Combined Effects of Obesity and Chronic Obstructive Pulmonary Disease on Dyspnea and Exercise Tolerance

Josuel Ora[1], Pierantonio Laveneziana[1], Dror Ofir[1], Athavudh Deesomchok[1], Katherine A. Webb[1], and Denis E. O'Donnell[1]

[1]Respiratory Investigation Unit, Department of Medicine, Queen's University and Kingston General Hospital, Kingston, Ontario, Canada

Rationale: **Severity of lung hyperinflation is known to influence the extent of dyspnea and exercise intolerance among patients with chronic obstructive pulmonary disease (COPD) with similar degrees of airway obstruction. Lung volume components are consistently affected by body mass index (BMI) in health and in disease.**

Objectives: **To explore the complex interactions between obesity, lung hyperinflation, dyspnea, and exercise performance in COPD.**

Methods: **We compared dyspnea intensity ratings and ventilatory responses (breathing pattern, operating lung volumes, and gas exchange) during symptom-limited incremental cycle exercise in well-characterized groups of 18 obese (mean BMI ± SD, 35 ± 4 kg/m^2) and 18 normal-weight (mean BMI ± SD, 22 ± 2 kg/m^2) patients with moderate to severe COPD.**

Measurements and Main Results: **Groups were well matched for FEV_1 (mean 49% predicted) and diffusing capacity (means >70% predicted), but resting lung hyperinflation (end-expiratory lung volume [EELV]) was significantly reduced in association with increasing BMI ($P < 0.005$). In the obese patients, peak symptom-limited oxygen uptake was increased ($P < 0.01$) and dyspnea ratings at a standardized ventilation were decreased ($P < 0.01$) compared with normal-weight patients. Ratings of dyspnea intensity at a standardized ventilation during exercise correlated well with the concurrent dynamic EELV/total lung capacity (TLC) ratio ($r = 0.68$; $P < 0.00001$) and with the resting EELV/TLC ($r = 0.67$; $P < 0.00001$).**

Conclusions: **The combined mechanical effects of obesity and COPD reduced operating lung volumes at rest and throughout exercise with favorable influences on dyspnea perception and peak oxygen uptake during cycle ergometry.**

Keywords: lung hyperinflation; lung volumes; respiratory mechanics; cycle ergometry

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Obesity and COPD frequently coexist and are increasing in prevalence. The impact of obesity on dynamic respiratory mechanics, dyspnea and exercise intolerance in patients with COPD is unknown.

What This Study Adds to the Field

Despite having greater metabolic and ventilatory requirements, obese COPD patients do not experience greater dyspnea and exercise limitation than normal-weight patients with comparable airway obstruction. This, in part, reflects the mechanical advantage of breathing at relatively lower lung volumes in obesity.

The prevalence of chronic obstructive pulmonary disease (COPD) and obesity is increasing dramatically throughout the western world (1, 2). Obesity is common in patients with COPD (3, 4), and population studies indicate that, paradoxically, its presence appears to convey a survival advantage (5). Although both of these common health problems have been studied extensively in isolation, the impact of their combination on respiratory pathophysiology and symptom intensity during exercise is largely unknown and is the main focus of this study.

The mechanical derangements of simple obesity are well established and include reduced respiratory system compliance with increased work and oxygen cost of breathing (6–8). Functional residual capacity (FRC) and expiratory reserve volume (ERV) are reduced in proportion to the increased body mass index (BMI) (9, 10). During activity, these mechanical abnormalities are compounded by the presence of increased ventilatory requirements secondary to the increased metabolic load (11–15).

The pathophysiologic hallmarks of moderate to severe COPD are expiratory flow limitation and lung hyperinflation (16). In the setting of the increased ventilatory demand of exercise (amplified by ventilation–perfusion abnormalities), further dynamic pulmonary hyperinflation (DH) occurs and precipitates mechanical limitation and intolerable dyspnea at relatively low levels of ventilation in patients with COPD compared with healthy subjects.

At first glance, it is reasonable to anticipate that when the derangements of dynamic ventilatory mechanics of COPD are coupled with the increased metabolic demands and mass loading effects of obesity, dyspnea and exercise intolerance should increase (17, 18). However, a recent study in obese adult women showed that during weight-supported cycle exercise, dyspnea/ventilation ($\dot{V}_E$) slopes were similar to those of normal weight (NW) control subjects (15). This was explained, at least in part, by the advantages of reduced FRC and by recruitment of resting inspiratory capacity (IC) in the setting of a preserved total lung capacity (TLC) in obese (OB) individuals.

In moderate to severe COPD, the severity of exertional dyspnea and exercise intolerance is closely linked to the magnitude of resting and dynamic lung hyperinflation during exercise (19–21). The inability to further expand V_T during exercise as a result of DH and the consequent neuromechanical uncoupling of the respiratory system augments perceived respiratory discomfort (22). Accordingly, small reductions in FRC (and increases in IC) after pharmacologic or surgical lung volume reduction have consistently been associated with improved neuromechanical coupling, dyspnea, and exercise endurance (23–25). Preliminary data from a population study in our laboratory indicate that among patients with similar FEV_1 (across GOLD stages I–IV), resting FRC varied inversely with BMI (26). We hypothesized that in OB patients with COPD,

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Correspondence and requests for reprints should be addressed to Denis E. O'Donnell, M.D., F.R.C.P.(I), F.R.C.P.(C), 102 Stuart Street, Kingston, ON, K7L 2V6 Canada. E-mail: odonnell@queensu.ca

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the reduced resting FRC and the reduced absolute operating lung volumes during exercise would partly counterbalance the negative sensory and mechanical consequences of severe lung hyperinflation in NW, FEV_1-matched patients. To test this hypothesis, we compared perceptual and ventilatory responses during incremental cycle exercise in well-characterized groups of OB and NW patients with moderate to severe COPD.

Some of the results of this study have previously been reported in the form of an abstract at the 2008 European Respiratory Society Annual Congress held in Berlin, Germany (http://www.ersnet.org/learning_resources_player/abstract_print_08/main_frameset.htm).

METHODS

Subjects

We compared 18 OB subjects (BMI >30 kg/m^2) with 18 age-matched NW (BMI 18.5–24.9 kg/m^2) with a clear diagnosis of COPD (FEV_1/FVC ratio <0.7). Subjects were clinically stable men or women, 40 to 75 years of age, with a baseline FEV_1 70% or less predicted. Exclusion criteria included: (*1*) the presence of a significant disease other than COPD that could contribute to dyspnea or exercise limitation (i.e., metabolic, cardiovascular, neuromuscular, musculoskeletal, or other respiratory diseases); (*2*) important contraindications to clinical exercise testing; (*3*) a clinical phenotype of emphysema with a D_{LCO} less than 40% predicted; (*4*) clinically significant desaturation of 4% or greater during the exercise test or the use of supplementary oxygen; and (*5*) patients who fit the extremes of physical activity levels (i.e., sedentary/housebound or excessively active/training). A subgroup of subjects (8 OB, 6 NW) with similar characteristics to the main group had arterialized capillary blood samples taken during testing.

Study Design

This was a cross-sectional study with ethical approval from the University and Hospital Health Sciences Research Ethics Board. After we obtained informed consent and performed appropriate screening of medical history, subjects completed two visits to the laboratory. The first visit included initial screening with familiarization to all testing procedures and questionnaires. The second visit included pulmonary function testing and symptom-limited cardiopulmonary exercise testing.

Procedures

During initial screening, basic anthropometric measurements were obtained. Chronic activity-related dyspnea was assessed using the modified Baseline Dyspnea Index (27). Routine spirometry, body plethysmography, single-breath D_{LCO}, and maximum inspiratory and expiratory mouth occlusion pressure (MIP and maximal expiratory pressure, measured at FRC and TLC, respectively) were performed (6200 Autobox DL and Vmax229d; SensorMedics, Yorba Linda, CA) in accordance with recommended techniques (28–32). Pulmonary function measurements were standardized as percentage of predicted normal values (33–38); predicted normal inspiratory capacity (IC) was calculated as predicted TLC minus predicted FRC.

Symptom-limited incremental exercise testing was conducted on an electronically braked cycle ergometer (Ergometrics 800S; SensorMedics, Yorba Linda, CA) using the Vmax229d Cardiopulmonary Exercise Testing System (SensorMedics) according to recommended guidelines (39) as previously described (15). Exercise tests consisted of a steady-state resting period and a 1-minute warm-up of unloaded pedaling followed by a stepwise protocol of 10- to 20-W increments. The anaerobic threshold (AT) was detected individually using three methods (40). For each individual, $\dot{V}O_2$ was standardized as a percentage of the predicted normal value corrected for ideal body weight (41). Arterialized capillary blood samples were obtained from a warmed earlobe for estimation of Pa_{CO_2} at rest and at peak exercise (ABL-5; Radiometer, Copenhagen, Denmark).

Statistical Analysis

A sample size of at least 16 was used to provide the power (80%) to detect a significant difference in dyspnea intensity (Borg scale) measured at a standardized exercise work rate based on a relevant difference in Borg ratings of ± 1, a SD of 1 for standardized Borg ratings found at our laboratory in a healthy older population, $\alpha = 0.05$, and a two-tailed test of significance. Group comparisons were made using unpaired *t* tests with appropriate Bonferroni adjustments for multiple comparisons. Measurements were compared at rest, at common standardized exercise work rates (20W, 40W), at an iso-$\dot{V}E$ of 25 L/min (data for this highest common $\dot{V}E$ achieved in all subjects' tests was interpolated between the nearest available measured points for each subject), and at peak exercise. Pearson correlations were used to establish associations between the chosen dependent variables (i.e., dyspnea intensity, exercise capacity) and relevant independent variables. A $P < 0.05$ level of statistical significance was used for all analyses. Results are expressed as means ± SD.

RESULTS

Subjects' characteristics are shown in Table 1. Eighteen OB patients with COPD (BMI range, 30–47 kg/m^2) and 18 FEV_1–matched NW (BMI range, 19.7–24.9 kg/m^2) patients with COPD were studied. The presence of the following comorbidities was balanced between groups: controlled hypertension (7 OB, 8 NW), hypercholesterolemia (4 OB, 6 NW), diabetes mellitus (4 OB, 2 NW), stable ischemic heart disease (4 OB, 2 NW), osteoarthritis (3 OB, 3 NW), and mild depression/anxiety (3 OB, 4 NW). Additional comorbidities in the OB group included hypothyroidism (n = 1), peptic ulcer (n = 1), irritable bowel disease (n = 1), GERD (n = 1), and sleep apnea (n = 2).

Pulmonary Function

Pulmonary function test results are summarized in Table 1. There were no significant differences between groups in spirometric measurements, D_{LCO}, specific airway resistance, or MIP. In absolute and relative terms, OB had a significantly smaller FRC and ERV compared with NW; TLC expressed as a percentage of predicted was significantly smaller ($P < 0.01$); the IC/TLC ratio was significantly larger ($P < 0.01$); and the OB group had a greater maximal expiratory pressure, which fell within the predicted normal range. In all subjects, BMI correlated significantly with FRC % predicted ($r = -0.50$; $P < 0.005$), FRC/TLC ($r = -0.53$; $P < 0.001$) or its inverse IC/TLC ($r = 0.53$; $P < 0.001$), and ERV % predicted ($r = -0.57$; $P < 0.001$).

Symptom-limited Cycle Exercise

The distribution of reasons for stopping exercise was similar ($P = 0.41$) in OB and NW subjects. Intensity ratings of dyspnea and leg discomfort relative to work rate were not significantly different in OB and NW subjects (Figure 1). Several responses to exercise are shown in Figure 1 and are summarized in Table 2. The OB group reached a higher peak $\dot{V}O_2$ and had an upward displaced and steeper $\dot{V}O_2$–work rate slope (11.4 ± 1.6 vs. 10.2 ± 1.8 mL/min/W; $P < 0.05$) compared with the NW group. The OB group also reached a significantly higher peak work rate than the NW group but not when expressed relative to the predicted normal value (50 ± 19 and 57 ± 20% predicted in the NW and OB groups, respectively). An anaerobic threshold (AT) was detected in 13 subjects within each group: $\dot{V}O_2$ at AT was significantly greater in the OB group compared with the NW group (1.09 ± 0.20 vs. 0.80 ± 0.21 L/min; $P = 0.001$) but was similar when expressed as a percentage of peak $\dot{V}O_2$ (79 ± 10 vs. 81 ± 14%; $P = 0.630$). Both groups had a similar resting heart rate and heart rate reserve at peak exercise. The O_2 pulse was significantly ($P < 0.05$) higher in the OB group at rest and throughout exercise due to the greater $\dot{V}O_2$. No patient showed evidence of significant cardiac ischemia or arrhythmia during exercise testing.

At the end of exercise, both groups stopped when they reached a critical ventilatory reserve ($\dot{V}E$/MVC <15% and a reduced

TABLE 1. SUBJECT CHARACTERISTICS*

	Normal Weight (*n* = 18)	Obese (*n* = 18)
Male, % of group	50	61
Age, years	65 ± 7	64 ± 9
Height, cm	167 ± 12	167 ± 9
Weight, kg	63 ± 9	97 ± 11†
Body mass index, kg/m^2	22.4 ± 1.7	34.8 ± 3.6†
Body surface area, m^2	1.7 ± 0.2	2.0 ± 0.2†
COPD duration, years	7 ± 5	10 ± 8
Smoking history, pack-years	44 ± 18	56 ± 45
Baseline dyspnea index, focal score	6.3 ± 1.2	6.3 ± 1.2
Pulmonary function:		
FEV_1, L (% predicted)	1.22 ± 0.5 (49 ± 12)	1.25 ± 0.2 (49 ± 8)
FVC, L (% predicted)	2.71 ± 0.8 (77 ± 13)	2.72 ± 0.6 (75 ± 11)
FEV_1/FVC,%	44 ± 7	47 ± 9
PEFR, L/s (% predicted)	3.8 ± 1.0 (56 ± 12)	4.1 ± 0.9 (59 ± 14)
FEF_{50}, L/s (% predicted)	0.5 ± 0.3 (12 ± 6)	0.6 ± 0.2 (14 ± 4)
D_{LCO}, mL/min/mm Hg (% predicted)	14.2 ± 5.6 (78 ± 28)	16.8 ± 4.1 (72 ± 15)
TLC, L (% predicted)	7.25 ± 1.55 (124 ± 13)	6.62 ± 1.38 (112 ± 11†)
FRC, L (% predicted)	5.28 ± 1.33 (166 ± 29)	4.39 ± 1.17‡ (137 ± 24†)
FRC/TLC, %	73 ± 6	66 ± 7†
RV, L (% predicted)	4.18 ± 1.18 (194 ± 53)	3.54 ± 1.01 (165 ± 32)
ERV, L (% predicted)	1.10 ± 0.44 (112 ± 34)	0.79 ± 0.39‡ (74 ± 26†)
IC, L (% predicted)	1.97 ± 0.56 (74 ± 16)	2.23 ± 0.48 (83 ± 16)
IC/TLC, %	27 ± 6	34 ± 7†
sRaw, cm H_2O s (% predicted)	27.2 ± 10.2 (647 ± 231)	24.0 ± 11.8 (559 ± 256)
MIP, cm H_2O (% predicted)	60 ± 22 (82 ± 28)	76 ± 27 (98 ± 45)
MEP, cm H_2O (% predicted)	101 ± 32 (63 ± 19)	155 ± 37† (89 ± 22†)

Abbreviations: ERV = expiratory reserve volume; FEF_{50} = forced expiratory flow at 50% of FVC; IC = inspiratory capacity; MIP = maximal inspiratory pressure measured at FRC; MEP = maximal expiratory pressure measured at TLC; PEFR = peak expiratory flow rate; RV = residual volume; sRaw = specific airway resistance.

* Values are means ± SD with percentage of the predicted normal value in parentheses.

† $P < 0.01$; ‡ $P < 0.05$, obese group vs. normal-weight group.

IRV <10% of TLC). Throughout exercise, $\dot{V}_E$ was significantly greater in the OB group at rest (by 2.7 L/min; $P = 0.0008$), at any given work rate (by at least 3 L/min; $P < 0.05$), and at peak exercise (by 9.1 L/min; $P = 0.015$). Although there was also a significantly heightened $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ in the OB group compared with NW group, the OB group showed greater ventilatory efficiency (i.e., $\dot{V}_E/\dot{V}_{CO_2}$ slopes were 28 ± 4 and 33 ± 6 in the OB and NW groups, respectively; $P < 0.05$). There were no significant differences in Sa_{O_2} or end-tidal CO_2 between groups, and no patients in either group had significant arterial O_2 desaturation, even at peak exercise. In the subgroup of subjects (8 OB, 6 NW) with arterialized blood samples, the calculated V_D/V_T ratio was similar at rest (52%) but lower at peak exercise in the OB group than in the NW group; thus, the decrease from rest to peak exercise was greater (more normal) in the OB group (−19 ± 8%) than the NW group (−9 ± 6%; $P = 0.021$).

Breathing Pattern and Operating Lung Volumes

Breathing pattern was similar in both groups when expressed relative to $\dot{V}_E$. However, the OB group breathed more rapidly than the NW group at rest (by 3.4 breaths/min; $P = 0.026$), at early work rates (20W: by 3.4 breaths/min; $P = 0.06$), and at peak exercise (by 4.6 breaths/min; $P = 0.05$) (Figure 1; Table 2). The dynamic EELV and EILV in percent of the TLC predicted were lower at rest and throughout exercise in the OB group compared with the NW group (Figure 2; Table 2). The magnitude of dynamic hyperinflation during exercise was similar in both groups ($\Delta EELV_{peak\text{-}rest}$ = 0.54 ± 0.27 vs. 0.52 ± 0.31 L; $P = 0.9$). At peak exercise, both groups reached a similar minimal IRV, but at this point, peak $\dot{V}_E$ in the OB group was 9 L/min greater than in the NW group; in other words, the subjects in the OB group reached their minimal IRV at a higher $\dot{V}_E$. Tidal and maximal flow-volume loops are shown for a representative subject in each group in Figure 3.

Correlates of Dyspnea and Exercise Capacity

Exertional dyspnea intensity at isoventilation correlated best with the concurrently measured dynamic EELV/TLC ($r = 0.68$; $P < 0.0001$) (Figure 4) as well as with several resting measurements: FRC/TLC or EELV/TLC ($r = 0.67$; $P < 0.0001$), RV/TLC ($r = 0.61$; $P < 0.0001$), IC % predicted ($r = 0.69$; $P < 0.0001$), FRC % predicted ($r = 0.54$; $P < 0.001$), $FEF_{50\%}$ ($r = 0.59$; $P < 0.001$), PEFR ($r = -0.55$; $P < 0.001$), and FEV_1% predicted ($r = -0.52$; $P < 0.005$). Peak $\dot{V}_{O_2}$ expressed as a percentage of predicted normal (taking into account ideal body weight) correlated well with resting: FRC/TLC ($r = -0.65$; $P < 0.0001$) (Figure 4), FRC % predicted ($r = -0.65$; $P < 0.0001$), RV % predicted ($r = -0.59$; $P < 0.0005$), IC % predicted ($r = 0.56$; $P < 0.001$), FEV_1% predicted ($r = 0.54$; $P = 0.001$), and BMI ($r = 0.49$; $P = 0.002$).

Dyspnea/$\dot{V}_E$ curves were shifted rightward with obesity, such that the inflection in this relationship where dyspnea intensity began to rise more quickly occurred at a higher $\dot{V}_E$ in the OB compared with the NW group (Figure 5). Dyspnea/$\dot{V}_{O_2}$ curves were also shifted rightward; at iso-$\dot{V}_{O_2}$ (750 ml/min), the mean dyspnea ratings were 1.33 and 2.86 Borg units in the OB and NW groups, respectively ($P < 0.05$). Dyspnea/IRV curves were superimposed in both groups, indicating the importance of mechanical ventilatory reserve to dyspnea causation (Figure 5).

DISCUSSION

The main findings of this study are: (*1*) OB patients with COPD did not experience greater dyspnea and exercise limitation than NW patients with comparable FEV_1. (*2*) In OB patients with COPD, dyspnea intensity ratings were reduced at any given $\dot{V}_E$ and $\dot{V}_{O_2}$ compared with NW patients with COPD. (*3*) Ventilatory requirements were increased for a given work rate in OB

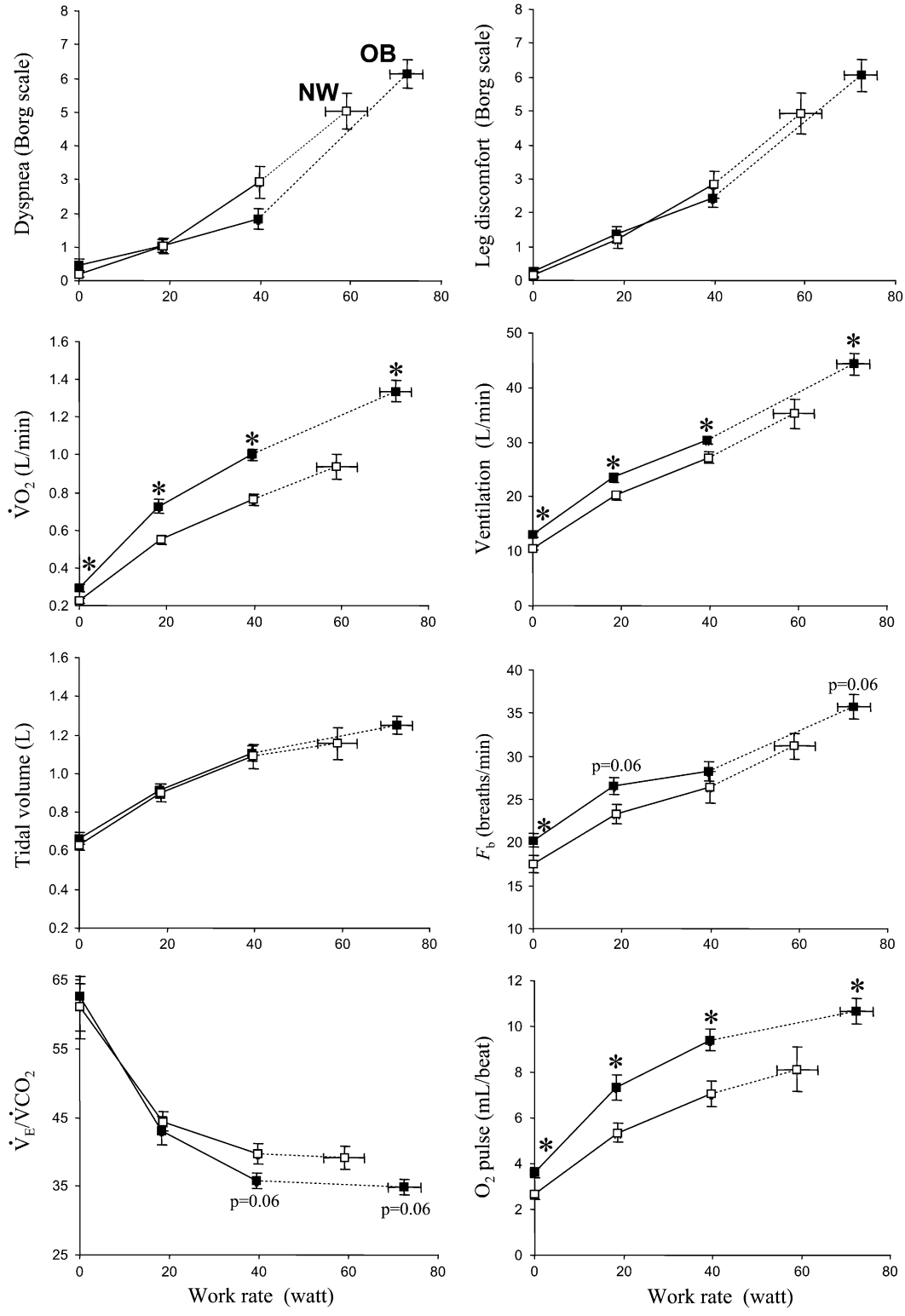

Figure 1. Dyspnea intensity, leg discomfort, $\dot{V}O_2$, $\dot{V}_E$, V_T, breathing frequency, ventilatory equivalent for carbon dioxide production ($\dot{V}_E/\dot{V}CO_2$), and O_2 pulse are shown in response to symptom-limited incremental cycle exercise in obese (OB) subjects with chronic obstructive pulmonary disease (COPD) (*closed squares*) and in normal-weight (NW) subjects with COPD (*open squares*). Despite the higher $\dot{V}_E$ and $\dot{V}O_2$ at any given work rate, the OB group did not experience greater dyspnea. Values are means ± SE. *$P < 0.05$, OB versus NW at standardized work rates or at peak exercise.

patients with COPD in association with the increased metabolic cost of pedaling. (*4*) The resting EELV/TLC ratio and dynamic operating lung volumes (EELV and EILV, standardized as % of predicted TLC) were uniformly lower in OB patients with COPD compared with NW patients with COPD.

Our groups were clearly demarcated by BMI but well matched for age, height, gender, smoking history, and presence of comorbidities. The average values for FEV_1 and D_{LCO} (expressed as % predicted) were similar across groups. However, plethysmographically derived lung volumes (FRC, TLC) were lower in the OB group (see below). Regardless of body weight, all of these study patients had clinically significant respiratory mechanical constraints and experienced severe exertional dyspnea and exercise intolerance.

The average peak symptom-limited $\dot{V}O_2$ (corrected for ideal body weight) was greater in the OB group compared with the NW group. $\dot{V}O_2$–work rate relationships were significantly higher in OB patients with COPD, likely reflecting their

TABLE 2. MEASUREMENTS AT REST, AT ISOVENTILATION, AND AT THE PEAK OF SYMPTOM-LIMITED INCREMENTAL CYCLE EXERCISE

	Rest		Iso-ventilation at 25 L/min		Peak	
	NW	OB	NW	OB	NW	OB
Dyspnea, Borg	0.2 ± 0.3	0.5 ± 0.8	2.4 ± 1.6	1.2 ± 1.1*	5.0 ± 2.4	6.1 ± 2.17
Leg discomfort, Borg	0.2 ± 0.5	0.3 ± 0.7	2.3 ± 1.6	1.5 ± 1.1	4.9 ± 2.7	6.1 ± 2.41
Work rate, watts	0	0	34 ± 10	24 ± 10*	59 ± 20	72 ± 19†
$\dot{V}O_2$, L/min	0.22 ± 0.06	0.29 ± 0.10†	0.69 ± 0.12	0.79 ± 0.15†	0.94 ± 0.31	1.34 ± 0.29*
$\dot{V}O_2$, % predicted maximum	14 ± 4	15 ± 5	45 ± 11	44 ± 11	58 ± 14	72 ± 12*
$\dot{V}CO_2$, L/min	0.18 ± 0.05	0.24 ± 0.08†	0.62 ± 0.12	0.65 ± 0.13	0.94 ± 0.37	1.30 ± 0.31*
$\dot{V}E$, L/min	11 ± 2	13 ± 3*	25	25	35 ± 12	44 ± 10†
V_T, L	0.63 ± 0.13	0.66 ± 0.15	1.03 ± 0.24	0.97 ± 0.17	1.15 ± 0.37	1.25 ± 0.24
V_T, % predicted VC	19 ± 6	18 ± 4	30 ± 7	27 ± 6	33 ± 6	35 ± 6
F_b, breaths/min	18 ± 4	21 ± 5	25 ± 6	27 ± 5	31 ± 7	36 ± 7†
T_I/T_{TOT}	0.38 ± 0.05	0.38 ± 0.05	0.40 ± 0.03	0.39 ± 0.02	0.41 ± 0.03	0.40 ± 0.03
V_T/T_E, L/s	0.29 ± 0.06	0.36 ± 0.08*	0.69 ± 0.05	0.70 ± 0.03	1.00 ± 0.33	1.22 ± 0.28†
IC, L	2.09 ± 0.54	2.22 ± 0.47	1.79 ± 0.62	1.94 ± 0.49	1.57 ± 0.50	1.60 ± 0.32
IC, % predicted	80 ± 18	82 ± 16	67 ± 15	71 ± 13	59 ± 11	59 ± 9
V_T/IC, %	31 ± 9	30 ± 7	60 ± 13	53 ± 15	74 ± 10	79 ± 10
EELV, L	5.15 ± 1.34	4.40 ± 1.21	5.45 ± 1.25	4.68 ± 1.19	5.67 ± 1.27	5.02 ± 1.25
EELV, % predicted TLC	88 ± 15	74 ± 14*	94 ± 15	79 ± 14*	98 ± 14	85 ± 13*
EELV/TLC, %	71 ± 7	66 ± 7†	75 ± 6	70 ± 6†	78 ± 5	75 ± 5
EILV/TLC, %	80 ± 6	76 ± 6	90 ± 5	86 ± 6†	94 ± 3	95 ± 3
IRV, L	1.46 ± 0.50	1.56 ± 0.44	0.76 ± 0.47	0.98 ± 0.52	0.42 ± 0.21	0.35 ± 0.19
IRV, % predicted TLC	25.1 ± 7.2	26.7 ± 6.9	12.5 ± 6.3	16.1 ± 7.5	7.0 ± 3.3	5.8 ± 2.9
$\dot{V}E/\dot{V}O_2$	50 ± 12	53 ± 29	37 ± 7	34 ± 8	38 ± 6	34 ± 6†
$V'_E/V'CO_2$	61 ± 16	65 ± 31	42 ± 9	41 ± 10	39 ± 8	35 ± 5
P_{ETCO_2}, mmHg	35 ± 3	36 ± 4	40 ± 5	42 ± 6	41 ± 5	44 ± 6
HR, beats/min	86 ± 8	82 ± 15	118 ± 22	103 ± 21†	126 ± 30	124 ± 19
Sp_{O_2}, %	95 ± 2	94 ± 2	95 ± 3	94 ± 2	93 ± 3	93 ± 3

Definition of abbreviations: EELV = end-expiratory lung volume; EILV = end-inspiratory lung volume; F_b = breathing frequency; HR = heart rate; IC = inspiratory capacity; IRV = inspiratory reserve volume; nw = normal weight; OB = obese; P_{ETCO_2} = end-tidal partial pressure of carbon dioxide; pred = predicted; Sp_{O_2} = oxygen saturation by pulse oximetry; T_I/T_{TOT} = inspiratory duty cycle; V_T/T_E = mean expiratory flow rate.

* Statistically different from normal-weight control group at $P < 0.01$.

† Statistically different from normal-weight control group at $P < 0.05$.

increased metabolic needs. During weight-supported cycle exercise, metabolic inefficiency is linked to the greater O_2 cost of movement and propulsion of their heavy limbs (11, 12, 15, 42, 43). This higher metabolic cost was associated with a small but consistent increase in $\dot{V}E$ (by ~3 L/min) for any given power output in OB patients with COPD. The increased ventilatory stimulation could not be attributed to earlier metabolic acidosis because average ventilatory thresholds were higher in the OB group versus the NW group. Increased chemostimulation as a result of greater disruption of pulmonary gas exchange is also unlikely. Indeed, the consistently reduced $\dot{V}E/\dot{V}CO_2$ slopes during exercise in OB compared with NW patients indicates

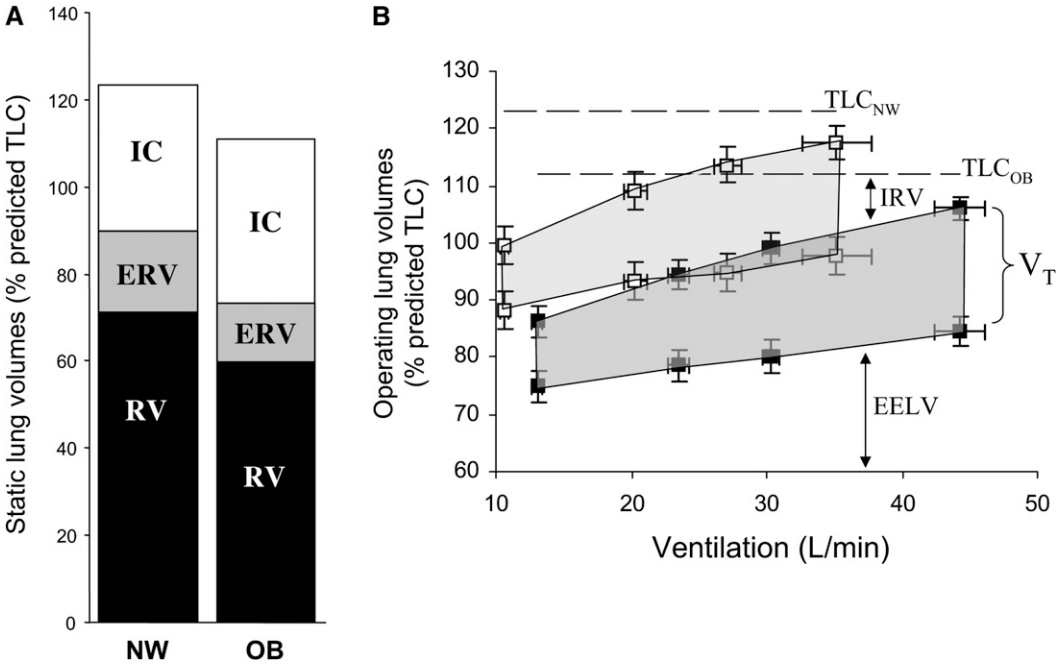

Figure 2. (*A*) Static lung volumes measured by body plethysmography at rest. Expiratory reserve volume (ERV) and functional residual capacity (FRC) (ERV + RV) were significantly ($P < 0.05$) lower in the obese (OB) group. (*B*) Lung volumes are shown from rest to peak exercise in OB patients with chronic obstructive pulmonary disease (COPD) (*closed squares*) and in normal-weight (NW) patients with COPD (*open squares*). In the OB compared with the NW group, end-expiratory lung volume (EELV) (standardized as a % of predicted TLC) was consistently lower (*$P < 0.01$) at rest and throughout exercise; the OB group reached an EELV at peak exercise that was similar to that of the NW group at the pre-exercise resting level. IC = inspiratory capacity; IRV = inspiratory reserve volume; V_T = tidal volume (*shaded area*); RV = residual volume. Values are means ± SE.

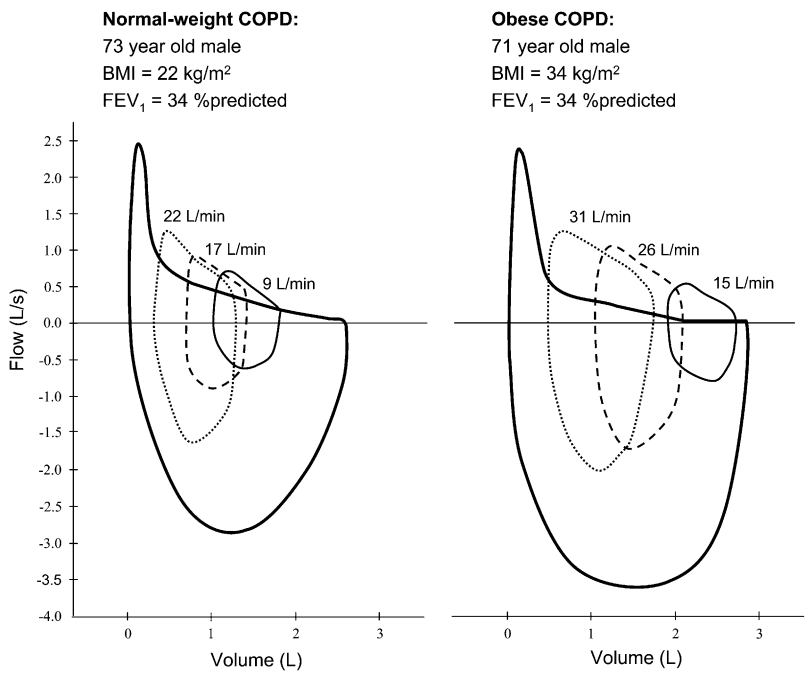

Figure 3. Tidal and maximal flow-volume loops are shown in representative subjects from each body mass index (BMI) group. Tidal loops are shown at steady-state rest (*solid loop*), at a cycle work rate of 20 watts (*dashed loop*), and at symptom-limited peak exercise (*dotted loop*) for each subject. The respective $\dot{V}_E$ is indicated for each tidal loop.

greater ventilatory efficiency in the former. Improved ventilation/perfusion relations have previously been described during exercise in obesity without respiratory disease (44). Physiological dead space measurements during exercise fell to a greater extent (i.e., more normally) in the OB than in the NW groups.

Why do patients with the combined mechanical abnormalities of obesity and COPD report lower dyspnea intensity ratings at a standardized $\dot{V}_E$ than their NW counterparts? This relatively reduced dyspnea intensity in OB patients with COPD could not be explained by improvements in Sa_{O_2} or CO_2 elimination. Breathing frequency at any given $\dot{V}_E$ was more rapid in the OB subjects compared with the NW subjects. This breathing pattern represents the appropriate compensatory response to minimize the mechanical effects of elastic loading and may help to reduce respiratory discomfort in obesity (15).

We suggest that improved static and dynamic ventilatory mechanics is the most likely contributory factor to reduced dyspnea intensity in OB patients with COPD. FRC was diminished (~0.9 L) in OB subjects compared with NW subjects. Peak exercise EELV in OB patients with COPD was similar to the baseline resting EELV in NW patients with COPD (i.e., 85 vs. 88% of the predicted TLC, respectively). The lower TLC (by 0.6 L) in OB patients with COPD likely reflects a relative reduction in lung and respiratory system compliance. Measurements of static inspiratory muscle strength, the other major determinant of TLC, were similar in both groups. These obesity-related effects were associated with a reduced EELV/TLC and preservation of IC/TLC, both of which may have favorable prognostic and physiologic implications for patients with COPD (21). Our results therefore confirm the previously reported association between BMI and IC/TLC by Casanova and colleagues (21).

The reduced FRC in OB patients with COPD would be expected to predispose patients to greater expiratory flow limitation (15, 45, 46). However, resting expiratory flow rates in the effort-independent range were not diminished in obesity, and specific airway resistance was similar across groups despite the lower absolute EELV in obesity. The pattern of DH from rest to peak exercise was similar in both groups. Mean expiratory flow rates and $\dot{V}_E$ during exercise were higher for a given work rate in OB patients with COPD despite the reduced operating lung volumes. Collectively, these results suggest that OB patients with COPD were not more predisposed to expiratory flow limitation. The mechanisms for the preserved (or enhanced) tidal expiratory flow rates in obesity, despite lower operating lung volumes, were not ascertained. One possible mechanism is better preserved static lung compliance and driving pressure for expiratory flow.

We have shown that the beneficial effects of DH on airway conductance in early exercise are negated by the increased elastic loading and functional weakening of the inspiratory muscles that are associated with breathing close to TLC (38).

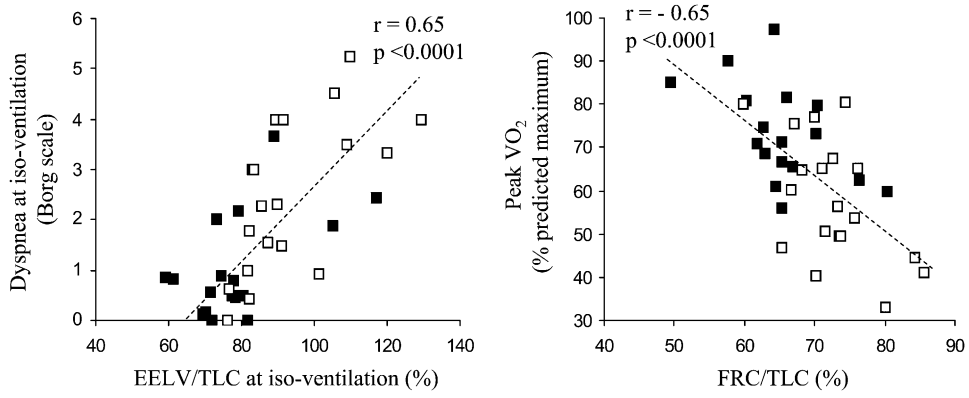

Figure 4. Significant correlations were found between Borg ratings of exertional dyspnea intensity at isoventilation and the concurrent end-expiratory lung volume (EELV)/TLC ratio (*left*) and between $\dot{V}_{O_2}$ at peak exercise and the resting functional residual capacity (FRC)/TLC ratio (*right*). The data shown are for obese (*solid squares*) and normal-weight (*open squares*) subjects with COPD.

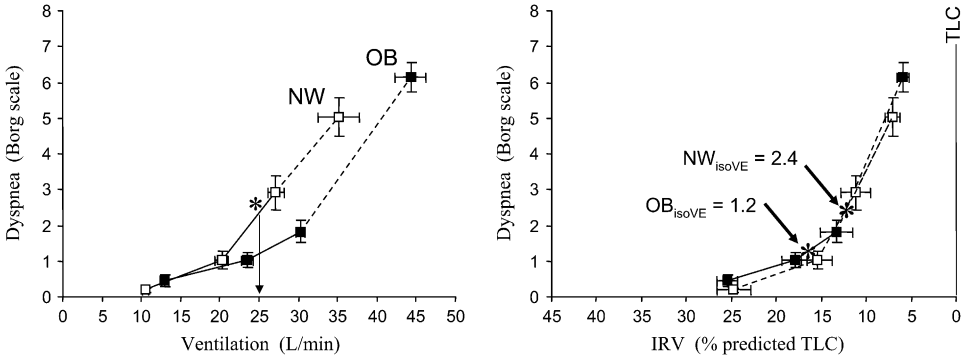

Figure 5. (*Left panel*) Obese (OB) subjects with chronic obstructive pulmonary disease (COPD) (*solid squares*) had a rightward shifted dyspnea/ventilation ($\dot{V}_E$) slope in comparison with normal-weight subjects with COPD (*open squares*). At an iso-$\dot{V}_E$ of 25 L/min (*vertical line with arrow*), dyspnea intensity was 1.2 ± 1.1 versus 2.4 ± 1.6 Borg units in OB versus NW ($P < 0.01$). (*Right panel*) In both groups, the relationship between dyspnea intensity and inspiratory reserve volume (IRV) (standardized as a % of predicted TLC) predicted were superimposed. At iso-$\dot{V}_E$, subjects in the OB group were on the flatter part of the dyspnea/IRV curve while NW subjects were on the steeper portion of the curve. Values are means ± SE. * $P < 0.01$ OB versus NW at iso-$\dot{V}_E$.

Dyspnea/$\dot{V}_E$ slopes were decreased, but dyspnea/IRV slopes were superimposed throughout exercise in both groups (Figure 5). As previously reported, dyspnea intensity rises sharply to intolerable levels after dynamic IRV reaches a critical minimal level (at ~10% TLC). The relatively reduced EELV in obesity meant that such patients reached this dyspnea inflection point later in exercise (at higher $\dot{V}_E$) than the more hyperinflated NW patients. Similar arguments were advanced to explain the lack of increase in breathlessness for any given ventilation during exercise in OB women compared with NW control subjects (15). Reduced dyspnea intensity ratings at a given $\dot{V}_E$ during exercise correlated well with decreased resting (and exercise) EELV/TLC ratios for the group as a whole ($P < 0.0001$). The determinants of an increased EELV/TLC ratio (i.e., high lung volumes, increased mechanical constraints on V_T expansion during exercise as a result of reduced IC, and increased respiratory muscle weakness) are potential contributors to dyspnea and poor exercise capacity in COPD. The corollary of this is that improvement in these physiologic indices in our OB patients has positive implications for dyspnea.

Based on the results of previous interventional studies (23–25), the reduced absolute lung volumes during exercise in the OB patients with COPD must mean reduced elastic/threshold loading and improved length–tension relations of the inspiratory muscles compared with more hyperinflated NW patients. Thus, the central motor command output (and central corollary discharge) required to drive the ventilatory muscles to achieve the required ventilation should be lower than in the NW (i.e., the more hyperinflated) group.

Both groups had evident heart rate reserve at peak exercise. Dynamic cardiac function during exercise, as estimated by indirect indices (i.e., O_2 pulse, ventilatory threshold, and peak $\dot{V}_{O_2}$), was superior in the OB group compared with the NW group. Possible explanations for this include intergroup differences in peripheral skeletal muscle function, in cardiovascular system function, or in cardiopulmonary interactions during exercise. By direct inquiry, both groups appeared to have similar daily activity levels (and therefore skeletal muscle conditioning effects), and patients with clinically overt cardiac impairment were excluded from the study. Recent studies have confirmed an association between the degree of lung hyperinflation and a reduction in O_2 pulse, a crude measure of stroke volume during exercise (47). Moreover, acute pharmacologic lung volume reduction in patients with COPD was associated with improvements in O_2 pulse during cycle exercise compared with placebo (48). The reduced lung hyperinflation in OB patients with COPD may improve dynamic cardiac function.

Study Limitations

We studied ventilatory and perceptual responses during cycle ergometry, and our results may have been different had we used weight-bearing exercise protocols for which metabolic and ventilatory requirements are known to be relatively increased, particularly in obesity. The mechanical advantages of reduced lung hyperinflation in OB patients with COPD should persist during walking, but earlier respiratory mechanical constraints (with associated negative sensory consequences) may occur at lower a $\dot{V}_E$ than during weight-supported exercise. Both groups were well matched for resting pulmonary function (including average D_{LCO}, which remained >70% predicted in both groups), but estimates of radiographic emphysema were not available. Individuals in both groups likely had some degree of emphysema based on the range of D_{LCO} and the extent of hyperinflation: D_{LCO} in OB and NW ranged from 51 to 97% and 41 to 134% predicted, respectively. We excluded underweight (BMI <18.5 kg/m^2) patients with severely reduced D_{LCO} (<40% predicted) and severe arterial oxygen desaturation during exercise. Our results therefore may not be generalizable to patients with severe emphysema. Measurements of body composition and the distribution patterns of fat mass were also not available in our study patients. However, the results of recent studies suggest that respiratory mechanical abnormalities in obesity are more closely associated with BMI than with fat distribution patterns *per se* (49, 50). The impact of comorbidities on dyspnea perception could not be ascertained, but comorbidities were similarly distributed across groups.

Conclusion

This was the first study to explore the relationship between obesity, operating lung volumes, and exercise intolerance in patients with moderate to severe COPD. Contrary to current beliefs, the combination of obesity and COPD was not associated with diminished exercise capacity or greater dyspnea compared with NW patients with similar reduction in FEV_1. The relatively reduced lung hyperinflation in OB patients with COPD meant that exercise performance was not compromised by greater perceived respiratory discomfort despite increased metabolic and ventilatory requirements. Thus, our results indicate that the interaction between BMI and lung hyperinflation influences the sensory and physiological responses to exercise among patients with a similar FEV_1.

Conflict of Interest Statement: J.O. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. P.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. D.O. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. K.A.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. D.E.O. has served on an advisory board for Boehringer, Pfizer, GSK, and Roche ($1,001–5,000), has received lecture fees from Boehringer, Pfizer, and GSK ($1,001–5,000), and has received industry-sponsored grants from Boehringer Ingelheim, GSK, and Merck Frost Canada ($100,001 or more) and from Novartis and Pfizer ($50,001–100,000).

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