) is shown relative to electrical activation of the diaphragm ($EMG_{di}/EMG_{di,max}$). $P_{di,insp.rise}$ at 30, 40, 50 $EMG_{di}/EMG_{di,max}$ and at peak exercise was significantly greater during cycle compared with treadmill exercise (* $p<0.05$). Data are means $\pm$ SEM.

Fig 5. Relationships between dyspnea intensity and **(A)** ventilation (V_E), **(C)** electrical activation of the diaphragm as a percentage of maximum ($EMG_{di}/EMG_{di,max}$), and **(D)** tidal esophageal pressure swings as a percentage of maximum ($P_{es,tidal}/P_{es,max}$) were similar between cycle and treadmill exercise. **(B)** Intensity ratings for unpleasantness of breathing relative to V_E were also similar. Data are means $\pm$ SEM.

646 **Table 1. Subject Characteristics**

Male : Female, n	6 : 6
Age, yrs	67 ± 8
Height, cm	167 ± 9
Weight, kg	103 ± 25
BMI, kg/m ²	36.6 ± 5.4
Waist circumference, cm:	
Male	134 ± 9
Female	113 ± 7
Waist-to-hip ratio:	
Male	1.05 ± 0.07
Female	0.92 ± 0.07
Total body fat*, %:	41 ± 2
Male (n=4)	40 ± 2
Female (n=5)	42 ± 3
Truncal fat mass*, % total trunk mass:	43 ± 5
Male (n=4)	45 ± 5
Female (n=5)	42 ± 5
Smoking history, pack-years	49 ± 35
Baseline Dyspnea Index, 0-12	6.5 ± 2.0
MRC dyspnea scale, 1-5	2.5 ± 0.8
Pulmonary Function†:	
FEV ₁ , L (% predicted)	1.43 ± 0.44 (60 ± 13)
FEV ₁ /FVC, %	50 ± 11
TLC, L (% predicted)	5.67 ± 1.24 (98 ± 10)
IC, L (% predicted)	2.37 ± 0.85 (89 ± 22)
FRC, L (% predicted)	3.30 ± 0.83 (105 ± 20)
RV, L (% predicted)	2.77 ± 0.73 (126 ± 29)

ERV, L (% predicted)	0.54 ± 0.28 (61 ± 35)
sRaw, cmH ₂ O•s (% predicted)	16.7 ± 7.9 (397 ± 177)
D _L CO, mL•min ⁻¹ •mmHg ⁻¹ (% predicted)	11.4 ± 4.6 (46 ± 10)
MIP, cmH ₂ O (% predicted)	68 ± 27 (89 ± 36)
MEP, cmH ₂ O (% predicted)	138 ± 56 (81 ± 22)
C _{Lst} , L/cmH ₂ O	0.27 ± 19
P _{Lst} , cmH ₂ O	20 ± 6

Values are means ± SD unless otherwise noted. MRC: Medical Research Council; FEV₁: 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; sR_{AW}: specific airway resistance; D_LCO: diffusing capacity of the lung for carbon monoxide; MIP: maximal inspiratory pressure measured at FRC; MEP: maximal expiratory pressure measured at TLC; C_{Lst}: static lung compliance; P_{Lst}: static lung recoil pressure.

* Measurements obtained by DEXA scan.

† Pulmonary function test measurements are pre-bronchodilator except forced spirometry which is post-bronchodilator.

Table 2. Cardiopulmonary measurements during rest and peak exercise

	Rest		Peak	
	Cycle	Treadmill	Cycle	Treadmill
Work rate, watts	0 ± 0	0 ± 0	73 ± 17	78 ± 22
Exercise time, mm:ss	0 ± 0	0 ± 0	14:09 ± 3:30	15:13 ± 4:41
Dyspnea, Borg scale	0.1 ± 0.2	0.2 ± 0.2	7.7 ± 2.5	7.1 ± 2.1
Leg discomfort, Borg scale	0.2 ± 0.3	0.2 ± 0.4	7.6 ± 2.4	5.8 ± 3.1 *
VO ₂ , L/min	0.44 ± 0.14	0.43 ± 0.17	1.55 ± 0.45	1.74 ± 0.59 *
VO ₂ , % predicted	23 ± 6	21 ± 10	84 ± 22	93 ± 25*
VCO ₂ , L/min	0.37 ± 0.12	0.34 ± 0.13	1.53 ± 0.40	1.61 ± 0.51
RER	0.83 ± 0.05	0.81 ± 0.11	0.99 ± 0.08	0.93 ± 0.11
V _E , L/min	15.6 ± 3.7	14.9 ± 4.5	49.0 ± 9.7	49.5 ± 13.0
V _E /MVV, %	35 ± 13	34 ± 13	107 ± 20	109 ± 22
V _E /VCO ₂	43.9 ± 6.0	44.9 ± 8.1	32.9 ± 5.4	31.3 ± 4.7 *
P _{ET} CO ₂ , mmHg	33.6 ± 2.6	33.1 ± 3.2	36.2 ± 5.9	37.5 ± 5.6 *
V _T , L	0.81 ± 0.24	0.81 ± 0.10	1.34 ± 0.36	1.34 ± 0.45
F _b , breaths/min	21 ± 5	20 ± 6	37 ± 7	38 ± 8
T _I /T _{TOT}	38 ± 5	37 ± 4	40 ± 4	41 ± 5
IC, L	2.38 ± 0.80	2.37 ± 0.79	1.73 ± 0.34	1.74 ± 0.54
IRV, L	1.57 ± 0.69	1.56 ± 0.55	0.38 ± 0.15	0.40 ± 0.18
Heart rate, beats/min	80 ± 8	80 ± 7	120 ± 16	126 ± 18
Heart rate, % predicted	48 ± 4	48 ± 4	72 ± 9	76 ± 10
SpO ₂ , %	95 ± 2	95 ± 3	91 ± 3	89 ± 4 *

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Values are means ± SD. VO₂: oxygen uptake; VCO₂: carbon dioxide production; RER: respiratory exchange ratio; V_E: ventilation; MVV: maximal voluntary ventilation; V_E/VCO₂: ventilatory equivalent for carbon dioxide production; P_{ET}CO₂: partial pressure of end-tidal carbon dioxide; V_T: tidal volume; F_b: breathing frequency; T_I/T_{TOT}: inspiratory duty cycle; IC: inspiratory capacity; IRV: inspiratory reserve volume; HR: heart rate; SpO₂: arterial oxygen saturation by pulse oximetry.

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* p<0.05 treadmill versus cycle test at peak exercise.

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667 **Table 3. Respiratory mechanical measurements during rest and peak exercise**

	Rest		Peak	
	Cycle	Treadmill	Cycle	Treadmill
Pdi,sn, cmH ₂ O	88.4 ± 19.6	89.5 ± 24.5	74.7 ± 22.6	65.0 ± 24.8
Pdi,IC, cmH ₂ O	68.3 ± 23.6	62.0 ± 18.8	49.7 ± 15.4	38.8 ± 10.2
Pes,tidal, cmH ₂ O	9.8 ± 3.6	10.4 ± 4.7	38.3 ± 17.8	37.9 ± 16.3
Pes,tidal, %Pes,max	9.8 ± 3.3	10.0 ± 4.4	37.9 ± 17.2	36.1 ± 15.8
VMR index	-0.6 ± 0.8	-0.1 ± 0.8*	0.5 ± 0.6	1.2 ± 0.4*
EMGdi/EMGdi,max, %	18 ± 10	19 ± 9	64 ± 14	72 ± 13*
Inspiratory muscle activity:				
Pes,insp, cmH ₂ O	-7.5 ± 2.2	-6.4 ± 3.4	-16.1 ± 2.2	-15.1 ± 5.2
Pes,insp, %Pes,IC	28 ± 10	22 ± 8	60 ± 16	71 ± 15
Pdi,insp, cmH ₂ O	26.7 ± 5.6	24.5 ± 4.9	34.1 ± 7.1	28.9 ± 5.4*
Pdi,insp, %Pdi,IC	42 ± 15	43 ± 14	71 ± 13	74 ± 10
Pdi,insp.rise, cmH ₂ O	10.0 ± 3.9	8.0 ± 2.8*	11.5 ± 6.1	8.3 ± 3.9*
Expiratory muscle activity:				
Pes,exp, cmH ₂ O	2.3 ± 2.8	4.0 ± 2.3*	22.2 ± 15.2	22.8 ± 13.1
Pga,exp, cmH ₂ O	20.2 ± 4.9	19.7 ± 4.3	37.0 ± 17.8	37.5 ± 13.7
Pga,exp rise, cmH ₂ O	2.3 ± 1.6	3.4 ± 2.5	22.3 ± 17.8	27.0 ± 16.6*
Pga,EI, cmH ₂ O	19.5 ± 5.0	18.2 ± 4.6	17.7 ± 6.2	10.1 ± 4.2*
Pga,EE, cmH ₂ O	16.6 ± 3.3	16.0 ± 6.8	26.8 ± 8.5	27.4 ± 6.9

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669 Values are means ± SD. See text for abbreviations.

670 *p<0.05 treadmill versus cycle exercise at that measurement point.

Cycle

Treadmill

(A) **(B)** **(C)** **(D)** **(E)** **(F)**