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Sex differences in exertional dyspnea in patients with mild COPD: Physiological mechanisms

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ABSTRACT

The purpose of this study was to evaluate the physiological basis for sex-differences in exercise-induced dyspnea in patients with mild COPD. We compared operating lung volumes, breathing pattern and dyspnea during incremental cycling in 32 men ($FEV_1 = 86 \pm 10\%$ predicted) and women ($FEV_1 = 86 \pm 12\%$ predicted) with mild COPD and 32 age-matched controls. There were no sex differences in dyspnea in the control group at any work-rate or ventilation ($\dot{V}_E$). Women with COPD had significantly greater dyspnea than men at 60 and 80 W. At 80 W, dyspnea ratings were 5.7 ± 2.3 and 3.3 ± 2.5 Borg units ($P < 0.05$) and the $\dot{V}_E$ to maximal ventilatory capacity ratio was 72% and 55% in women and men, respectively ($P < 0.05$). Comparable increases in dynamic hyperinflation were seen in both male and female COPD groups at symptom limitation but women reached tidal volume constraints at a lower work rate and $\dot{V}_E$ than men. Superimposing mild COPD on the normal aging effects had greater sensory consequences in women because of their naturally reduced ventilatory reserve.

1. Introduction

The study of sex differences in the clinical manifestations of COPD is highly relevant given the increasing incidence of COPD in younger women (van Durme et al., 2009) and the increasing mortality in women with this condition (Mannino et al., 2002). Moreover, women with COPD report greater levels of anxiety and depression (Laurin et al., 2007), report a poorer health-related quality of life (de Torres et al., 2005; Martinez et al., 2007), may have different pathophysiological manifestations (Martinez et al., 2007), and may be more susceptible to the effects of tobacco than men (Langhammer et al., 2000, 2003; Prescott et al., 1997). Women tend to experience greater dyspnea than men with comparable COPD severity when this symptom is evaluated using standardized task-based questionnaires (de Torres et al., 2005, 2007; Martinez et al., 2007). The physiological mechanisms for this sex disparity are unknown and are the main focus of this study.

Recent studies have shown that individuals with milder COPD have poorer self-reported health status and experience greater activity limitation than healthy control populations (Ferrer et al., 1997; Miravitlles et al., 2009; Troosters et al., 2010). In one recent study, patients with mild COPD, but with extensive small airway dysfunction, experienced greater dyspnea during exercise than age-matched healthy controls. Major contributors to the increased dyspnea included higher ventilatory requirements due to ventilation/perfusion abnormalities and greater intrinsic mechanical loading of the respiratory muscles due to the effects of dynamic pulmonary hyperinflation (Ofir et al., 2008a). A second study in patients with mild COPD confirmed the role of dynamic hyperinflation in dyspnea causation: relief of exertional dyspnea for a given ventilation following bronchodilator treatment was related to reductions in lung volumes (O'Donnell et al., 2009).

We reasoned that when the pathophysiological changes of mild COPD are superimposed on the aging respiratory system, the sensory consequences would be amplified in women compared with men. Women have smaller airways, lung volumes and respiratory musculature compared with age-matched men (Sheel and Guenette, 2008; Sheel et al., 2004, 2009) and have a higher mechanical work of breathing during exercise (Guenette et al., 2007, 2009). It follows that increased mechanical loading of COPD will result in greater fractional contractile respiratory muscle effort requirements to generate a given ventilation in women compared with men. Thus, perceived breathing effort will be relatively greater in women with COPD. Accordingly, the objectives of the study were: (1) to determine if dyspnea intensity was significantly higher at a given ventilation ($\dot{V}_E$) and absolute work rate in women with COPD compared with age-matched men with COPD; (2) to determine if sex differences in dyspnea in COPD were related to natural differences in respiratory system reserve as assessed by analysis of breathing pattern and operating lung volumes during exercise.

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2. Methods

2.1. Subjects

Sixteen male and 16 female patients with mild COPD (post-bronchodilator $FEV_1 \geq 80\%$ predicted and $FEV_1/FVC < 0.7$ (Rabe et al., 2007)) and 32 healthy age-matched men ($n = 16$) and women ($n = 16$) with normal spirometry participated in this study. Subjects were excluded if they had: metabolic, cardiovascular or any other respiratory disease that may contribute to dyspnea; or neuromuscular diseases, musculoskeletal abnormalities or any other condition that might interfere with exercise testing.

2.2. Study design

This study received ethical approval from the University and Hospital Human Research Ethics Board. On day 1, subjects gave informed consent and completed medical history screening and chronic activity-related dyspnea questionnaires (Baseline Dyspnea Index (Mahler et al., 1984) and Medical Research Council dyspnea scale (Fletcher et al., 1959)). On day 2, subjects performed pulmonary function testing and cardiopulmonary exercise testing. COPD patients were asked to refrain from using bronchodilator medications for between 8 and 72 h, depending on if the medication was short- or long-acting. All subjects were encouraged to avoid alcohol, caffeine and heavy meals for at least 4 h, and to avoid strenuous exercise for at least 12 h before testing.

2.3. Pulmonary function

Spirometry, body plethysmography, single-breath diffusing capacity for carbon monoxide (DLCO) and maximal mouth pressures were performed according to recommendations (ATS, 2002; MacIntyre et al., 2005; Miller et al., 2005a,b; Wanger et al., 2005) using an automated testing system (Vs62j Body Plethysmograph and Vmax229d; SensorMedics, Yorba Linda, CA). The COPD group also performed pre- and post-bronchodilator (400 mcg salbutamol) pulmonary function testing. All measurements are expressed as percentages of predicted normal values (Black and Hyatt, 1969; Briscoe and Dubois, 1958; Burrows et al., 1961; Crapo et al., 1982; Hamilton et al., 1995; Morris et al., 1988).

2.4. Cardiopulmonary exercise testing

Exercise was performed on an electronically braked cycle ergometer (Ergometrics 800S; SensorMedics) using the Vmax229d Cardiopulmonary Exercise Testing System (SensorMedics) according to recommended guidelines (ATS, 2003) and as previously described (Ofir et al., 2007). Exercise tests consisted of steady-state rest, a 1 min warm-up, and 20 W step-wise increases in work rate every 2 min until symptom-limitation (i.e., peak exercise). On exercise cessation, subjects were asked to verbalize their main reason(s) for stopping exercise.

2.5. Measurements

Subjects rated the intensity of their "breathing discomfort" and "leg discomfort" at rest and throughout exercise by pointing to a modified 10-point Borg scale. The scale's endpoints were anchored such that '0' represented "no breathing/leg discomfort" and '10' represented "the most severe breathing/leg discomfort ever experienced or imagined." Arterial oxygen saturation by pulse oximetry, heart rate by electrocardiography and blood pressure by auscultation were measured at rest and throughout exercise. Minute ventilation ($\dot{V}_E$), oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO_2}$), partial pressure of end-tidal CO_2 ($P_{ET_{CO_2}}$), tidal volume (V_T), and breathing frequency were measured breath-by-breath and averaged over 30-s epochs. End-expiratory lung volume (EELV) and end-inspiratory lung volume (EILV) were estimated from IC maneuvers as previously described (O'Donnell et al., 2001). IC maneuvers were performed during the final 30 s of each 2 min exercise stage. Maximal ventilatory capacity (MVC) was estimated by multiplying FEV_1 by 35 (Gandevia and Hugh-Jones, 1957).

2.6. Analysis

A sample size of 16 subjects per group was used to provide the power to detect a significant difference in dyspnea as previously described (Ofir et al., 2008a). Descriptive characteristics and exercise responses for a given work rate were compared using a 2×2 ANOVA for sex and group (COPD vs. control). Tukey's post hoc test was used to make four pairwise comparisons (male COPD vs. female COPD, male control vs. female control, male COPD vs. male control, female COPD vs. female control) for selected variables. Exercise response slopes (e.g., dyspnea vs. $\dot{V}_E$) were calculated using linear regression analysis across the range of data points measured during exercise for each individual subject. Reasons for stopping exercise were analyzed as frequency statistics and compared using the Fisher's exact test. Results were expressed as means ± SD unless otherwise stated. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Subject characteristics

Descriptive characteristics of the subjects are summarized in Table 1 and exercise data are shown in Table 2. COPD patients met spirometric criteria for mild COPD (post-bronchodilator $FEV_1 \geq 80\%$ predicted and $FEV_1/FVC < 0.7$ (Rabe et al., 2007)) and 29 of the 32 patients were below the lower limit of normal (LLN) for FEV_1/FVC as estimated by sex specific equations from Hankinson et al. (1999). The 3 patients that were above the LLN differed by an average FEV_1/FVC of <0.04. Men and women with COPD were well matched for body mass index (BMI), smoking history, chronic activity-related dyspnea, percent predicted peak $\dot{V}_{O_2}$, percent predicted pulmonary function parameters, and disease severity (i.e., post-bronchodilator FEV_1/FVC and FEV_1% predicted). Men and women with COPD demonstrated significantly greater expiratory flow limitation, lung hyperinflation, a reduced DLCO and chronic activity-related dyspnea relative to their respective controls.

3.2. Perceptual responses to exercise

The selection frequency of main reasons for stopping exercise was not significantly different across sexes within the COPD and control groups. However, breathing discomfort, either alone or in combination with leg discomfort, was chosen as a primary reason for stopping exercise in 69% of women with COPD compared with 38% of men with COPD, 38% of healthy women and 44% of healthy men.

Exertional dyspnea intensity plotted against absolute work rate showed (Fig. 1A): (1) greater dyspnea in the COPD groups than their healthy counterparts, (2) greater dyspnea in women than men with COPD at work rates of 60 W and 80 W, with the men reaching a higher peak work rate but a similar peak dyspnea intensity, and (3) no sex difference at any given work rate in the healthy control group. In both groups, there were no major sex differences in the dyspnea response to exercise when work rate was normalized to account for differences in body mass (Fig. 1B). Similar findings were found for intensity of leg discomfort (Fig. 1C and D).

Table 1
Subject characteristics and pulmonary function in men and women with mild COPD and healthy controls.

	Male COPD	Female COPD	Male control	Female control	
Age (yr)	67 ± 8	62 ± 6	69 ± 5	66 ± 4	*
Height (cm)	175 ± 8	160 ± 7	172 ± 6	163 ± 6	*,†
Mass (kg)	87.5 ± 15.6	67.2 ± 14.4	80.1 ± 10.6	68.4 ± 10.0	*,†
Body mass index (kg/m2)	28.4 ± 4.4	26.2 ± 5.4	27.0 ± 3.4	25.9 ± 3.2	NS
BDI focal score (0–12)	8.4 ± 1.9	8.4 ± 1.7	11.5 ± 1.1	10.6 ± 1.2	§,‡
MRC dyspnea scale (1–5)	0.8 ± 0.4	0.9 ± 0.8	0.1 ± 0.3	0.1 ± 0.3	§,‡
Cigarette smoking (pack yrs)	45 ± 25	49 ± 25	3 ± 5	3 ± 5	§,‡
FEV_1 post-β_2-agonist (% predicted)	92 ± 7	93 ± 11	–	–	NS
FEV_1/FVC post-β_2-agonist (%)	60.0 ± 6.7	62.6 ± 4.6	–	–	NS
FEV_1 (% predicted)	86 ± 10	86 ± 12	117 ± 17	114 ± 17	§,‡
FVC (% predicted)	102 ± 14	101 ± 10	109 ± 15	113 ± 13	‡
FEV_1/FVC (%)	58.3 ± 7.5	61.6 ± 6.5	73.7 ± 7.9	72.4 ± 5.6	§,‡
FEV_1/FVC (% predicted)	85 ± 11	85 ± 9	108 ± 11	101 ± 8	†,§,‡
FEV_1/FVC (LLN*)	65 ± 2	68 ± 1	64 ± 1	67 ± 1	
PEF (% predicted)	88 ± 18	91 ± 12	116 ± 17	115 ± 16	§,‡
$FEF_{25-75\%}$ (% predicted)	38 ± 11	34 ± 13	97 ± 41	72 ± 29	†,§,‡
IC (% predicted)	105 ± 20	101 ± 20	107 ± 17	109 ± 16	NS
FRC (% predicted)	119 ± 22	113 ± 19	100 ± 17	106 ± 15	§
TLC (% predicted)	112 ± 10	107 ± 12	103 ± 12	107 ± 10	NS
RV (% predicted)	128 ± 17	114 ± 26	91 ± 18	88 ± 15	*,§,‡
sRaw (% predicted)	266 ± 83	269 ± 110	130 ± 29	143 ± 44	§,‡
MIP (% predicted)	97 ± 30	112 ± 34	117 ± ± 27	99 ± 35	NS
MEP (% predicted)	79 ± 27	74 ± 14	103 ± 21	89 ± 32	§
DLco/VA (% predicted)	90 ± 19	89 ± 17	107 ± 18	108 ± 15	§,‡

Pulmonary function parameters are pre-bronchodilator (β_2-agonist) unless otherwise stated. BDI = modified Baseline Dyspnea Index; MRC = Medical Research Council; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; PEF = peak expiratory flow; $FEF_{25-75\%}$ = forced expiratory flow between 25 and 75% of FVC; IC = inspiratory capacity; FRC = functional residual capacity; TLC = total lung capacity; RV = residual volume; sRaw = specific airways resistance; MIP = maximal inspiratory pressure; MEP = maximal expiratory pressure; DL_{CO} = diffusing capacity of the lung for carbon monoxide; VA = alveolar volume. Values are means ± SD. LLN* = lower limit of normal calculated from Hankinson et al. (1999) based on sex and age.

* Male vs. female COPD ($P < 0.05$).
† Male vs. female control ($P < 0.05$).
§ COPD vs. control male ($P < 0.05$).
‡ COPD vs. control female ($P < 0.05$).
NS Not significantly different ($P > 0.05$).

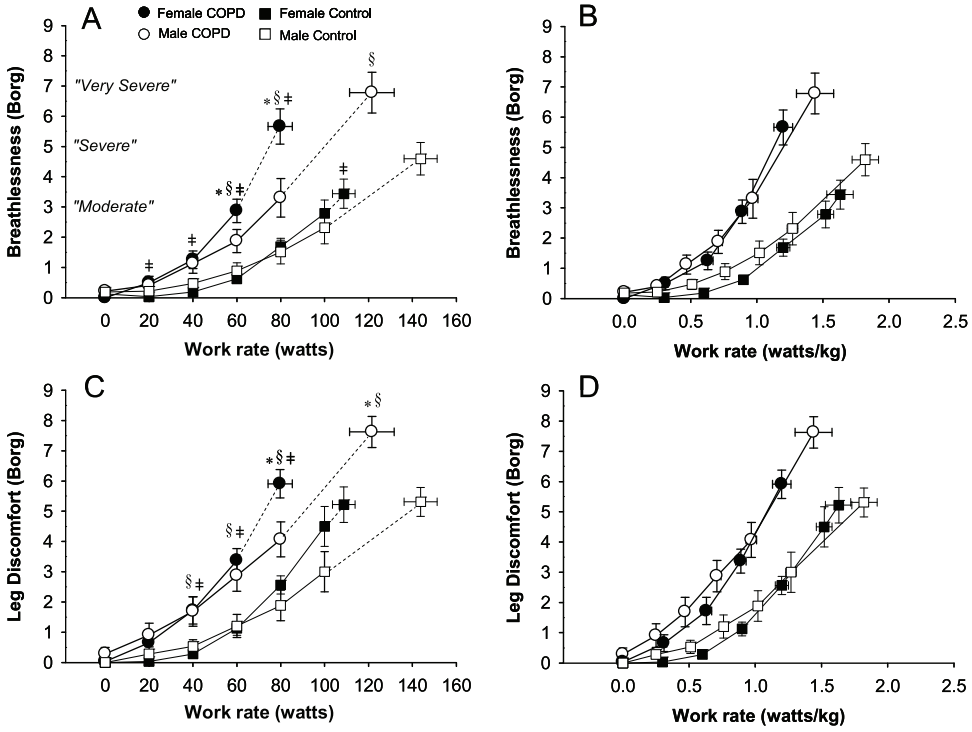

Fig. 1. Intensity of breathlessness and leg discomfort vs. absolute work rate and work rate normalized for body mass. Values are means ± SE. *Male vs. female COPD ($P < 0.05$); †male vs. female control ($P < 0.05$); §COPD vs. control male ($P < 0.05$); ‡COPD vs. control female ($P < 0.05$).

Table 2
Measurements at the tidal volume inflection ("plateau") and at symptom-limited peak exercise.

	V_T plateau					Peak exercise				
	Male COPD	Female COPD	Male control	Female control		Male COPD	Female COPD	Male control	Female control	
Dyspnea (Borg)	3.9 ± 2.1	2.3 ± 1.7	1.8 ± 1.6	1.2 ± 1.0	*,§	6.8 ± 2.7	5.7 ± 2.3	4.6 ± 2.1	3.4 ± 1.9	§,‡
Leg discomfort (Borg)	5.0 ± 2.4	2.8 ± 1.3	2.4 ± 2.0	2.0 ± 1.4	*,§	7.6 ± 2.1	5.9 ± 1.9	5.3 ± 1.9	5.2 ± 2.4	*,§
Work rate (W)	98 ± 33	62 ± 20	104 ± 30	78 ± 20	*,†	122 ± 41	80 ± 22	145 ± 31	109 ± 21	*,†,§,‡
$\dot{V}_{O_2}$ (L/min)	1.58 ± 0.33	1.00 ± 0.26	1.71 ± 0.46	1.28 ± 0.29	*,†,‡	1.89 ± 0.54	1.22 ± 0.29	2.31 ± 0.51	1.70 ± 0.40	*,†,§,‡
(% predicted max)	(63 ± 9)	(61 ± 14)	(71 ± 15)	(83 ± 16)	†,‡	(74 ± 16)	(76 ± 14)	(96 ± 18)	(109 ± 23)	§,‡
$\dot{V}_{CO_2}$ (L/min)	1.59 ± 0.38	1.00 ± 0.26	1.80 ± 0.49	1.32 ± 0.27	*,†,‡	2.03 ± 0.63	1.29 ± 0.31	2.60 ± 0.56	1.93 ± 0.35	*,†,§,‡
RER	1.00 ± 0.05	1.00 ± 0.09	1.05 ± 0.07	1.04 ± 0.10	NS	1.07 ± 0.06	1.07 ± 0.11	1.13 ± 0.06	1.15 ± 0.11	‡
HR (beats/min)	132 ± 27	124 ± 20	124 ± 14	124 ± 14	NS	139 ± 23	136 ± 18	150 ± 16	147 ± 15	NS
SpO_2 (%)	96 ± 1	96 ± 3	96 ± 2	95 ± 5	NS	96 ± 2	96 ± 4	95 ± 2	96 ± 3	NS
$\dot{V}_E$ (L/min)	53.2 ± 12.9	32.3 ± 6.6	50.8 ± 15.4	38.4 ± 8.1	*,†	74.1 ± 23.4	44.5 ± 10.3	86.8 ± 26.6	66.2 ± 15.4	*,†,‡
(% estimated MVC)	(61 ± 14)	(52 ± 9)	(47 ± 9)	(48 ± 8)	*,§	(84 ± 22)	(72 ± 19)	(80 ± 21)	(83 ± 16)	NS
$\dot{V}_E/\dot{V}_{O_2}$	33.6 ± 5.3	33.4 ± 5.8	29.5 ± 2.8	30.2 ± 4.3	§	39.1 ± 5.5	37.2 ± 6.6	37.2 ± 5.3	39.5 ± 6.8	NS
$\dot{V}_E/\dot{V}_{CO_2}$	33.8 ± 4.7	33.7 ± 6.3	28.0 ± 1.8	29.3 ± 3.8	§,‡	36.5 ± 5.0	34.8 ± 6.2	33.1 ± 4.2	34.3 ± 4.8	NS
$P_{ET_{CO_2}}$ (mmHg)	39.0 ± 4.4	40.3 ± 6.9	47.8 ± 8.8	45.6 ± 10.6	§	34.9 ± 4.3	37.4 ± 5.3	40.1 ± 7.6	38.4 ± 9.7	NS
f (breaths/min)	26 ± 5	26 ± 6	23 ± 4	28 ± 4	†	36 ± 7	35 ± 8	36 ± 10	42 ± 12	NS
V_T (L)	2.07 ± 0.42	1.31 ± 0.23	2.17 ± 0.49	1.38 ± 0.26	*,†	2.04 ± 0.48	1.31 ± 0.29	2.45 ± 0.49	1.51 ± 0.22	*,†,§
ΔIC from rest (L)	−0.29 ± 0.32	-0.24 ± 0.24	0.21 ± 0.42	0.13 ± 0.23	§,‡	−0.56 ± 0.34	−0.36 ± 0.31	0.12 ± 0.40	−0.01 ± 0.30	§,‡
V_T/IC (%)	68 ± 9	62 ± 10	65 ± 9	54 ± 11	†,‡	72 ± 12	69 ± 13	76 ± 13	64 ± 9	†
IRV (L)	0.99 ± 0.38	0.84 ± 0.33	1.16 ± 0.42	1.20 ± 0.42	‡	0.84 ± 0.44	0.63 ± 0.32	0.80 ± 0.50	0.89 ± 0.35	NS

Tidal volume (V_T) plateau data are from subjects with a detectable V_T inflection (13 female COPD, 14 male COPD, 16 female control, 14 male control). Peak exercise data are from all men and women (16 per group). $\dot{V}_{O_2}$ = oxygen uptake; $\dot{V}_{CO_2}$ = carbon dioxide production; RER = respiratory exchange ratio; HR = heart rate; SpO_2 = pulse oximetry derived arterial O_2 saturation; $\dot{V}_E$ = minute ventilation; $P_{ET_{CO_2}}$ = partial pressure of end-tidal CO_2; f = breathing frequency; V_T = tidal volume; IC = inspiratory capacity; IRV = inspiratory reserve volume. Values are means ± SD.

* Male vs. female COPD ($P < 0.05$).

† Male vs. female control ($P < 0.05$).

§ COPD vs. control male ($P < 0.05$).

‡ COPD vs. control female ($P < 0.05$).

NS Not significantly different ($P > 0.05$).

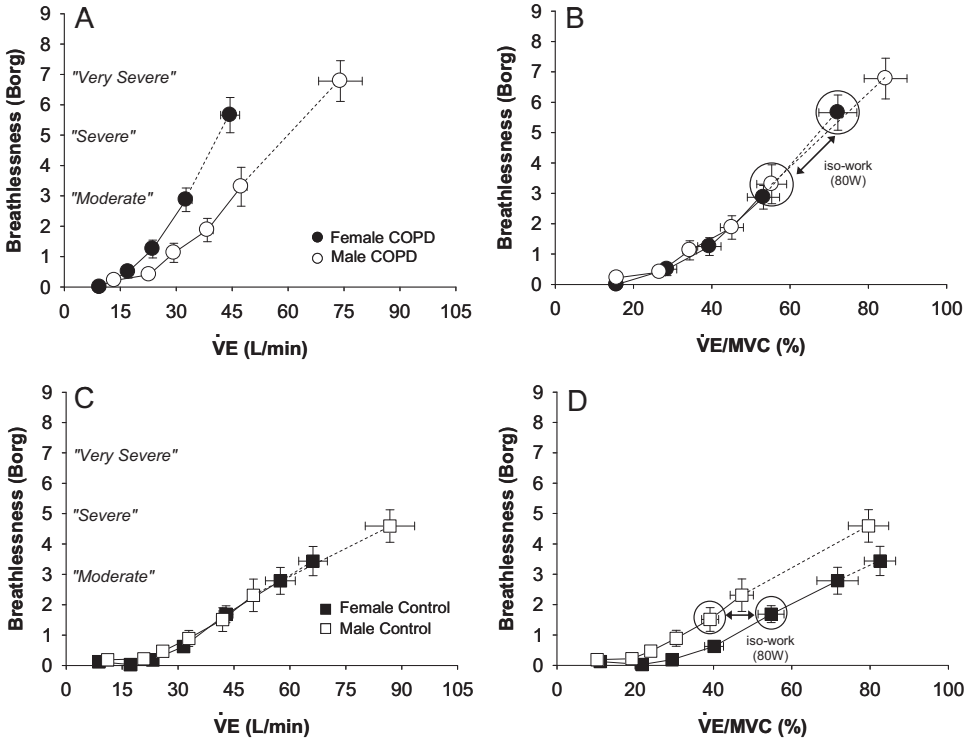

Fig. 2. Breathlessness vs. absolute minute ventilation ($\dot{V}_E$) and $\dot{V}_E$ expressed as a percentage of estimated maximal ventilatory capacity (MVC). At a work rate of 80 W (the highest absolute work rate comparison between men and women with COPD), the $\dot{V}_E$/MVC ratio was 72% in women and 55% in men with COPD with corresponding breathlessness ratings of 5.7 and 3.3 Borg units, respectively. At the same work rate in the healthy controls, the $\dot{V}_E$/MVC ratio was 55% in women and 39% in men with corresponding breathlessness ratings of 1.7 and 1.5 Borg units, respectively. Values are means ± SE.

To account for potential group and/or sex differences in the ventilatory response to exercise that may contribute to dyspnea, we also evaluated dyspnea intensity relative to $\dot{V}_E$ (Fig. 2). Women with COPD had higher dyspnea ratings for any given $\dot{V}_E$ relative to men with COPD and the magnitude of this difference increased disproportionately with increasing $\dot{V}_E$: slopes were 50% greater in women than men (0.20 ± 0.06 vs. 0.13 ± 0.06, respectively, $P < 0.01$) (Fig. 2A). However, dyspnea ratings in men and women with COPD were superimposed when $\dot{V}_E$ was normalized as a percentage of predicted MVC to account for the reduced ventilatory capacity in women (Fig. 2B). There were no sex differences seen in dyspnea vs. $\dot{V}_E$ in the control group (Fig. 2C); however, females had a rightward shift in this relationship when $\dot{V}_E$ was expressed relative to predicted MVC (Fig. 2D). The male COPD group had dyspnea/$\dot{V}_E$ slopes that were 75% greater than the male control group whereas the female COPD group was 168% greater than the female control group.

3.3. Physiological responses to exercise

Physiological measurements were plotted against absolute work rate in order to identify possible reasons for the greater dyspnea in women with COPD for a given work rate relative to men. Measurements plotted against absolute work rate in COPD showed that (Figs. 3–5): men had a significantly higher $\dot{V}_{O_2}$ than females at all levels which was abolished when expressed per unit of body mass; women had higher RER values than men at the higher levels of exercise; there were no sex differences for $\dot{V}_E/\dot{V}_{CO_2}$ or $P_{ET_{CO_2}}$ but COPD as a whole was associated with greater $\dot{V}_E/\dot{V}_{CO_2}$ and lower $P_{ET_{CO_2}}$ than in health; V_T and $\dot{V}_E$ were higher in men and breathing frequency was higher in women throughout most exercise intensities.

More detailed analysis of operating lung volumes and breathing pattern showed that EELV increased progressively throughout exercise in men and women with COPD whereas EELV remained at or below resting values in the healthy control groups throughout exercise (Fig. 6). At symptom-limited peak, men with COPD reduced their IC by 0.56 ± 0.34 L (range: −1.11 to −0.03 L) whereas women reduced their IC by 0.36 ± 0.31 L (range: −0.88 to +0.26 L) with no difference between sexes ($P > 0.05$). There were no sex differences in the regulation of EELV or EILV (expressed as % predicted TLC) within the COPD or control groups at any given work rate (Fig. 6A and B). Mild COPD consistently resulted in markedly higher EILV and EELV values relative to their respective controls in both sexes across all absolute work rates (Fig. 6C and D). Thirteen females and 14 males with COPD demonstrated a clear inflection in V_T during exercise. The V_T at the point of inflection was not different from that at peak exercise in these women (1.31 ± 0.23 vs. 1.34 ± 0.28 L, $P > 0.05$) and men (2.07 ± 0.42 vs. 2.09 ± 0.50 L, $P > 0.05$) suggesting a true plateau in V_T in each group. This plateau occurred at a lower absolute $\dot{V}_E$, $\dot{V}_{O_2}$, and work rate ($P < 0.01$) and at a lower relative fraction of the MVC in women compared with men ($P < 0.05$) (Table 2). Sixteen healthy women experienced a plateau in V_T which also occurred at a lower absolute $\dot{V}_E$, $\dot{V}_{O_2}$, and work rate than the 14 healthy men that demonstrated a V_T plateau ($P < 0.01$).

4. Discussion

The main findings of this study were as follows: (1) the pathophysiological abnormalities associated with mild COPD had greater sensory consequences in women than men at absolute work rates and ventilations. (2) Mild COPD was associated with comparable abnormalities in ventilatory demand and mechanical loading in both sexes relative to healthy controls. (3) The greater intensity of dyspnea in women during a given ventilation and work rate primar-

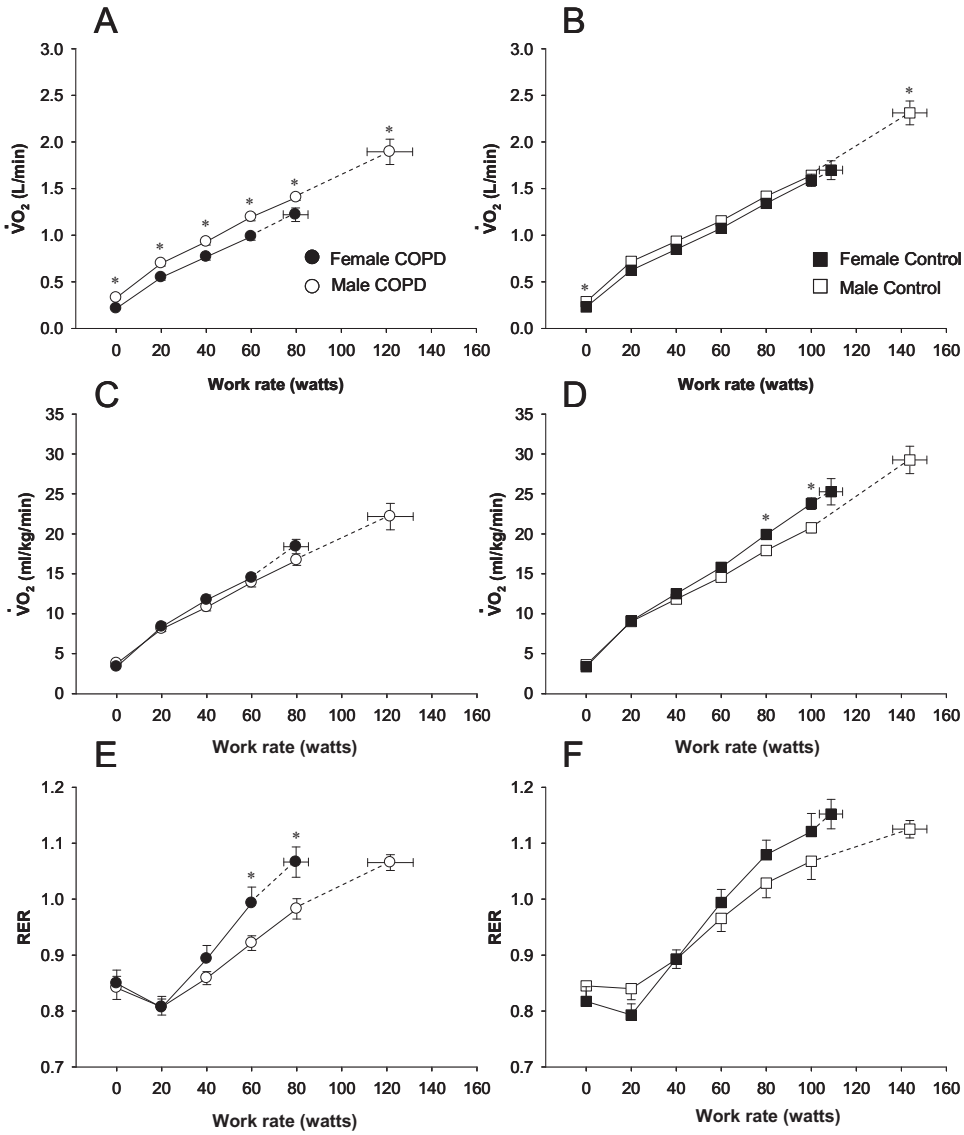

Fig. 3. Oxygen consumption ($\dot{V}_{O_2}$) and respiratory exchange ratio (RER) vs. absolute work rate. Values are means ± SE. *Significantly different at a standardized absolute work rate or at peak exercise (final data point) ($P < 0.05$).

ily reflected their relatively smaller lungs, airways and muscle mass as manifest by the presence of significant dynamic mechanical constraints on tidal volume expansion at a relatively lower ventilation and work rate during exercise.

Our *a priori* objective was to compare sensory responses during a standardized "absolute" physical task or stimulus in order to provide mechanistic insight into the consistent clinical observation that women with COPD experience greater dyspnea than

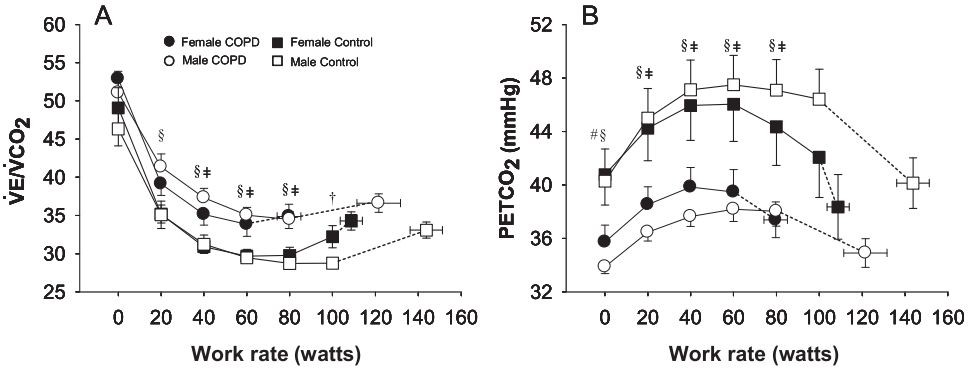

Fig. 4. Ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}_{CO_2}$) and the partial pressure of end-tidal CO_2 ($P_{ET_{CO_2}}$) vs. work rate. Values are means ± SE. †Male vs. female control ($P < 0.05$); §COPD vs. control male ($P < 0.05$); ‡COPD vs. control female ($P < 0.05$); #COPD vs. control female ($P = 0.05$).

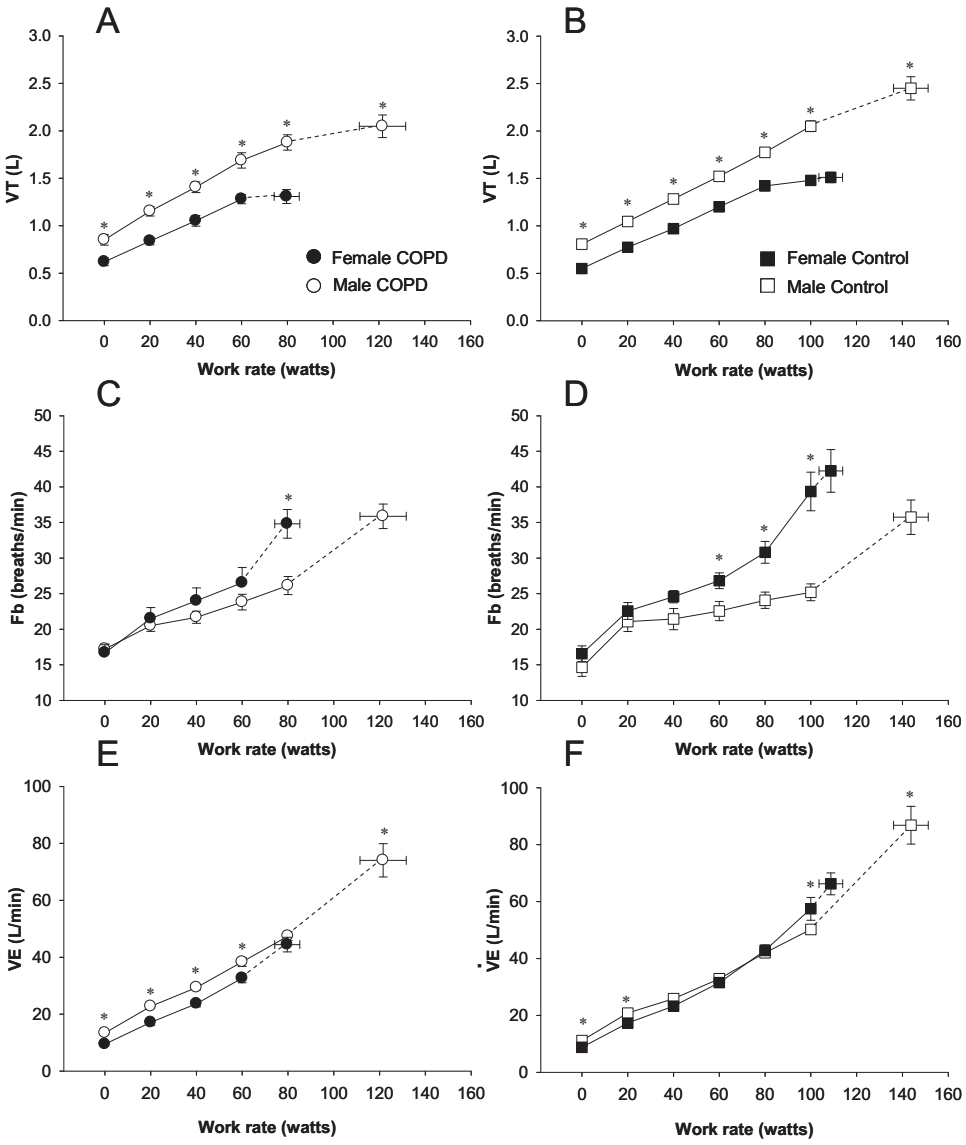

Fig. 5. Tidal volume (V_T), breathing frequency (Fb) and minute ventilation ($\dot{V}_E$ vs. absolute work rate). Values are means ± SE. *Significantly different at a standardized absolute work rate or at peak exercise (final data point) ($P < 0.05$).

men during activities of daily living (de Torres et al., 2005, 2007; Martinez et al., 2007). The most appropriate way to do this in a laboratory setting is to make physiological comparisons at absolute work rates. However, it is important to acknowledge that sex differences in dyspnea disappeared when work rate was normalized to account for differences in body mass (Fig. 1B) or when ventilation was normalized to account for differences in ventilatory capacity (Fig. 2B). These normalization strategies help us account for known sex differences in size, mass and strength. Had we focussed exclusively on these relative comparisons, we would conclude that women with COPD do not experience more dyspnea than men during exercise. However this would not explain why women experience more troublesome dyspnea than men with comparable COPD severity during activities of daily living or during standard cardio-pulmonary exercise testing used to clinically evaluate dyspnea severity. It is therefore necessary to present both absolute and relative comparisons as we have done in this study since both provide complimentary information.

Our COPD patients had a significant smoking history, mild-to-moderate activity related dyspnea and were classified as having mild COPD according to GOLD stage I criteria and nearly all patients had FEV_1/FVC values below the lower limit of normal for a reference population. The presence of clinically significant small airway dysfunction was evident by typical changes in the configuration of the maximum expiratory flow-volume curve and consistent increases in air trapping. The men and women with COPD were well matched for BMI, smoking history, the presence of comorbidities, chronic dyspnea ratings, relative fitness level (based on % predicted peak symptom-limited $\dot{V}_{O_2}$) and most pulmonary function parameters (expressed as % predicted). As such, we were able to directly evaluate the influence of biological sex on dyspnea, ventilatory responses and exercise tolerance in these well-matched patients.

Both male and female healthy control groups were capable of exercising to high work rates (i.e., 80 W – the highest mean absolute work rate achieved by the female COPD group) while only rating mild breathing discomfort (<2 Borg units). Dyspnea/$\dot{V}_E$ and dyspnea/work rate plots were similar in healthy men and women, likely reflecting the fact that, regardless of sex, the respiratory system in this older healthy control group had sufficient reserve to accommodate the increased ventilatory requirements of a demanding physical task with little respiratory discomfort. Surprisingly, despite the healthy women working at a higher fraction of their

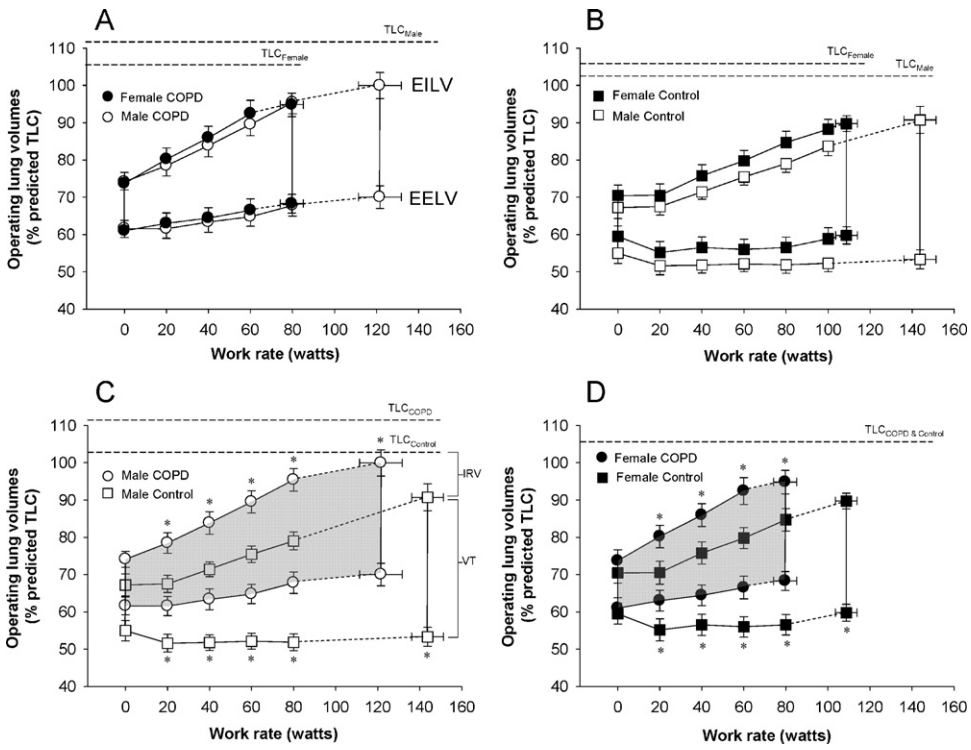

Fig. 6. End-expiratory lung volume (EELV) and end-inspiratory lung volume (EILV) expressed as a percentage of predicted total lung capacity (TLC) vs. absolute work rate. IRV = inspiratory reserve volume; V_T = tidal volume. Values are means ± SE. *Significantly different at a standardized absolute work rate or at peak exercise (final data point) ($P < 0.05$).

maximum capacity for any given work rate, they did not experience more dyspnea than the healthy males. This contrasts recent work in healthy aging during treadmill exercise by Ofir et al. (2008b). However, it should be noted that the absolute dyspnea ratings in the present study and in the work of Ofir et al. (2008b) were consistently small throughout all submaximal exercise intensities (<3 Borg Units – i.e., below "moderate") suggesting that any modest sex difference in health is likely of minimal clinical significance.

The present study is the first to demonstrate that the presence of mild COPD resulted in greater sensory consequences in older women than in FEV_1-matched men of similar age. Women with COPD had higher dyspnea ratings for any given absolute work rate or ventilation. In fact, significant differences in dyspnea occurred at a relatively low oxygen consumption (~14 mL/kg/min) and work rate (60 W) which, when converted to a metabolic equivalent (4 MET), is well within moderate intensity activities of daily living such as general gardening, outdoor sweeping, leisurely cycling and walking up stairs, among others (Ainsworth et al., 2000). To explain greater exertional dyspnea intensity in women, we considered the following potential mechanisms: (1) sex differences in pathophysiological abnormalities of COPD, i.e., ventilatory requirements and pattern of change in dynamic respiratory mechanics during exercise and (2) an earlier onset of dynamic mechanical ventilatory constraints and a relatively increased ventilatory demand-capacity ratio at any given $\dot{V}_E$ in women due to their smaller lungs and airways.

4.1. Dynamic ventilatory mechanics during exercise in mild COPD

Sex differences in breathing pattern reflected the known differences in resting IC – the true operating limit for V_T expansion in patients with expiratory flow limitation. Given the relatively reduced IC, the naturally smaller airway diameters and relative tachypneic breathing pattern in women, we postulated that the presence of mild COPD would predispose to greater dynamic pulmonary hyperinflation (or IC reduction) during exercise than men. This was not the case: mean reduction in IC from rest to peak exercise was 16% in both women and men with COPD. However, it must be noted that this reduction occurred over a much narrower range of increasing $\dot{V}_E$ in women (change in $\dot{V}_E = 35 \pm 10$ L/min) compared with men (change in $\dot{V}_E = 61 \pm 23$ L/min) ($P < 0.001$). Even though both groups had apparent ventilatory reserve at end-exercise based on estimated breathing reserve ($\dot{V}_E$/MVC), this traditional evaluation of ventilatory limitation may be imprecise in patients with mild COPD. Significant ventilatory constraints such as high a V_T/IC ratio, a plateau in the V_T response with accompanying tachypnea and severe exertional dyspnea were present to a similar degree in men and women with COPD at the limits of tolerance. However, greater ventilatory constraints were evident in women with COPD: EILV increased to reach a critically reduced dynamic IRV (e.g., the V_T plateau) over a substantially lower ventilation range at relatively low work rates compared with men (Table 2). At the limits of tolerance in women with COPD, when the $\dot{V}_E$/MVC was on average only 72%, perusal of the exercise flow-volume loops indicate significant limiting constraints on further tidal volume expansion compared with men as illustrated in Fig. 7.

4.2. Sex differences in dyspnea in COPD: mechanisms

In contrast to the situation in health, dyspnea was consistently increased for any given ventilation in women compared with men in the mild COPD groups. This was noticeable even at lower levels of ventilation and became more pronounced towards the end of exercise. We have previously argued that increases in dyspnea at a standardized ventilation during exercise in mild COPD indicates the presence of greater intrinsic mechanical loading or reduced strength of the respiratory muscles (O'Donnell et al., 2009). The increase in dyspnea from the V_T inflection (in those with a detectable plateau) to the limit of tolerance was 3.5 ± 1.9 and 3.4 ± 1.4 Borg units in women and men with COPD,

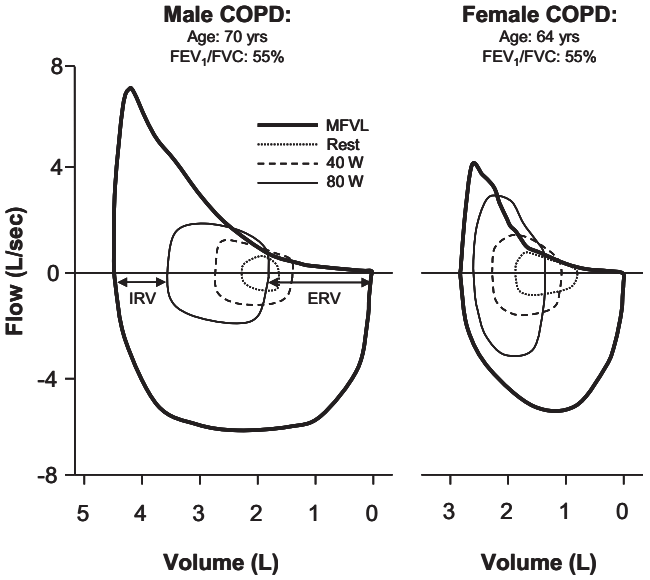

Fig. 7. Individual example of tidal flow-volume loops at rest and during exercise in an individual male and female subject with mild COPD. Tidal breaths are positioned within the resting maximal flow volume loop (MFVL) according to end-expiratory lung volume (EELV). The female subject has greater encroachment of her MFVL, has a greater increase in EELV relative to resting values and has a smaller inspiratory reserve volume (IRV) for a given absolute work rate of 40 and 80 W. The corresponding dyspnea ratings at 80 W in the male and female are 3 and 7 Borg Units, respectively. This is due, in large part, to the fact that the female subject is breathing at a much higher fraction of her maximal ventilatory capacity while performing the same absolute task as her male counterpart. ERV, expiratory reserve volume.

respectively. However, this steep increase in dyspnea to intolerable levels occurred over a much smaller range of increasing ventilation in women than in men with COPD (change in $\dot{V}_E = 14 \pm 6$ vs. 24 ± 17 L/min, $P < 0.05$) and at much lower work rates (Table 2). Thus, these health-COPD differences in dyspnea intensity for a given $\dot{V}_E$ were particularly pronounced in women, and likely reflect the earlier onset of dynamic ventilatory constraints and associated mechanical loading of relatively weaker respiratory muscles.

It is well established that women have smaller lungs and airways relative to height-matched men resulting in a reduced ventilatory capacity available during exercise (Sheel and Guenette, 2008) and these differences in size are the main explanation for the sex differences in dyspnea observed in the present study. Sex differences in dyspnea for any absolute ventilation disappeared when $\dot{V}_E$ was normalized to each subject's estimated MVC (Fig. 2B). At a work rate of 80 W when $\dot{V}_E$ was ~45 L/min, both the $\dot{V}_E$/MVC and simultaneous dyspnea ratings were greater in women than men. These data support the notion that the mechanical and ventilatory abnormalities of mild COPD have greater implications in women who have a naturally reduced ventilatory reserve.

This study confirmed that dyspnea intensity in patients with COPD during exercise rises linearly with $\dot{V}_E$/MVC, the original dyspnea index (Gandevia and Hugh-Jones, 1957). At a peak $\dot{V}_E$ of ~45 L/min (representing 72% of MVC) in women, EELV increased by ~0.4 L above an already increased baseline value. At a comparable $\dot{V}_E$ in men (representing only 55% MVC), EELV had increased by the same absolute amount but in this case was easily accommodated with only modest respiratory discomfort, likely due to substantially greater respiratory muscle mass and strength in men. Accordingly, for a standardized physical task or $\dot{V}_E$, central motor command output (and perceived respiratory effort) required to drive the respiratory muscles likely represents a higher fraction of the maximal possible motor output in women than men. The contention that a higher amplitude of central motor command output (and central corollary discharge) to the contracting skeletal muscles occurred in women is bolstered by our finding of greater parallel increases in perceived leg effort in women with COPD for a given work rate (Fig. 1).

4.3. Limitations

We must acknowledge that sex differences in perceived dyspnea may be influenced by psychosocial and gender-related contextual factors, including stoicism, perceptual acuity and communication which were not measured in the current study. Furthermore, the maximal ventilatory capacity was estimated according to $FEV_1 \times 35$ (Gandevia and Hugh-Jones, 1957). This traditional approach provides a general approximation of ventilatory capacity but is limited because it may underestimate the true ventilatory capacity in some COPD patients (Jones et al., 1971; Killian et al., 1992). This limitation was circumvented by additionally evaluating dynamic ventilatory constraints at peak exercise in each individual. Furthermore, any potential variability in our estimated ventilatory capacity was likely consistent across both sexes and would not change the overall conclusion that sex differences in dyspnea disappear when $\dot{V}_E$ is normalized to account for sex differences in ventilatory capacity. Finally, our experimental approach allowed us to assess physiological mechanisms of dypsnea in men and women by standardizing the physical task during cycle exercise in a laboratory setting. However, we acknowledge that extrapolating these findings to daily activities (e.g., gardening, stair climbing, etc.) must be done with caution.

5. Conclusions

The results extend those of previous studies (O'Donnell et al., 2009; Ofir et al., 2008a) that have exposed significant ventilatory and mechanical abnormalities and attendant respiratory discomfort during physical activity in smokers with a largely preserved FEV_1. Unique to this study is the finding that the sensory consequences of mild COPD were much more pronounced in women than men. We found that, in contrast to the situation in health, women with mild COPD have greater dyspnea for any given ventilation, work rate and metabolic requirement than their male counterparts. Comparisons of sensory responses at absolute and relative work rates allowed us to conclude that baseline sex differences in body size was the primary factor in explaining the disparity in respiratory sensation during physical activity in COPD patients. In contrast, we did not observe any differences in dyspnea in the healthy controls, despite the women being smaller. This strongly suggests that superimposing mild levels of airway obstruction on relatively smaller lungs and airways in women results in significantly greater sensory consequences compared with men.

Disclosures

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

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