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Effect of obesity on respiratory mechanics during rest and exercise in COPD

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Ora J, Laveneziana P, Wadell K, Preston M, Webb KA, O'Donnell DE. Effect of obesity on respiratory mechanics during rest and exercise in COPD. *J Appl Physiol* 111: 10–19, 2011. First published February 24, 2011; doi:10.1152/japplphysiol.01131.2010.—The presence of obesity in COPD appears not to be a disadvantage with respect to dyspnea and weight-supported cycle exercise performance. We hypothesized that one explanation for this might be that the volume-reducing effects of obesity convey mechanical and respiratory muscle function advantages. Twelve obese chronic obstructive pulmonary disease (COPD) (OB) [forced expiratory volume in 1 s (FEV_1) = 60%predicted; body mass index (BMI) = 32 ± 1 kg/m^2; mean ± SD] and 12 age-matched, normal-weight COPD (NW) (FEV_1 = 59%predicted; BMI = 23 ± 2 kg/m^2) subjects were compared at rest and during symptom-limited constant-work-rate exercise at 75% of their maximum. Measurements included pulmonary function tests, operating lung volumes, esophageal pressure, and gastric pressure. OB vs. NW had a reduced total lung capacity (109 vs. 124%predicted; $P < 0.05$) and resting end-expiratory lung volume (130 vs. 158%predicted; $P < 0.05$). At rest, there was no difference in respiratory muscle strength but OB had greater ($P < 0.05$) static recoil and intra-abdominal pressures than NW. Peak ventilation, oxygen consumption, and exercise endurance times were similar in OB and NW. Pulmonary resistance fell ($P < 0.05$) at the onset of exercise in OB but not in NW. Resting inspiratory capacity, dyspnea/ventilation plots, and the ratio of respiratory muscle effort to tidal volume displacement were similar, as was the dynamic performance of the respiratory muscles including the diaphragm. In conclusion, the lack of increase in dyspnea and exercise intolerance in OB vs. NW could not be attributed to improvement in respiratory muscle function. Potential contributory factors included alterations in the elastic properties of the lungs, raised intra-abdominal pressures, reduced lung hyperinflation, and preserved inspiratory capacity.

cycle ergometry; lung hyperinflation; lung volumes; respiratory mechanics

OBESITY is increasingly recognized as an important comorbidity in patients with COPD (11, 43). The coexistence of these two common conditions has potentially important physiological (34), clinical, and even prognostic implications that are currently poorly understood (13).

In patients without airway disease, obesity is associated with a restrictive ventilatory deficit due to reduced respiratory system compliance (4, 27, 36). The lower static lung volumes in obesity predispose to increased airway resistance and expiratory flow limitation (33, 35). The lower resting end-expiratory lung volume (EELV) [and expiratory reserve volume (ERV)] in obese individuals is associated with an increased resting inspiratory capacity (IC) compared with lean individuals (18, 33). We have suggested that this, in conjunction with dynamic increases in EELV during exercise toward the predicted natural relaxation volume of the respiratory system, may counterbalance some of the negative mechanical effects of obesity (3, 33).

The evaluation of the combined mechanical effects of mild obesity and COPD is highly relevant given the evidence that EELV diminishes exponentially with increasing BMI and that significant volume effects are seen even in the overweight range (18, 29). We have recently reported that resting IC, symptom-limited peak oxygen uptake ($\dot{V}O_2$), and exertional dyspnea intensity ratings were not negatively impacted by obesity in patients with COPD (34). A recent retrospective analysis of a larger COPD cohort again confirmed that increased BMI was not a disadvantage with respect to resting IC, constant-work-rate cycle endurance time, or dyspnea intensity (20). The main objective of the present study was to better understand this surprising preservation of exercise capacity in patients with combined COPD and obesity.

The effect of obesity on respiratory muscle/mechanical factors during exercise in any given individual with COPD is difficult to predict but likely reflects the balance of several factors. Potential negative influences include increased elastic loading of the respiratory muscles, increased metabolic and ventilatory requirements, and increased airway dysfunction and pulmonary resistance at the lower absolute lung volumes. Potential positive counterbalancing effects include improved operating length of the diaphragm at a lower EELV and increased driving pressure for expiratory flow due to increased static lung recoil. The present study extends our previous work by measuring these complex interactions in some detail. Specifically, our objective was to determine the effect of obesity on ventilatory mechanics and respiratory muscle function during rest and exercise in patients with COPD. Our hypothesis was that obesity in COPD would be associated with increased static lung recoil pressure, a reduced EELV, a preserved or enhanced IC, increased intra-abdominal pressure, and improved diaphragmatic function during exercise. These obesity-related physiological differences would ensure that neuromechanical uncoupling of the respiratory system and the associated exertional dyspnea are not further amplified when compared with normal-weight COPD patients. To test this hypothesis, we compared dyspnea ratings, operating lung volumes, breathing pattern, respiratory pressure-derived measurements at rest, and during symptom-limited, constant-work-rate cycle exercise in obese and normal weight patients with moderate to severe COPD.

METHODS

Subjects. We studied 12 subjects with mild obesity (OB) [body mass index (BMI) 30.0–34.9 kg/m^2] and 12 age-matched normal-weight subjects (NW) (BMI 18.5–24.9 kg/m^2). Subjects were clinically stable men or women, 55–85

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years of age, with a clear diagnosis of COPD [forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) < 0.7] and a $FEV_1 \leq 80\%$predicted. Exclusion criteria included *1*) the presence of a 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*) patients who fit the extremes of physical activity levels, i.e., sedentary/housebound or excessively active/training; and *4*) a low BMI in the underweight range <18.5 kg/m^2.

Study design. This cross-sectional study received ethical approval from the Queen's University and Affiliated Hospitals Health Sciences Research Ethics Board. After obtaining informed consent and screening of medical history, subjects completed two visits. *Visit 1* included evaluation of chronic activity-related dyspnea (12, 22), familiarization to all testing procedures, and incremental cardiopulmonary cycle exercise testing. *Visit 2* included complete pulmonary function tests, measurement of static respiratory mechanics, and a constant-work-rate (CWR) exercise test with detailed dynamic respiratory mechanical measurements.

Procedures. Spirometry, body plethysmography, single-breath diffusing capacity, and maximal respiratory mouth pressures were performed using automated equipment (Vmax 229d with Autobox 6200 DL; SensorMedics, Yorba Linda, CA) according to recommended standards (1, 21, 24, 46). Static lung compliance (C_Lst) and static lung recoil pressure (P_Lst) were also measured (Vmax229d; SensorMedics) (15). Measurements were expressed as percentages of predicted normal values (5, 7, 8, 9, 16, 19, 26); predicted inspiratory capacity (IC) was calculated as predicted total lung capacity (TLC) minus predicted functional residual capacity (FRC).

Symptom-limited exercise tests were conducted on an electrically braked cycle ergometer (Ergometrics 800S; SensorMedics) with a cardiopulmonary exercise testing system (Vmax229d; SensorMedics) as previously described (30). Incremental tests consisted of a 1-min warm-up of loadless pedaling followed by 1-min increments of 10 W each. CWR tests consisted of a 1-min warm-up followed by an increase in work rate to 75% of the maximal incremental work rate; endurance time was defined as the duration of loaded pedaling. Measurements included breath-by-breath cardiopulmonary and metabolic parameters; intensity of dyspnea (breathing discomfort) and leg discomfort rated using the 10-point Borg scale (6); operating lung volumes derived from IC maneuvers (31); and esophageal pressure (Pes)- and gastric pressure (Pga)-derived respiratory mechanical measurements collected continuously with an integrated data-acquisition setup (30). Exercise parameters were compared with the predicted normal values of Jones (17). Peak $\dot{V}_{O_2}$ was standardized as a percentage of the predicted normal value corrected for ideal body weight (47). Ventilation ($\dot{V}_E$) was compared with the maximal ventilatory capacity (MVC) estimated by multiplying the measured FEV_1 by 35 (14).

Pressure-derived respiratory mechanical measurements. Pes was measured in all subjects and Pga in a subset of 15 subjects ($n = 8$ NW, $n = 7$ OB). Transdiaphragmatic pressure (Pdi) was calculated by electronic subtraction of Pes from Pga (1). Sniff and cough maneuvers were performed preexercise at rest and immediately at end exercise to obtain maximum values for Pes (Pes,sniff), Pdi (Pdi,sniff) and Pga (Pga,cough) (1).

The tidal swing (Pes,tidal) and the inspiratory swing (Pes,insp) were defined as the amplitude of the Pes waveform during tidal breathing and during inspiration, respectively. Accepted formulas were used to calculate total lung resistance (R_L); dynamic lung compliance ($C_L$dyn); the pressure-time product of the respiratory (PTPes), diaphragm (PTPdi), and expiratory muscles (PTPga); and the tension-time index of the diaphragm (TTIdi) and the inspiratory muscles (TTIes) (1, 45). Activation of the expiratory muscles was evaluated by measurement of the expiratory gastric rise (Pga,rise) and the peak expiratory Pga (Pga,exp) during tidal breathing (48). End expiration (EE) was the beginning of the inspiratory effort from the Pes waveform. Dynamic intrinsic positive end-expiratory pressure (PEEPi) was measured as the negative deflection in Pes from EE to the onset of inspiratory flow (46) and corrected (PEEPi,corr) by subtracting Pga,rise (28). The ventilatory muscle recruitment (VMR) index was determined as the slope of the line between points of zero flow at end-expiration (EE0flow) and end-inspiration (EI0flow) for the Pga-Pes plots (ΔPga/ΔPes): negative slopes represent increased contribution by the diaphragm, and more positive slopes represent increased contribution by inspiratory muscles of the ribcage and the expiratory muscles (23).

Statistical analysis. Results are expressed as means ± SD unless otherwise specified. A $P < 0.05$ level of statistical significance was used for all analyses. Between-group baseline comparisons were made using unpaired *t*-tests. Group comparisons of exercise parameters were made using unpaired *t*-tests with a Bonferroni adjustment for repeated measurements: three

Table 1. *Subject characteristics*

	NW ($n = 12$)	OB ($n = 12$)
Male, *n* (%)	6 (50)	6 (50)
Age, yr	68 ± 8	68 ± 4
Height, cm	169 ± 13	167 ± 9
Weight, kg	67.3 ± 12.0	90.3 ± 12.1*
Weight, % of ideal	95 ± 8	131 ± 5*
Body mass index, kg/m^2	23.4 ± 1.8	32.2 ± 1.2*
Smoking history, pack-yr	61 ± 35	68 ± 54
COPD duration, yr	8 ± 6	10 ± 10
Baseline dyspnea index, focal score (0–12)ı	6.7 ± 1.2	6.2 ± 0.8
Magnitude of effort 0–4	2.4 ± 0.5	1.8 ± 0.4*
Magnitude of task 0–4	1.9 ± 0.3	1.8 ± 0.5
Functional impairment 0–4	2.3 ± 0.8	2.6 ± 0.7
Medical Research Council, dyspnea scale (1–5)†	2.4 ± 0.7	2.7 ± 0.8
Peak incremental work rate, W (% predicted maximum)‡	71 ± 36 (56 ± 20)	70 ± 19 (59 ± 21)
Peak incremental $\dot{V}_{O_2}$, l/min (% predicted maximum)‡	1.14 ± 0.58 (73 ± 19)	1.18 ± 0.31 (71 ± 18)
Peak incremental $\dot{V}_E$, l/min (% estimated MVC)	43.7 ± 24.1 (95 ± 15)	39.2 ± 8.6 (92 ± 18)

Values are means ± SD. COPD, chronic obstructive pulmonary disease; OB, obese COPD subjects; NW, normal-weight COPD subjects; $\dot{V}_{O_2}$, oxygen consumption; $\dot{V}_E$, ventilation. *$P < 0.05$, OB vs. NW group. †Chronic activity-related dyspnea was rated by the baseline dyspnea index focal score (12 none, 0 very severe) and its components (4 none, 0 very severe) (22) and the Medical Research Council dyspnea scale (1 not troubled by breathlessness, 5 too breathless to leave the house or breathless when dressing or undressing) (12). ‡Predicted peak incremental work rate from Jones (17) and predicted peak $\dot{V}_{O_2}$ based on ideal body weight from Wasserman et al.(47).

main evaluation time points (i.e., rest, a standardized exercise time of 2 min, and peak exercise) meant that an uncorrected P value of <0.0167 was considered as significant. Within-group exercise comparisons (i.e., rest vs. 1 min or 2 min, rest vs. peak) were made using paired t-tests. Regression analysis was performed to establish associations between the dependent variables (i.e., peak $\dot{V}O_2$, dyspnea intensity) and relevant independent variables; group (categorical variable) and its interaction term (group $\times$ independent variable) were included within the regression models.

RESULTS

Twelve COPD patients with mild obesity (OB) and 12 age-, sex-, and FEV_1-matched normal-weight (NW) COPD patients were studied (Table 1). Chronic activity-related dyspnea was of moderate degree (i.e., shortness of breath while walking or climbing stairs) and largely similar across groups. Measurements of work rate, $\dot{V}O_2$ and $\dot{V}E$ at the peak of incremental cycle exercise were also similar across groups. The presence of the following comorbidities was balanced between groups: controlled hypertension ($n = 6$ OB, 5 NW), hypercholesterolemia (6 OB, 4 NW), diabetes mellitus type 2 (2 OB, 2 NW), and stable ischemic heart disease (2 OB, 2 NW). Chest CT scans done clinically were available for evaluation of emphysema in 6 NW and 10 OB subjects: emphysema was present in all 6 (4 mild, 2 moderate) of these NW subjects and in 8 (3 mild, 5 moderate-severe) out of the 10 OB subjects.

Pulmonary function and static respiratory mechanical measurements. Resting pulmonary function and respiratory mechanical measurements are summarized in Table 2. Compared with NW, OB had a significantly ($P < 0.05$) smaller expiratory reserve volume (ERV), TLC, and plethysmographic FRC when expressed as a percentage of predicted normal. P_Lst and the coefficient of retraction (P_Lst/TLC) were both greater ($P < 0.05$) in OB compared with NW. Maximum inspiratory and expiratory pressure-generating capacity was similar across groups.

Symptom-limited cycle exercise. $\dot{V}O_2$/work rate slopes during incremental cycle exercise were similar in the OB and NW groups (10.6 ± 3.2 and 10.7 ± 3.1 ml·min^{-1}·W^{-1}, respectively); however, the $\dot{V}O_2$ was greater in OB compared with NW by a mean difference of 46–97 ml/min at rest and at each common work rate between 10 and 40 W. Within each group, the peak $\dot{V}O_2$ and $\dot{V}E$ were similar for the incremental (Table 1) and CWR (Table 3) cycle tests.

Cardiopulmonary responses to the CWR exercise test are summarized in Table 3 and shown in Fig. 1. The CWR work rate (53 ± 16 and 54 ± 29 W) and exercise endurance time (6.0 ± 2.1 and 5.7 ± 3.5 min) were similar in OB and NW, respectively. At the end of the CWR test, both groups stopped when they reached a critical ventilatory reserve: $\dot{V}E$/MVC $>85\%$ and a reduced IRV $< 10\%$TLC. At rest and at any given time during exercise, there was no significant difference in $\dot{V}E$ or partial pressure of end-tidal carbon dioxide ($P_{ET_{CO_2}}$) between groups, but the OB group had smaller ($P < 0.05$) ventilatory equivalents for CO_2 ($\dot{V}E/\dot{V}CO_2$) at rest and at peak exercise. Although oxygen saturation (SpO_2) was similar at rest and at peak exercise across groups, the OB group experienced greater ($P < 0.05$) oxygen desaturation than the NW group in the first minute of exercise.

The dynamic EELV was lower by over 1.0 liter or 15% of predicted TLC at rest through to peak exercise in the OB compared with NW group (Fig. 2*A*). However, IC measurements and the magnitude of dynamic hyperinflation (i.e., de-

Table 2. *Pulmonary function and static respiratory mechanical measurements*

	NW	OB
FEV_1, liters (%predicted)	1.33 ± 0.64 (59 ± 17)	1.26 ± 0.21 (60 ± 13)
FVC, liters (%predicted)	3.10 ± 1.18 (95 ± 16)	2.80 ± 0.60 (92 ± 20)
FEV_1/FVC,%	42 ± 8	47 ± 12
PEFR, l/s (%predicted)	4.4 ± 1.4 (68 ± 16)	4.4 ± 0.7 (73 ± 16)
FEF_{50}, l/s (%predicted)	0.5 ± 0.4 (12 ± 8)	0.5 ± 0.2 (14 ± 6)
TLC, liters (%predicted)	7.44 ± 1.97 (124 ± 15)	6.35 ± 1.66 (109 ± 30*)
IC, liters (%predicted)	2.24 ± 0.86 (81 ± 18)	2.18 ± 0.35 (84 ± 15)
FRC, liters (%predicted)	5.20 ± 1.37 (158 ± 27)	4.18 ± 1.51 (130 ± 38*)
RV, liters (%predicted)	3.83 ± 1.04 (170 ± 43)	3.42 ± 1.29 (154 ± 53)
RV/TLC, %	52 ± 11	52 ± 9
ERV, liters (%predicted)	1.37 ± 0.69 (134 ± 50)	0.76 ± 0.42* (80 ± 38*)
sRaw, cmH_2O·s (%predicted)	22.5 ± 9.3 (544 ± 218)	21.5 ± 11.8 (512 ± 270)
D_{LCO}, ml·min^{-1}·mmHg^{-1} (%predicted)	13.9 ± 6.5 (75 ± 26)	14.6 ± 5.0 (67 ± 20)
D_{LCO}/V_A, ml·min^{-1}·mmHg^{-1} l^{-1} (%predicted)	2.86 ± 0.69 (77 ± 16)	3.45 ± 0.88 (93 ± 23)
MIP, cmH_2O (%predicted)	-67 ± 22 (89 ± 30)	-76 ± 16 (108 ± 38)
MEP, cmH_2O (%predicted)	121 ± 28 (75 ± 17)	125 ± 46 (77 ± 24)
C_Lst, l/cmH_2O	0.37 ± 0.13	0.29 ± 0.12
P_Lst, cmH_2O (%predicted)	21.3 ± 5.9 (77 ± 37)	27.4 ± 8.1* (97 ± 25)
Coefficient of retraction, cmH_2O/l	3.1 ± 1.4	4.5 ± 1.5*
Sniff Pes, cmH_2O	-64 ± 18	-65 ± 11
Sniff Pdi, cmH_2O†	114 ± 27	127 ± 25
Cough Pga, cmH_2O†	137 ± 66	177 ± 69

Values are means $\pm$ SD with percentage of the predicted normal value in parentheses. D_{LCO}, diffusing capacity of the lung for carbon monoxide; ERV, expiratory reserve volume; FEF_{50}, forced expiratory flow at 50% of FVC; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; MIP, maximal inspiratory pressure measured at FRC; MEP, maximal expiratory pressure measured at total lung capacity (TLC); PEFR, peak expiratory flow rate; RV, residual volume; sRaw, specific airway resistance; C_Lst, static lung compliance; P_Lst, static lung recoil pressure; Pes, esophageal pressure; Pdi, transdiaphragmatic pressure; Pga, gastric pressure. *$P < 0.05$ obese versus normal-weight group. †Measured in a subset of $n = 8$ NW and $n = 7$ OB subjects.

Table 3. *Measurements during CWR exercise at 75% of incremental peak work rate*

	Rest		2 min		Peak	
	NW	OB	NW	OB	NW	OB
Dyspnea, Borg	0.2 ± 0.4	0.3 ± 0.6	2.7 ± 2.3	2.8 ± 1.8	6.6 ± 2.8	6.8 ± 2.2
Leg discomfort, Borg	0.2 ± 0.6	0.3 ± 0.6	2.8 ± 2.0	2.9 ± 1.1	6.1 ± 3.2	6.6 ± 2.4
Work rate, W	0	0	54 ± 29	53 ± 16	54 ± 29	53 ± 16
$\dot{V}O_2$, l/min	0.22 ± 0.10	0.29 ± 0.10	0.82 ± 0.30	0.93 ± 0.20	1.10 ± 0.47	1.19 ± 0.30
$\dot{V}CO_2$, l/min	0.18 ± 0.08	0.24 ± 0.08	0.69 ± 0.27	0.77 ± 0.18	1.04 ± 0.44	1.16 ± 0.33
Heart rate, beats/min	77 ± 9	85 ± 13	106 ± 18	113 ± 21	127 ± 19	120 ± 15
SpO_2, %	95.5 ± 1.4	95.1 ± 1.8	94.3 ± 2.3	92.3 ± 2.8	93.6 ± 3.4	93.8 ± 3.6
$\dot{V}E$, l/min	11.1 ± 3.4	12.1 ± 3.2	27.9 ± 8.3	27.5 ± 3.9	41.7 ± 16.7	40.2 ± 9.3
P_{ETCO_2}, mmHg	35 ± 4	36 ± 5	39 ± 5	41 ± 6	39 ± 7	41 ± 7
V_T, liters	0.61 ± 0.12	0.66 ± 0.18	1.14 ± 0.37	1.03 ± 0.16	1.22 ± 0.36	1.15 ± 0.23
T_I/T_{TOT}	0.38 ± 0.06	0.36 ± 0.05	0.40 ± 0.06	0.39 ± 0.03	0.41 ± 0.06	0.38 ± 0.03
Peak tidal expiratory flow, l/s	0.60 ± 0.21	0.72 ± 0.16	1.29 ± 0.36	1.57 ± 0.34	1.98 ± 0.69	2.20 ± 0.63
IC, liters	2.37 ± 0.77	2.20 ± 0.37	1.84 ± 0.76	1.79 ± 0.38	1.63 ± 0.57	1.66 ± 0.36
ΔIC from rest, liters	0	0	−0.53 ± 0.26	−0.46 ± 0.32	−0.74 ± 0.40	−0.59 ± 0.29
IRV, liters	1.76 ± 0.69	1.54 ± 0.37	0.71 ± 0.53	0.76 ± 0.30	0.41 ± 0.28	0.51 ± 0.22
EELV, liters	5.33 ± 1.29	4.15 ± 1.50*	5.60 ± 1.52	4.56 ± 1.67	5.81 ± 1.65	4.69 ± 1.59
EELV, % pred TLC	86 ± 14	70 ± 20*	93 ± 17	78 ± 23	97 ± 17	80 ± 22*
EILV/TLC, %	77 ± 6	75 ± 7	91 ± 7	87 ± 5	94 ± 5	92 ± 4

Values are means ± SD. *$P < 0.05$, OB vs. NW group at the same measurement point. See text for abbreviations.

crease in IC) were not significantly different between groups at rest through to peak exercise. Despite comparable IC values, the minimum Pes during the maximal effort to TLC during these maneuvers was greater in OB compared with NW at rest by a mean difference of 8 cmH_2O ($P < 0.05$) and by 6–7 cmH_2O throughout exercise (Fig. 2*B*). This minimum Pes at TLC did not change significantly from rest to peak exercise in either group, indicating good reliability of maximum efforts for measurement of IC throughout testing.

Dynamic respiratory mechanics during rest and exercise. Respiratory muscle/mechanical measurements are provided in Table 4. Pressure-derived measurements were largely similar in the OB and NW groups at rest, except expiratory and end-expiratory Pes and Pga were significantly ($P < 0.05$) more positive in the OB compared with NW group. Patterns of respiratory mechanical responses to exercise were similar across groups with a few exceptions (Table 4, Fig. 3). Tidal inspiratory and expiratory swings of Pes (Fig. 2*B*), Pga, and Pdi were similar between groups during exercise. Although Pga was ~8 cmH_2O greater on average throughout exercise in OB vs. NW, the difference did not reach statistical significance. In the first minute of loaded exercise, R_L fell signifi-

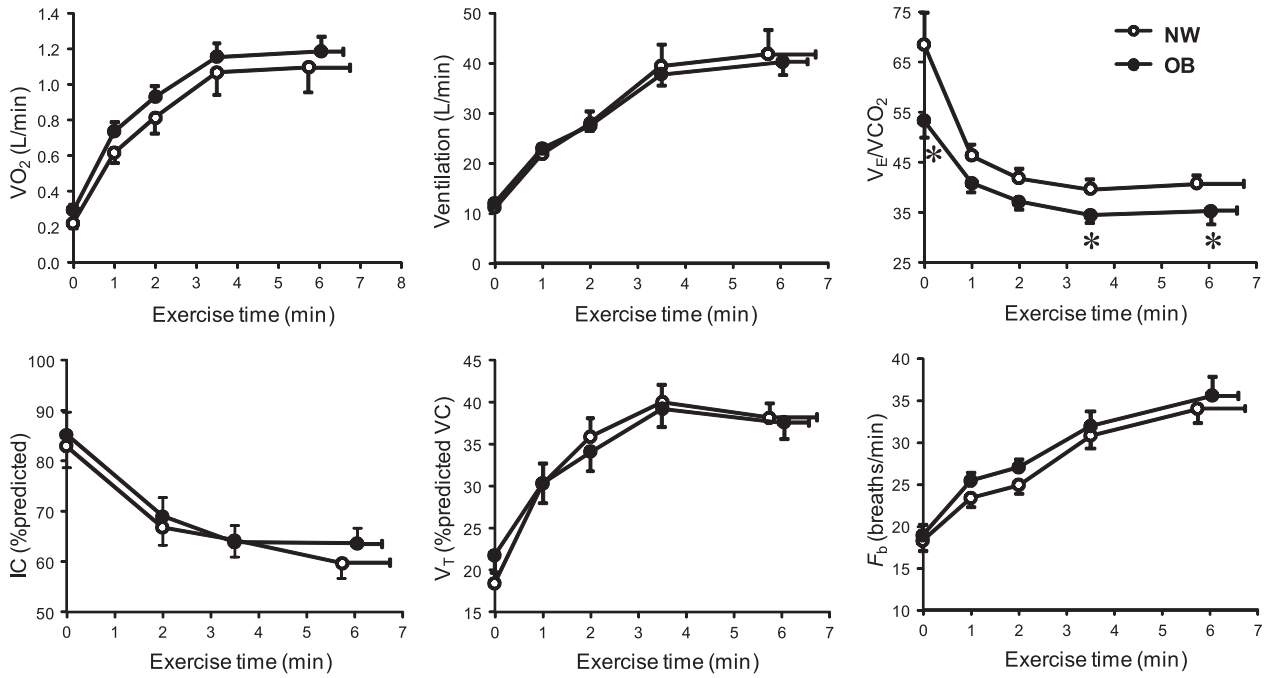

Fig. 1. Oxygen consumption ($\dot{V}O_2$), ventilation ($\dot{V}E$), the ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$), inspiratory capacity (IC), tidal volume (V_T), and breathing frequency (F_b) are shown in response to symptom-limited constant-work-rate cycle exercise in obese chronic obstructive pulmonary disease (COPD) (OB) subjects (●) and in normal-weight COPD (NW) subjects (○). Values are means ± SE. *$P < 0.05$, OB vs. NW at rest, a standardized exercise time, or at peak exercise.

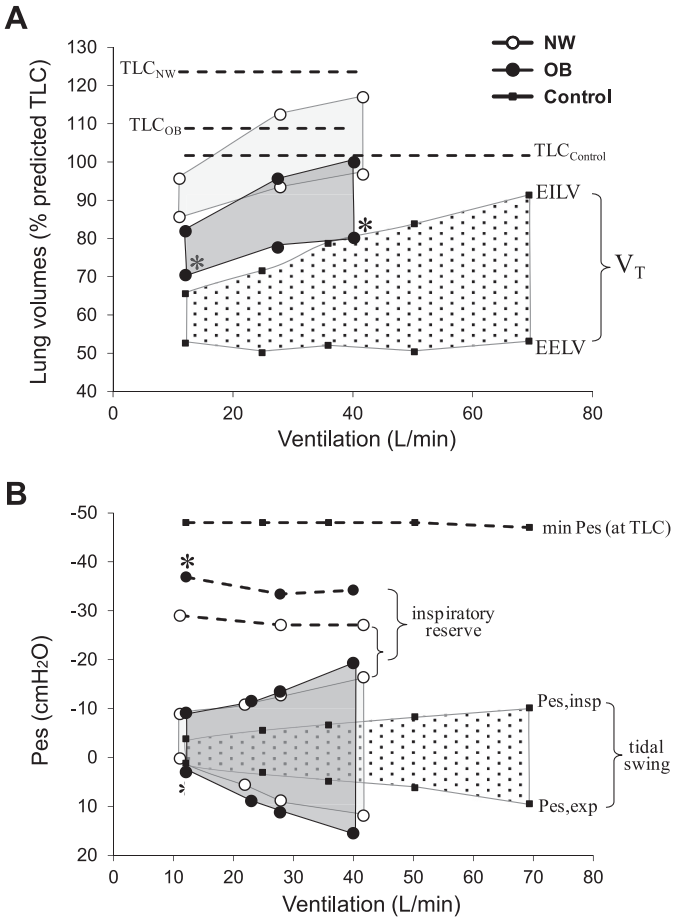

Fig. 2. *A*: operating lung volumes are shown in response to constant-work-rate cycle exercise in obese COPD (OB) subjects (●) and in normal-weight COPD (NW) subjects (○). VT (*shaded area*) responses to exercise were similar across COPD groups. End-expiratory lung volume (EELV) was significantly lower in OB compared with NW subjects at rest and peak exercise (*$P < 0.05$). *B*: inspiratory (Pes,insp) and expiratory esophageal pressure (Pes,exp) measurements are shown during constant-work-rate exercise in OB and NW groups. Although expiratory Pes was greater at rest in OB compared with NW subjects, tidal Pes swings (*shaded area*) were comparable throughout exercise. The dynamic peak inspiratory Pes (min Pes) during IC maneuvers was greater (*$P < 0.05$) in the OB group at rest and did not change significantly during exercise in either group. Historic data from an age-matched healthy control group (■) tested in the same laboratory during incremental cycle exercise are also shown (32). EILV, end-inspiratory lung volume; TLC, total lung capacity. Values are means.

cantly ($P = 0.008$) in the OB group, then returned back to baseline levels by end exercise. R_L remained similar throughout rest and exercise in the NW group but was not statistically different from the OB group at any exercise time point. In contrast, $C_L$dyn remained stable throughout rest and exercise in the OB group but fell significantly ($P = 0.001$) from rest to peak exercise in the NW group. The VMR was similar between groups at rest, increased significantly ($P = 0.029$) within the first minute of exercise in the NW group while remaining constant in the OB group, then increased in parallel throughout the remainder of the exercise test (Fig. 4).

Correlates of exertional dyspnea and peak $\dot{V}O_2$. Exertional dyspnea intensity was similar in the OB and NW groups when expressed relative to CWR exercise time, $\dot{V}E$, IRV%predicted-TLC, or PTPes (Fig. 5). Across groups, peak symptom-limited $\dot{V}O_2$%predicted correlated significantly with peak V_T%predictedVC ($P = 0.003$, partial $r = 0.602$) as well as peak IC%predicted ($P = 0.024$, partial $r = 0.480$), and resting IC%predicted ($P = 0.010$, partial $r = 0.534$); in turn, peak V_T%predictedVC correlated with the peak IC%predicted ($P = 0.008$, partial $r = 0.548$). Dyspnea ratings throughout exercise correlated best with (all $P < 0.0005$) PTPes/min (partial $r = 0.817$), $\dot{V}E$/MVC (partial $r = 0.711$), IRV%predictedTLC (partial $r = 0.707$), V_T/IC (partial $r = 0.710$) and tidal Pes/Pes,sniff (partial $r = 0.678$). PTPes/min (partial $r = 0.873$), tidal Pes/Pes,sniff (partial $r = 0.665$), and V_T/IC (partial $r = 0.841$) increased in direct proportion ($P < 0.0005$) with increases in $\dot{V}E$/MVC during exercise; while IRV%predictedTLC (partial $r = 0.841$) and IC%predicted (partial $r = 0.623$) correlated inversely ($P < 0.0005$) with $\dot{V}E$/MVC. Correlates of dyspnea and peak $\dot{V}O_2$ were similar across groups.

DISCUSSION

The main findings of this study are as follows: *1*) at rest, static lung volumes were lower, while P_Lst and Pga were higher in the OB compared with the NW groups; *2*) exercise performance was not diminished in the obese; *3*) despite lower absolute operating lung volumes, pulmonary resistance during exercise was not increased in OB; *4*) ventilatory muscle recruitment patterns were broadly similar in the two groups apart from minor delays early in exercise in the increase in the VMR index determined from Pga/Pes plots (i.e., diaphragmatic derecruitment) in the obese; and *5*) resting IC, effort-displacement ratios, and dyspnea/$\dot{V}E$ plots during exercise were not significantly affected by the presence of mild obesity.

Patients in the two COPD groups were well matched for smoking history, severity of airway obstruction (FEV_1), distribution of comorbidities, and sex representation. They showed comparable reduction in exercise capacity (mean peak $\dot{V}O_2$ was reduced by ~30% compared with predicted normal values) with severe exertional dyspnea due to limiting respiratory mechanical constraints. Thus, at the limits of tolerance, breathing reserve (as reflected by high $\dot{V}E$/MVC and V_T/IC ratios) was critically reduced in both groups. Peak symptom-limited $\dot{V}O_2$ was similar during the incremental and CWR cycle tests in both groups. This confirms that the CWR cycle endurance test was indeed a maximal effort test: physiological limits were reached and patients expended maximal motivational effort and reported severe dyspnea.

Differences in resting respiratory mechanics. The OB group was heavier than the NW group by an average of 23 kg. In accordance with previous studies in healthy populations and in patients with airway disease, resting TLC, EELV, and ERV were decreased with the increase in BMI (10, 18, 34). The decreased EELV likely reflects the decreased chest wall and lung compliance known to be associated with obesity (27, 36, 37, 40). Despite the lower lung volumes in OB, plethysmographically determined airway resistance and other measures of airway obstruction were not significantly increased.

The elastic properties of the lung were different in OB and NW. Thus the static lung elastic recoil as measured by P_Lst and the coefficient of retraction was greater, and closer to values predicted for health, in OB. We believe that differences in lung elastance reflect independent effects of obesity in patients with the heterogeneous pathophysiology of COPD rather than the

Table 4. *Respiratory muscle/mechanical measurements*

	Rest		2 min		Peak	
	NW	OB	NW	OB	NW	OB
Pes-derived measurements (n = 12 per group)						
Pes,exp, cmH_2O	0.2 ± 2.1	3.0 ± 3.0*	8.8 ± 6.9	11.2 ± 6.8	11.9 ± 4.9	15.5 ± 11.0
Pes,insp, cmH_2O	−8.9 ± 3.1	−9.1 ± 2.1	−12.6 ± 4.4	−13.5 ± 4.0	−16.4 ± 5.3	−19.3 ± 4.8
PesEE, cmH_2O	−1.6 ± 2.1	1.0 ± 3.3*	7.2 ± 6.6	10.0 ± 6.1	10.4 ± 5.0	14.4 ± 11.0
PesEE0flow, cmH_2O	−3.5 ± 1.8	−1.8 ± 2.8	−1.6 ± 5.5	−0.2 ± 3.9	−0.7 ± 7.2	−0.6 ± 6.7
TTIes,insp	0.014 ± 0.011	0.024 ± 0.020	0.041 ± 0.043	0.056 ± 0.048	0.066 ± 0.042	0.064 ± 0.057
PTPes, cmH_2O·s/min	72 ± 33	103 ± 30	194 ± 90	203 ± 49	259 ± 56	285 ± 53
Pga- and Pdi-derived measurements (n = 8 NW, n = 7 OB)						
VMR (ΔPga/ΔPes)	−3.4 ± 0.9	−3.1 ± 2.0	−0.0 ± 0.9	−1.2 ± 1.7	0.7 ± 0.9	0.4 ± 1.5
PEEPi,corr, cmH_2O	1.5 ± 2.1	2.2 ± 2.2	6.3 ± 4.7	8.1 ± 8.8	7.2 ± 11.0	10.5 ± 14.7
Pga,rise, cmH_2O	0.8 ± 1.0	0.8 ± 1.4	6.8 ± 5.1	6.2 ± 2.9	12.9 ± 6.9	14.7 ± 5.6
PgaEE0flow, cmH_2O	6.5 ± 6.7	16.9 ± 4.9*	14.0 ± 7.5	20.3 ± 7.3	17.7 ± 12.6	22.9 ± 6.1
Pga,exp, cmH_2O	12.6 ± 7.3	20.2 ± 4.5*	19.4 ± 7.7	25.6 ± 7.8	24.3 ± 13.0	32.3.± 8.5
PTPga, cmH_2O·s/min	59 ± 24	70 ± 21	152 ± 94	151 ± 75	243 ± 148	292 ± 153
Pdi,tidal, cmH_2O	12.5 ± 4.5	17.4 ± 6.0	20.0 ± 7.1	22.1 ± 9.6	20.6 ± 13.5	20.3 ± 9.7
TTIdi,insp swing	0.027 ± 0.015	0.039 ± 0.014	0.025 ± 0.013	0.025 ± 0.010	0.025 ± 0.021	0.017 ± 0.005
PTPdi, cmH_2O·s/min	136 ± 70	165 ± 56	203 ± 77	231 ± 98	187 ± 117	227 ± 84

Values are means ± SD. *$P < 0.05$, OB vs. NW group at the same measurement point. See text for abbreviations.

fortuitous selection of different clinical phenotypes of COPD in the obese and lean groups (i.e., airways disease vs. emphysema predominant, respectively): *1*) we excluded underweight patients with clinically overt advanced emphysema; *2*) diffusing capacity of the lung for carbon monoxide (D_LCO) was moderately reduced and not significantly different across the two groups; *3*) although patients in the OB COPD group had comparatively lower lung volumes, they still had had significant lung hyperinflation (FRC = 130% predicted); and *4*) qualitative radiological assessments of available CT scans in 10/12 obese COPD patients indicated the presence of structural emphysema ranging from mild to moderate severity in the majority.

Intra-abdominal pressure measured by gastric balloon (in the sitting position) in a subgroup of patients was consistently elevated in OB by close to 10 cmH_2O compared with NW. This likely reflects the mass-loading effects of adipose tissue on the chest wall and abdomen (39, 41). Measures of static respiratory muscle strength (including the diaphragm) were not significantly higher in the obese group despite the significantly

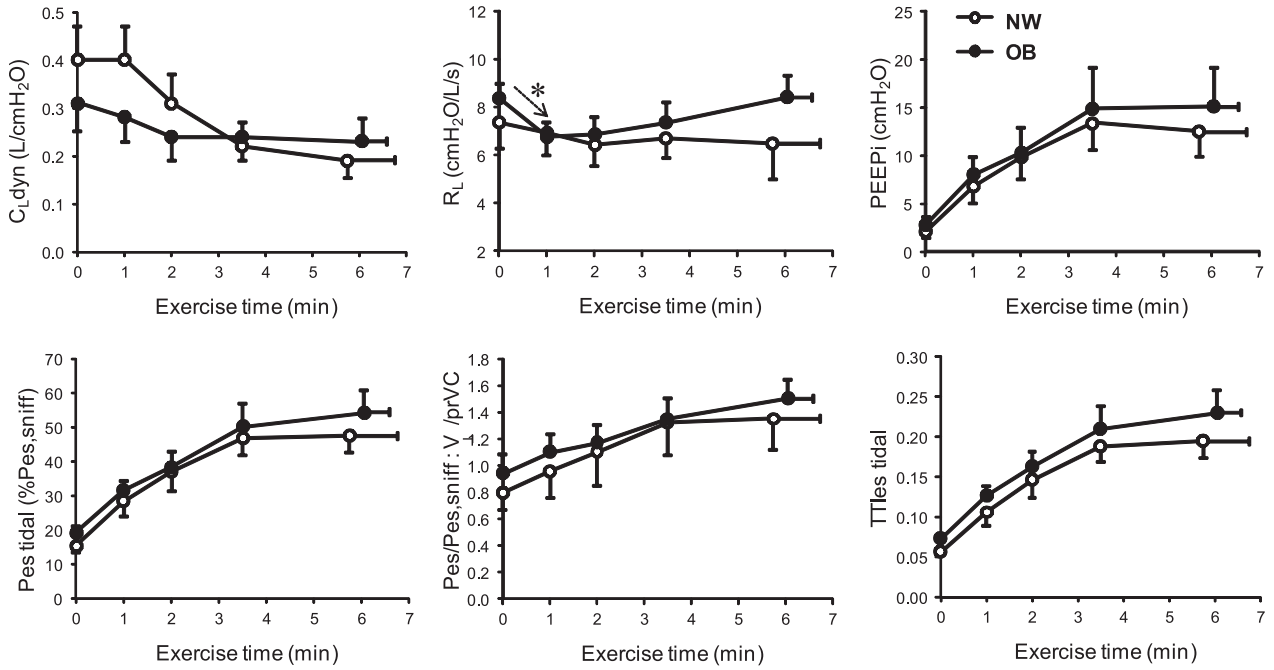

Fig. 3. Dynamic lung compliance ($C_L$dyn), total lung resistance (R_L), dynamic intrinsic positive end-expiratory pressure (PEEPi), respiratory effort (tidal Pes/Pes,sniff), the effort-displacement ratio (Pes/Pes,sniff:V_T/predictedVC) and the tension-time index of the respiratory muscles (TTIes) are shown in response to constant-work-rate cycle exercise in obese COPD (OB) subjects (●) and in normal-weight COPD (NW) subjects (○). R_L remained stable throughout exercise in NW but decreased significantly (*$P < 0.05$) early in exercise (rest vs. 1 min) in OB. Values are means ± SE.

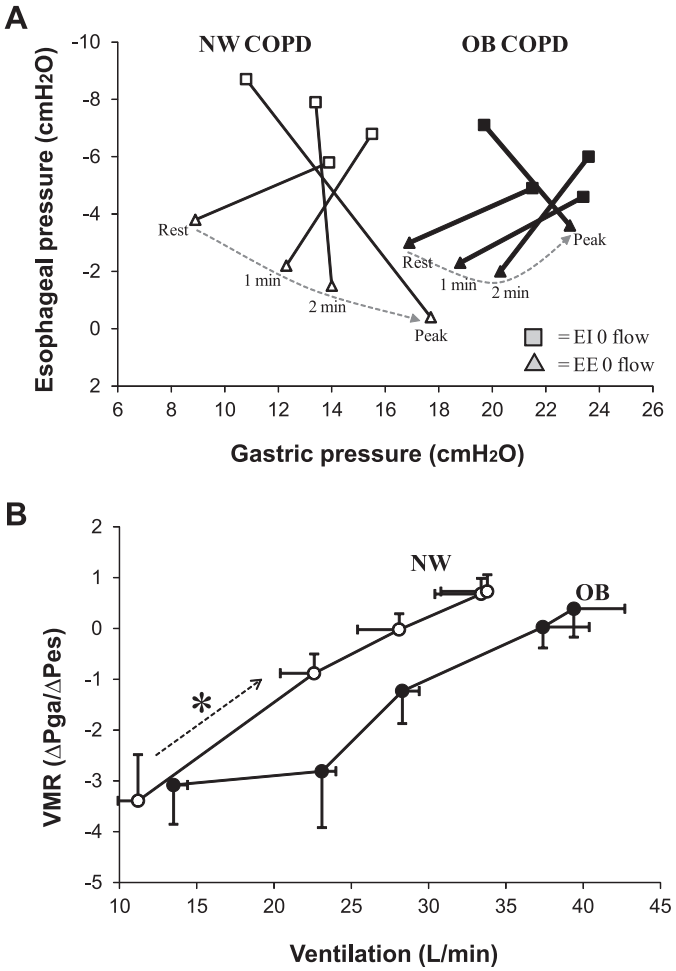

Fig. 4. *A*: esophageal pressure (Pes) over gastric pressure (Pga) values at points of zero flow end-expiration (EE0flow) and end-inspiration (EI0flow) are shown at standardized points during constant-work-rate exercise testing: rest, 1 min, 2 min, and peak. The slope of each segment (ΔPes/ΔPga) represents the ventilator muscle recruitment (VMR) index. *B*: the VMR index is plotted over exercise time. In the first minute of exercise, VMR increased significantly ($P < 0.05$) in the NW group but remained constant in the OB group. Thereafter, VMR increased in parallel relative to ventilation. ●, Obese COPD (OB); ○, normal-weight COPD. Values are means ± SE. *$P < 0.05$, OB vs. NW at rest, a standardized exercise time, or at peak exercise.

lower EELV. Lack of intergroup difference in effort-dependent measures of muscle strength may reflect the well-documented adaptations of the diaphragm in those with the most severe lung hyperinflation (42).

Differences in dynamic respiratory mechanics and muscle function during exercise. Peak symptom-limited $\dot{V}O_2$ (expressed as a percentage of predicted based on ideal body weight), exercise endurance times, and dyspnea intensity ratings were similar in both groups. In contrast to our previous study using incremental cycle exercise, the rise in $\dot{V}O_2$ and $\dot{V}E$ was not significantly increased in the OB vs. the NW group during CWR exercise. This reflects the balance between the modestly increased metabolic load in OB and improved ventilatory efficiency in this group: ventilatory equivalent for CO_2 was lower at rest and during exercise in OB (Fig. 1). A better ventilatory efficiency is consistent with the notion that ventilation-perfusion relations were less disrupted in the OB patients during exercise (49). The finding of a lack of group differences in ventilatory responses to exercise was fortuitous with respect to the comparison of dynamic mechanics and respiratory muscle performance that we undertook.

Despite the relatively lower lung volumes in OB, the ability to generate maximal tidal expiratory flow rates and to increase alveolar ventilation in pace with metabolic demand was not compromised to a greater extent in OB than in NW. Thus the changes in $P_{ET}CO_2$ and SpO_2 from rest to exercise termination were similar in both groups. It is possible that in the OB group, the better preserved P_Lst (and the attendant increased driving pressure for expiratory flow) compensated for the possible disadvantage with respect to airway function of breathing at lung volumes closer to residual volume. It is interesting to speculate that better preservation of the elastic properties of the lungs and in operating lung volumes seen in the obese group may lead to improved airway and respiratory muscle function. We could find no evidence of greater mechanical constraints on V_T expansion or of greater ventilatory limitation during exercise in OB. Indeed, in accordance with our previous study, the volume and timing components of breathing and the rate and extent of dynamic hyperinflation were not different in OB and NW. It is noteworthy that measured pulmonary resistance was not increased in OB despite the lower EELV (Fig. 3). In fact, in contrast to NW, pulmonary resistance transiently but consistently fell slightly at the onset of exercise as EELV dynamically increased. This suggests the presence of a greater lung volume-dependent component in the increased resistance in OB compared with control.

The static strength of the inspiratory and expiratory muscles (measured at rest) was not diminished at the limits of tolerance in either group. Intra-abdominal pressures were significantly elevated at rest and to a similar degree throughout exercise. However, the pattern of expiratory muscle activation (measured by Pga,rise) was similar in both groups. The pressure-time product and the tension-time index of the inspiratory and expiratory muscles during exercise were also similar.

We were particularly interested in comparing diaphragmatic function in obese and lean COPD as the lower absolute lung volumes (by almost 1.0 liter) and increased intra-abdominal pressures in OB patients could theoretically optimize the configuration (i.e., cephaloid shift) and length-tension relations of this muscle. However, we were unable to show any such advantages in the OB group other than a minor delay in the time course of derecruitment of the diaphragm (and recruitment of accessory muscles) during early exercise in the OB compared with NW patients as indicated by analysis of the tidal Pes and Pga plots (Fig. 4) (23, 25). The pressure-time product and pattern of rise in Pdi during exercise were not different in the two groups. The lack of a significant between-group difference in Pga is probably related to inadequate power as a result of the small sample size and the large variability in the measurement.

The mechanical loads on the inspiratory muscles were relatively greater in OB: P_Lst was higher and the unmeasured chest wall compliance was also likely to be lower in this group. However, measures of $C_L$dyn and PEEPi during exercise were not significantly different between groups. This contention that the elastic load is increased in obesity is supported by the finding that the pressure requirements to generate IC of similar magnitude at rest and serially throughout exercise were consistently higher in the obese patients (Fig. 2*B*). It is noteworthy that during spontaneous breathing throughout exercise, tidal

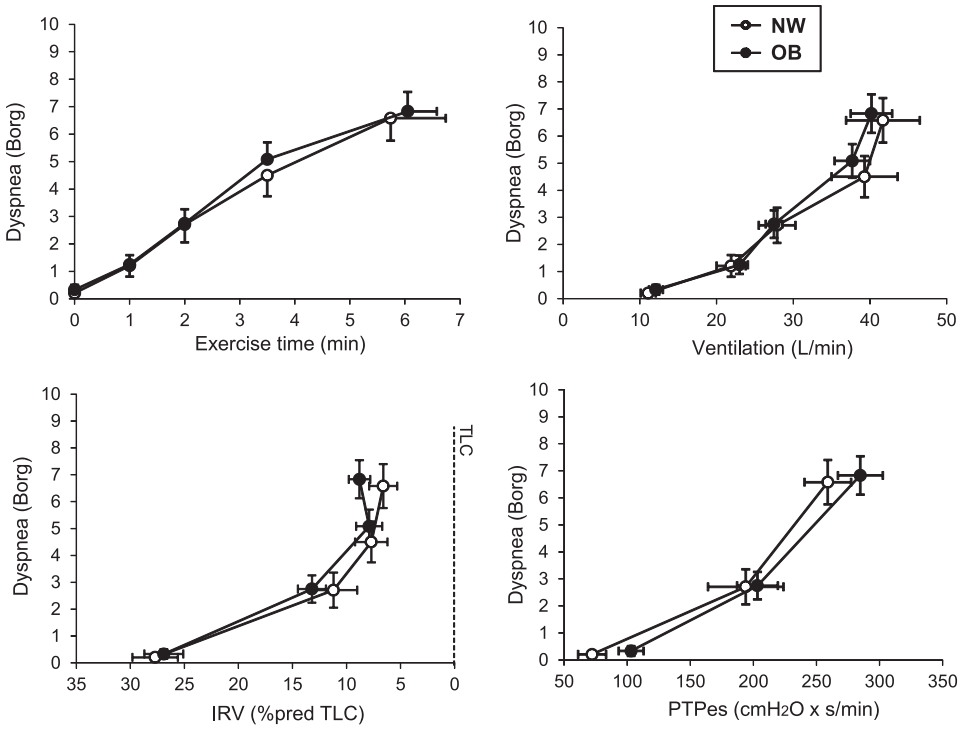

Fig. 5. Dyspnea intensity is shown relative to exercise time, $\dot{V}_E$, inspiratory reserve volume (IRV), and the esophageal pressure-time product per minute (PTPes/min) during constant-work-rate cycle exercise in obese COPD (OB) subjects (●) and in normal-weight COPD (NW) subjects (○). These relationships were strikingly similar in both groups. Values are means ± SE.

pressure swings (for a similar V_T) relative to maximum were not different between the groups, suggesting that the net load-capacity ratio of the respiratory muscles was essentially similar.

Lack of increase in exertional dyspnea intensity in obesity. In contrast to our previous study (34), dyspnea/$\dot{V}_E$ slopes in OB were not lower but similar to that of NW during exercise. This finding confirms the results reported by Laviolette et al.(20) in a large group of men with COPD and lung hyperinflation using a similar CWR protocol. There are several possible reasons for the apparent disparity between results of our two studies. *1*) This study, unlike the previous study ($n = 18$ per group)(34), may not have been sufficiently powered to detect significant differences in dyspnea between the groups. *2*) The present study includes patients with only mild obesity (BMI 30–35 kg/m^2) and more moderate airway obstruction, while our previous study included subjects with a greater BMI range and more severe COPD. We have recently reported that the volume-reducing effects of increased BMI are most pronounced in those with severe COPD (29). We postulate, therefore, that the effects of obesity on operating lung volumes would be greater and more consistent in a sample of patients with higher BMI and more advanced COPD than our present group. We further speculate that greater obesity-related lung volume-reducing effects with higher BMI would be associated with more consistent reductions in perceived exertional dyspnea for a given ventilation. *3*) The exercise protocol used in this study (CWR) was different from that used in our previous study (incremental). *4*) Relatively small sample sizes in both studies can potentially result in greater variability in physiological responses within and between studies (low power).

The relationship between dyspnea intensity and $\dot{V}_E$ during exercise in COPD reflects the extent of the underlying mechanical abnormalities and respiratory muscle function. Thus manipulations of the mechanical load by bronchodilators in COPD patients have been shown to consistently affect this relationship; dyspnea is diminished at a given $\dot{V}_E$ (38). The finding that dyspnea/$\dot{V}_E$ plots were similar in obese and lean COPD groups bolsters the argument that the net balance between intrinsic mechanical loading of the respiratory muscles and their maximal force-generating capacity was similar. We have previously argued that the IC is an important predictor of dyspnea intensity in COPD (31). The smaller the IC, the more V_T encroaches during exercise on the upper reaches of the respiratory system's sigmoidal pressure-volume curve where there is widening disparity between central neural drive and the mechanical response of the respiratory system, i.e., neuromechanical uncoupling. Despite the difference in absolute lung volumes, the dynamic IC and IRV were similar throughout exercise in both groups so it is not surprising that the relationship between contractile respiratory muscle effort and V_T displacement (i.e., effort-displacement ratio) and corresponding dyspnea intensity ratings were also similar. Moreover, by correlative analysis, previously established contributory factors to dyspnea intensity that included indexes of mechanical constraints on tidal volume expansion (V_T/IC, IRV) and increased respiratory effort (pressure-time product, Pes/Pes,sniff) were similar across groups. Each of these variables was also associated with the concurrent $\dot{V}_E$/MVC, i.e., they were indexes reflective of ventilatory reserve.

Limitations. Our patients had mild to moderate increases in BMI and the results may not be applicable to patients with morbid obesity. Accurate measurements of body composition and adipose tissue distribution were not available to confirm and quantify the extent of obesity. However, recent reports suggest that mechanical derangements of obesity are more closely correlated with increasing BMI than with fat distribution patterns per se (2, 44). We believe that the changes in static lung volumes and resting respi-

ratory mechanics in higher BMI group are consistent with the presence of significant obesity. We may have underestimated the mechanical consequences in the OB group as measures of chest wall compliance were not available. Estimates of fat-free mass were higher in subsets of OB than in NW, which raises the possibility that increased skeletal muscle strength played a role in maintaining exercise performance in the former. Our studies were conducted using cycle ergometry; thus our results may have been different had we used treadmill where the metabolic load is known to be greater.

In conclusion, increased BMI was shown to have consistent effects on static lung recoil pressure and on operating lung volumes and ventilatory efficiency during exercise, all of which were potentially advantageous. There were small but consistent improvements in pulmonary resistance and diaphragmatic function early in exercise in OB that were not seen in NW. In obesity, the lower EELV did not compromise airway function likely because of the preservation of static lung recoil pressure driving expiratory flow. Furthermore, the increased elastic loading in the obese was accommodated by the respiratory muscles whose operating length was likely more favorable than the leaner more hyperinflated group. Thus the ability of the obese group to increase ventilation in pace with metabolic demand was not compromised. We propose that the lack of greater respiratory discomfort or exercise curtailment in obese COPD patients fundamentally reflects the fact that, regardless of differences in absolute lung volumes, the resting IC was similar to the lean group. Thus breathing pattern, the dynamic performance of the respiratory muscles, and effort-displacement ratios were remarkably similar throughout exercise in lean and obese COPD patients.

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DISCLOSURES

Denis O'Donnell has served on advisory boards for Boehringer Ingelheim, GSK, Novartis, Nycomed, and Pfizer; has received lecture fees from Astra Zeneca, Boehringer Ingelheim, GSK, and Pfizer; and has received industry-sponsored grants from Astra Zeneca, Boehringer Ingelheim, GSK, Merck Frosst Canada, Novartis, and Pfizer.

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