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Does the Respiratory System Limit Exercise in Mild COPD?

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AT A GLANCE COMMENTARY

Scientific knowledge on the subject: Variable abnormalities of dynamic respiratory mechanics and ventilatory demand have been identified during exercise in symptomatic patients with mild COPD. It is not known if these factors constitute a true physiological limit to exercise in this population since traditional estimates of breathing reserve are usually in the normal range.

What this study adds to the field: This is the first study to utilize selective loading of the respiratory system to determine if ventilatory limitation to exercise exists in mild COPD. The results demonstrate that the respiratory system reaches its true physiological limit at a lower peak ventilation and power output in patients with GOLD stage I COPD compared with healthy age-matched participants.

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ABSTRACT

Rationale: It is not known if abnormal dynamic respiratory mechanics actually limit exercise in patients with mild COPD. We reasoned that failure to increase peak ventilation and tidal volume (V_T) in response to dead space (DS) loading during exercise would indicate true ventilatory limitation to exercise in mild COPD.

Objectives: To compare the effects of DS loading during exercise on ventilation, breathing pattern, operating lung volumes and dyspnea intensity in mild symptomatic COPD subjects and age- and sex-matched healthy controls.

Methods, Measurements and Main Results: Twenty subjects with GOLD stage I COPD and 20 healthy subjects completed two symptom-limited incremental cycle exercise tests, in randomized order: unloaded control (CTRL) and added DS of 0.6L. Peak oxygen uptake and ventilation were significantly lower in COPD than in health by 36% and 41%, respectively. With added DS compared to CTRL, both groups had small decreases in peak work rate and no significant increase in peak ventilation. In health, peak V_T and end-inspiratory lung volume (EILV) increased significantly with DS. In contrast, the COPD group failed to increase peak EILV and had a significantly smaller increase in peak V_T during DS. At 60W, a 50% smaller increase in V_T ($p<0.001$) in response to added DS in COPD compared with health was associated with a greater increase in dyspnea intensity ($p=0.0005$).

Conclusions: These results show that the respiratory system reached or approached its physiological limit in mild COPD at a lower peak work rate and ventilation than in healthy participants.

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Key words: exercise limitation, tidal volume, dead space loading, dyspnea.

INTRODUCTION

Compared with non-smoking healthy populations, smokers with milder COPD show decreased health-related quality of life (1-3) increased activity-related dyspnea and reduced physical activity levels (4-8). The mechanisms of dyspnea and activity restriction in milder COPD are not fully understood.

Increased peripheral airways resistance is the dominant physiological abnormality of COPD. Cross-sectional population studies have confirmed that vast pathophysiological heterogeneity can exist in milder COPD (9). It is clear that the presence of apparently minor airflow obstruction (as measured by spirometry) may obscure widespread inflammatory damage to the peripheral airways, lung parenchyma and its vasculature (10,11). Previous studies conducted at rest have successfully quantified the extent of small airway dysfunction and pulmonary gas exchange impairment in mild COPD (12-14). Reported abnormalities include: reduced static lung recoil pressure, maldistribution of ventilation, early airway closure and increased pulmonary gas-trapping (12-14). More recently, it has been shown that these physiological perturbations are amplified during the stress of cycle exercise (15-17). Thus, compared with age-matched healthy controls, peak ventilation (V_E) and exercise capacity were diminished in symptomatic patients with mild COPD (15,16).

We have proposed that increased ventilatory requirements at any given power output, increased dynamic gas-trapping and mechanical constraints on tidal volume (V_T) expansion may contribute to reduced peak V_E and peak oxygen uptake (VO_2) in mild COPD. However, it remains unclear whether such factors actually constitute a ventilatory limitation to exercise in this population. Thus, most patients with mild COPD appear to have adequate ventilatory reserve, as traditionally estimated by peak V_E as a percentage of maximal ventilatory capacity, at the limits of tolerance (15,16). However, this approach has well established limitations and may not be

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useful in patients with mild COPD who have a largely preserved FEV_1.

In contrast to the situation in more advanced COPD, selective unloading of the respiratory system using inhaled bronchodilators (with or without inhaled corticosteroids) in mild COPD was not consistently associated with increased submaximal V_E, decreased dyspnea or improved exercise tolerance (17,18). The studies were inconclusive and several possible explanations for the negative results could be considered: the respiratory system does not limit exercise performance in mild COPD patients in whom leg discomfort is often the dominant exercise-limiting symptom, the level of unloading was insufficient, or exercise intolerance is multifactorial such that unloading the respiratory system stressed another system (e.g., peripheral muscles) which then replaced it as the locus of exercise limitation.

In the current study, we sought to determine if mechanical factors were the proximate limitation to exercise in mild COPD by selectively stressing the respiratory system by adding dead space (DS) to the breathing apparatus. This approach is in accordance with the definition of limitation proposed by Whipp and Pardy as "those factors that actually prevent a particular function from increasing in the face of an increased requirement for ventilation" (19). Previous studies have shown that added DS during exercise results in significant increases in peak V_T and V_E and preservation of exercise capacity, at least in younger healthy participants (20-22). Brown et al. (23) used DS loading to demonstrate that impaired respiratory mechanics was the proximate limitation to exercise in advanced COPD. We reasoned that in mild COPD, the inability to further increase end-inspiratory lung volume (EILV), V_T and V_E at standardized work rates and at the peak of exercise in response to DS loading would indicate true respiratory limitation to exercise, particularly in the setting of adequate cardiac reserve. We also postulated that DS loading in the face of such mechanical constraints on V_T expansion would lead to an earlier onset of intolerable dyspnea in COPD but not in health. We therefore compared breathing pattern,

operating lung volumes and dyspnea intensity ratings during incremental cycle exercise with DS loading or unloaded control in patients with mild COPD and age- and sex-matched healthy individuals. Some preliminary results of this study are reported in the form of an abstract (24).

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METHODS

Subjects

Subjects included 20 patients with GOLD stage I COPD (25) and 20 healthy age- and sex-matched participants with no significant smoking history and normal spirometry. Subjects were excluded if they had other medical conditions that could contribute to dyspnea or exercise limitation, or if they had any contraindication to exercise testing.

Study Design

This randomized, controlled, cross-sectional study (ClinicalTrials.gov identifier: NCT00975403) received ethical approval from the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (DMED-1243-09). After written informed consent, subjects completed 3 visits scheduled 2-10 days apart at the same time of day. Visit 1 included medical screening, anthropometric measurements, symptom and activity assessments, pre- and post-bronchodilator (400μg salbutamol) pulmonary function tests and a symptom-limited incremental cycle exercise test for familiarization purposes. At visits 2 and 3, pulmonary function tests were followed by an incremental exercise test performed under either control (CTRL) or added DS conditions, in randomized order. COPD subjects withdrew short- and long-acting bronchodilators for 6 and 24 hours prior to visits, respectively.

Subject Characterization

Chronic activity-related dyspnea was assessed with the Baseline Dyspnea Index (26). The Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire estimated weekly caloric expenditure (27). Computed tomography (CT) scans of the chest were assessed quantitatively for extent of emphysema by density mask analysis (28). Detailed pulmonary function tests were performed using automated equipment (Vmax229d, Vs62j and Masterscreen

IOS; SensorMedics, Yorba Linda, CA)(29-34); measurements were expressed as percentages of predicted normal values (35-40).

Cardiopulmonary Exercise Testing

Symptom-limited incremental exercise tests were performed on an electronically-braked cycle ergometer (Ergometrics 800S; SensorMedics) using a cardiopulmonary exercise testing system (Vmax229d; SensorMedics) as previously described (15,41). Tests consisted of a steady-state resting period, a 1-min warm-up of unloaded pedaling, followed by 2-min increments of 20 W each. Breath-by-breath measurements were evaluated as 30 s averages at rest, at each work rate and at peak exercise (the last 30s of loaded pedaling). Operating lung volumes were derived from inspiratory capacity (IC) measurements at rest, each stage of exercise and peak exercise (42). Subjects rated their intensity of breathing and leg discomfort at rest, each stage of exercise and peak exercise with the modified 10-point Borg scale (43); zero represented "no discomfort" and 10 represented "the most severe discomfort they could imagine experiencing." At end-exercise, subjects verbalized their main reason(s) for stopping exercise.

Dead Space

An added dead space (35-mm plastic tubing) with a volume of 600 mL was inserted between the mouthpiece and a two-way non-rebreathing Hans Rudolph valve. The low resistance breathing circuit was similar to that used in a previous study (22). Although the DS arrangement was not concealed, subjects were naïve to the purpose of the DS and gave no indication of being aware of the added DS throughout the experiment. VO_2 and carbon dioxide output (VCO_2) measurements were not available under DS conditions since the testing system could not accurately correct for the large dead space volume used in this study.

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Statistical Analysis

A sample size of 20 per group provided 80% power to detect a 1 Borg unit difference between groups in dyspnea intensity at a standardized work rate during incremental cycle exercise, based on a SD of 1 unit, α=0.05 and a 2-tailed test of significance; this also provided at least 80% power for within-group comparisons. Between-group comparisons of subject characteristics were performed using unpaired t-tests. A repeated measures analysis of variance (ANOVA) was performed to evaluate differences between testing conditions (CTRL and DS) for measurements at rest, at standardized work rates and at peak exercise; the group by condition interaction term in this analysis was used to test if DS-CTRL changes were different between the two groups. Paired t-tests were applied to evaluate the DS-induced changes within groups, in particular for those variables with a significant group by condition interaction in the repeated measures ANOVA. Reasons for stopping exercise were compared using Fisher's exact test. Results are reported as means ± SD unless otherwise specified. A $p<0.05$ was used for statistical significance.

RESULTS

Subjects

Subject characteristics are summarized in Table 1. Groups were well matched for age, sex, height and body mass index. COPD subjects were more symptomatic, had reduced physical activity levels and exercise capacity, and had significant pulmonary function abnormalities compared with healthy controls. Chest CT scans in 18 of the 20 COPD subjects revealed 14±8% of the lung as low attenuation areas (LAA) using a threshold of -950 Hounsfield units (HU), or 30±10% using a threshold of -910 HU.

More details about subjects can be found in the ***online data supplement***.

Baseline abnormalities in exercise performance in mild COPD were evaluated during the CTRL test. Measurements at peak exercise are shown in Table 2. Compared to healthy controls, subjects with COPD showed: reduced peak work rate and VO_2, reduced peak V_E and V_T, greater ventilatory demands (V_E-work rate slopes) and ventilatory inefficiency (V_E/VCO_2), earlier anaerobic threshold, elevated EELV and EILV (in conjunction with reduced IC and inspiratory reserve volume (IRV)) at rest and throughout exercise, and increased exertional dyspnea intensity (***online data supplement***). Although the distribution of reasons for stopping exercise was not significantly different across groups, 50% of COPD subjects stopped because of breathing discomfort, either alone or in combination with leg discomfort, while leg discomfort was the dominant reason for stopping in 65% of healthy subjects.

Physiological Effects of Added Dead Space on Exercise

Sequence order was balanced with 10 COPD subjects and 13 healthy subjects undergoing CTRL testing first. There were no significant sequence effects for any of the main endpoints.

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Measurements at peak exercise are summarized in Table 2. With DS compared with CTRL, exercise duration decreased significantly by 0.8±0.7 and 1.0±0.8 min, and the attained peak work rate decreased by 9±10 and 10±12 W, in the healthy and the COPD groups, respectively (all $p<0.0005$). These differences corresponded to a decrease in total cumulative work of 10±8% in the healthy group and 21±14% in the COPD group. By repeated measures ANOVA, there were no between-group differences in the physiological responses to DS at peak exercise.

The magnitude of increase in V_E with added DS was not different between groups at rest or at a given work rate: V_E increased by 7.6 and 7.4 L/min at rest in the healthy and COPD groups, respectively; and by 9.7-11.3 L/min at work rates up to 60W (Figure 1). Mean peak V_E did not increase significantly in either group, however, inter-subject variability in the peak V_E response was large in both groups as indicated by the wide SD (Table 2). Compared with CTRL, breathing with added DS resulted in similar increases in end-tidal carbon dioxide tension ($P_{ET}CO_2$) in both groups at rest and throughout exercise (Figure 1). When the ventilatory response to added DS was examined at progressive work rates (44), $V_E/P_{ET}CO_2$ slopes were found to be similar within- and between-groups at the 20, 40 and 60 W loads (Figure 2). The slope of this response at peak exercise was significantly reduced compared with lower work rates within both groups (20-60W in COPD, 20-100W in health; $p<0.05$) and was not statistically different between groups despite the higher peak V_E and work rate in the healthy group compared with the COPD group.

The DS-induced increase in V_E was accomplished by increasing V_T with no significant change in breathing frequency (F_b) (Figure 3). In both health and COPD, the increase in V_T was achieved by increasing EILV and encroaching further on the IRV without changing EELV or IC (Figure 3). In the healthy group, the mean increase in V_T was 0.43 L at rest, 0.56-0.60 L at

standardized work rates during exercise, and 0.20 L at peak exercise. In COPD, the mean increase in V_T at rest was similar at 0.41 L, but the increase in V_T during exercise was significantly less than that in the healthy group at 20, 40 and 60 W ($p<0.01$) and tapered off progressively with increasing work rate. The smaller V_T response in the COPD group was associated with a smaller IRV throughout exercise: at end-exercise, IRV reached a similarly reduced level in both COPD and health but at a significantly lower peak V_E in the former. During exercise with added DS compared with CTRL, there were no consistent changes in breath timing, while inspiratory and expiratory flows increased in direct proportion to increases in V_E in both groups.

DS had no significant effect on oxygen saturation (SpO_2) at rest or at submaximal work rates in either group, however, both groups decreased SpO_2 at peak exercise by 1±2% ($p=0.05$). In health, breathing with added DS had no significant effect on heart rate at rest or at peak exercise, but heart rate increased by approximately 3 beats/min at standardized work rates during exercise (only reaching statistical significance at 20W). Similarly in COPD, added DS did not affect resting or peak heart rate and increased heart rate at submaximal work rates by between 3.8 and 5.2 beats/min ($p<0.05$).

Sensory Consequences of Added Dead Space during Exercise

In the healthy group, the main reasons for stopping exercise were not significantly different between the CTRL and DS conditions. In the COPD group, the proportion of subjects who chose breathing discomfort as the primary reason for stopping exercise increased from 5% in the CTRL test to 40% in the DS test ($p<0.05$); this was accompanied by a decrease in the proportion of subjects who chose leg discomfort as the main reasons for stopping exercise ($p=0.06$).

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There was a significant between-group difference in the magnitude of the dyspnea response to DS at 40W, 60W and peak exercise ($p<0.05$). In COPD, added DS did not change dyspnea intensity at rest or at 20W, but significantly ($p<0.05$) increased dyspnea ratings at 40W, 60W and at peak exercise compared with CTRL (Figure 4). In contrast, DS in health had no significant effect on dyspnea intensity ratings at these lower work rates (20-60W) or at peak exercise, but resulted in a small increase in dyspnea intensity at intermediate work rates. Dyspnea/V_E plots did not change significantly in response to DS in either group (Figure 4).

DISCUSSION

The main findings of this study were as follows: *1)* we confirmed that patients with mild COPD had greater respiratory impairment, lower peak V_E, and greater dyspnea and exercise intolerance than age-matched healthy controls; *2)* on average, selective stress on the respiratory system by adding DS was associated with small decreases in peak work rate and exercise duration with no significant increase in peak V_E in both health and COPD; *3)* critical mechanical constraints on V_T expansion were present at a relatively lower peak work in COPD in contrast to health, such that V_T increases during DS loading were significantly less in COPD, and; *4)* added DS was associated with greater increases in dyspnea intensity ratings at lower work rates in COPD compared with health.

Our patients met GOLD stage I spirometric criteria for COPD and reported greater chronic dyspnea and reduced daily activity levels compared with age- and sex-matched healthy controls. Thirteen subjects had a previous diagnosis of COPD and 60% of the sample was already receiving regular medications for perceived breathing difficulty. Despite the largely preserved FEV_1, there was evidence of significant peripheral airway obstruction and CT scans confirmed minor structural emphysema in the majority.

CPET Responses in Mild COPD

Consistent with the results of recent studies, COPD patients reported severe dyspnea and leg discomfort at a lower peak work rate than in health. Ventilatory requirements were increased, EELV and EILV were consistently elevated, and peak V_T and V_E were significantly diminished. The cause of the increased ventilatory demand remains uncertain: V_E/VCO_2 was slightly but consistently elevated compared with health at standardized work rates, suggesting reduced efficiency of CO_2 elimination due to higher physiological dead space or alterations in the central

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respiratory controller. Gagnon et al recently showed that during cycle exercise in patients with advanced COPD, spinal anesthesia with an intrathecal infusion of fentanyl was associated with a reduction in V_E/VCO_2, presumably by interrupting afferent inputs from Type III and IV receptors in the active locomotor muscles (45). The extent to which this mechanism contributed to the higher V_E/VCO_2 in our mild COPD patients could not be determined. Compared with the healthy group, our COPD subjects had significantly lower anaerobic thresholds, and greater heart rates and perceived leg discomfort at submaximal work rates. Collectively, these results suggest that the less active COPD patients were more likely to be deconditioned. However, formal assessment of cardiac function and systemic oxygen delivery is required to determine if associated acid/base disturbances stimulated ventilation in this group.

The question arises whether the combination of increased ventilatory demand and dynamic mechanical abnormalities outlined above resulted in actual ventilatory limitation to exercise in our patients? A peak V_E of 69 % of maximum voluntary ventilation (MVV) suggests a normal breathing reserve but is not a measure of ventilatory limitation *per se* (46). The finding that the V_T/IC ratio reached 68% and that EILV reached 90% predicted TLC at a peak V_E of only 56 L/min (in the presence of adequate cardiac reserve) suggests that mechanical factors or the associated severe respiratory discomfort could have limited (or opposed) further increases in V_E to support a higher peak work rate.

Effect of DS Loading

Most studies that have examined the effects of DS loading were conducted in young, untrained, healthy individuals and have concluded that ventilatory limitation does not normally contribute to exercise limitation: peak V_E (and V_T) increased and peak work rate was similar to unloaded control (20-22). In contrast, ventilatory constraints are more likely to contribute to exercise

limitation in athletic young or older individuals who are able to achieve high peak work rates (44,47,48). In our healthy older participants at end-exercise, peak VO_2 and power output was normal or greater than normal, cardiovascular limits were reached or approached (peak HR was 90% predicted, on average), and estimated breathing reserve averaged 27% (V_E/MVV was 73%). Important respiratory mechanical constraints at peak exercise in these subjects included an inability to decrease EELV and an EILV reaching 87% of TLC. Consistent with the results of a previous study in older healthy individuals (49), average peak V_E was not significantly increased by added DS despite increases in V_T and EILV, and mean peak power output was modestly but significantly reduced. It is noteworthy that healthy individuals did not develop a compensatory tachypnea to maintain peak V_E under DS loading for reasons that are not clear. Collectively, our results provide evidence that in healthy older individuals, both the cardiac and respiratory systems had reached or approached their physiological limits at end-exercise under control conditions.

The effect of DS loading in mild COPD was in the same direction as in health: average peak V_E did not increase significantly and peak power output decreased significantly. However, ventilatory limitation occurred at a substantially lower power output and V_E in this group. At the highest equivalent work rate completed by both groups (when peak V_E was 56 L/min in COPD), the increases in V_T during DS loading were smaller in COPD and were significantly decreased compared with health (Figure 3). These results confirm that the respiratory system reached or approached its physiological limit in COPD under unloaded conditions at a lower peak work rate and in the presence of adequate cardiac reserve.

When the ventilatory response to added DS was examined in the manner proposed by McClaren et al (44), $V_E/P_{ET}CO_2$ slopes were found to be similar within- and between-groups at comparable submaximal work rates (Figure 2). However, $V_E/P_{ET}CO_2$ slopes were significantly

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reduced at peak exercise in both groups and were not different between groups despite the lower peak V_E and work rate in the COPD group. These results indicate that the respiratory system and its central controller adequately fulfilled its primary task of CO_2 elimination during exercise in mild COPD, albeit at the expense of greater mechanical constraints and dyspnea at relatively lower V_E in the COPD group.

Sensory Effects of DS Loading during Exercise

Dyspnea intensity ratings were greater at any given work rate and V_E in mild COPD than in health, likely as a result of the combination of heightened ventilatory requirements and the presence of greater respiratory mechanical abnormalities, both of which are associated with increased contractile respiratory muscle effort (50). Of interest, DS loading was associated with consistently higher dyspnea ratings at standardized work rates during exercise in the COPD group and this symptom became more likely to be selected as the dominant exercise-limiting symptom by this group. The greater increase in dyspnea at lower submaximal work rates in COPD than in health with added DS, is explained by the steeper dyspnea/V_E relation in the former. This steeper slope, in turn, reflects the greater mechanical derangements that exist in mild COPD.

In both groups, participants stop exercising when V_T expanded to reach a critically reduced IRV of ~10% TLC during both control and DS conditions. However, with the increased chemical stimulation, this mechanical limit was reached at a lower work rate, particularly in COPD where it was linked to an earlier rise in dyspnea to severe levels. These data support our previous contention that critical limits of V_T expansion at the minimal IRV are more important in determining the rise of dyspnea during exercise than increases in EELV (decreases in IC) *per se* (51).

A number of experimental studies in health have shown that perceived dyspnea (or "air hunger") rises sharply if the normal V_T response is restricted, either voluntarily or by external imposition, in the setting of an increased ventilatory drive to breathe (22,52,53). For example, when the normal V_T increase was restricted by chest wall strapping during exercise in healthy participants, imposition of the DS resulted in earlier exercise termination, compared with the unrestricted condition, due to a steeper rise in dyspnea to intolerable levels (22). We believe that similar mechanisms are at play in our mild COPD patients at higher exercise levels. Thus, the widening disparity between increased central neural drive (sensed by increased central corollary discharge), likely amplified by metabolic acidosis and the limited volume displacement of the respiratory system (sensed by multiple mechanoreceptors), may also form the basis for the increased respiratory discomfort during DS loading in COPD (50).

Limitations

Groups could not be matched for fitness levels at study entry and our healthy controls were generally more active than COPD patients. Thus, we cannot exclude the possibility that deconditioning could have contributed to ventilatory limitation in some COPD volunteers. We used a standardized DS of 0.6 L in all participants knowing that individual ventilatory responses will vary with lung size. However, average V_E increased during submaximal exercise to a similar extent in both groups, indicating a comparable physiological stress with DS loading. Moreover, the main outcome of interest was within-subject effects of DS loading on physiological and sensory parameters in groups that were carefully matched for age and sex. Participants were not blinded to the DS intervention but were naïve to the specific purpose of the experiments. Breathing pattern responses during DS were remarkably consistent throughout exercise in all participants, making the possibility of non-physiological alterations in breathing pattern due to

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awareness of additional tubing in the circuit less likely. The lack of measurements of VCO_2 and arterial PCO_2 during the dead space condition meant that we were unable to assess ventilatory efficiency.

Conclusions and Implications

While older healthy individuals reached a peak VO_2 that was at or above the predicted level, evidence of both ventilatory and cardiac limitation was present at the limits of tolerance. By contrast, at a significantly lower peak power output and V_E in the COPD group, the respiratory system had reached or approached its physiological limit, in the setting of adequate cardiac reserve. Although responses to DS loading were qualitatively similar in both groups, critical mechanical constraints or limitation and greater breathing discomfort occurred at a much lower V_E in the COPD group.

We propose that the troublesome chronic dyspnea and reduced daily activity levels reported by our mild COPD group is related, in part, to the abnormal respiratory mechanics and higher ventilatory demand associated with physical work in this group. Thus, the largely preserved FEV_1 and normal breathing reserve (MVV-peak V_E) as conventionally derived, underestimated significant dynamic mechanical constraints to increasing ventilation during exercise. Our results set the stage for further studies designed to evaluate the impact of combined interventions that improve respiratory mechanics (e.g., bronchodilators) and reduce ventilatory demand (e.g., exercise training) in patients with mild COPD who report persistent activity-related dyspnea.

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TABLE 1. SUBJECT CHARACTERISTICS

	Healthy	Mild COPD
Male : Female, n	11 : 9	11 : 9
Age, yr	65 ± 8	68 ± 6
Height, cm	167 ± 9	166 ± 9
Body mass index, kg/m^2	26.9 ± 2.8	27.4 ± 6.3
Smoking history, pack-years	0.2 ± 0.7	42.6 ± 21.6*
BDI focal score (0-12)	11.4 ± 0.9	8.7 ± 2.0*
CHAMPS, kcal/wk for all activities	5966 ± 2975	2535 ± 2392*
Peak work rate, W (% predicted)	162 ± 55 (121 ± 32)	92 ± 26* (75 ± 22*)
Peak VO_2, L/min (% predicted)	2.45 ± 0.84 (142 ± 33)	1.58 ± 0.45* (100 ± 20*)
VO_2 at AT, L/min	1.29 ± 0.51	0.94 ± 0.21*
Post-bronchodilator FEV_1, L	3.12 ± 0.67 (122 ± 11)	2.26 ± 0.50* (95 ± 11*)
Post-bronchodilator FEV_1/FVC, %	77 ± 5	61 ± 5*
Pre-bronchodilator Pulmonary Function (% predicted):		
FEV_1, L	2.96 ± 0.72 (117 ± 13)	2.08 ± 0.45* (87 ± 11*)
FEV_1/FVC, %	74 ± 6	59 ± 5*
PEFR, L/s	8.61 ± 2.58 (125 ± 24)	6.37 ± 1.69* (96 ± 18*)
$FEF_{25-75\%}$, L/s	2.35 ± 1.04 (89 ± 13)	0.82 ± 0.29* (33 ± 10*)
IC, L	3.01± 0.82 (111 ± 18)	2.59 ± 0.62 (99 ± 18*)
SVC, L	4.17 ± 0.92 (116 ± 12)	3.70 ± 0.71 (108 ± 14)
FRC, L	2.92 ± 0.63 (93 ± 23)	3.48 ±0.76* (112 ± 20*)
RV, L	1.76 ± 0.44 (83 ± 21)	2.38 ± 0.67* (108 ± 29*)
TLC, L	5.93 ± 0.97 (102 ± 13)	6.07 ± 1.11 (106 ± 12)
sRaw, cmH_2O•s	5.4 ± 2.2 (129 ± 57)	10.3 ± 5.1* (243 ± 107*)
D_LCO, mL/min/mmHg	21.5 ± 5.5 (104 ± 17)	16.2 ± 4.2* (82 ± 16*)
MIP, cmH_2O	90 ± 26 (115 ± 24)	76 ± 27 (98 ± 33)
MVV, L/min	127.9 ± 30.7	83.2 ± 24.9*
Closing volume, L	0.57 ± 0.71	0.55 ± 0.34
N_2 slope, %/L	2.8 ± 1.1 (197 ± 71)	5.9 ± 2.2* (406 ± 210*)
R5, $cmH_2O/L/s$	4.1 ± 1.2	5.1 ± 1.8†
R5-20, $cmH_2O/L/s$	12.4 ± 7.2	25.3 ± 10.1*
X5, $cmH_2O/L/s$	-1.1 ± 0.5	-1.8 ± 1.2*
*F*res, Hz	11.4 ± 3.2	16.9 ± 4.5*

Values are means ± SD. Percentage of predicted normal values are in parentheses.
* $p<0.05$, † $p=0.05$ COPD versus healthy group.

Abbreviations: BDI = modified Baseline Dyspnea Index; CHAMPS = Community Healthy Activities Model Program for Seniors questionnaire; AT = anaerobic threshold; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; TLC = total lung capacity; FRC = functional residual capacity; RV = residual volume; IC = inspiratory capacity; PEFR = peak expiratory flow rate; $FEF_{25–75\%}$ = force expiratory flow between 25 and 75% of FVC; $FEF_{50\%}$ = forced expired flow at 50% of vital capacity; MVV = maximal voluntary ventilation; DL_{CO} = diffusing capacity of the lung for carbon monoxide; sRaw = specific airway resistance; MIP = maximal inspiratory pressure; R5 = resistance at 5 Hz; R5-20 = difference in resistance between 5 Hz and 20 Hz; X5 = distal capacitive reactance at 5 Hz ; *F*res = resonant frequency during impulse oscillometry.

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TABLE 2. MEASUREMENTS AT PEAK INCREMENTAL CYCLE EXERCISE DURING CONTROL (CTRL) AND ADDED DEAD SPACE (DS) CONDITIONS

	Healthy		COPD	
	CTRL	**DS**	**CTRL**	**DS**
Exercise duration, min	15.9 ± 5.7	15.2 ± 5.7*	8.7 ± 2.6†	7.6 ± 2.7*
Work rate, W	162 ± 58	158 ± 57*	92 ± 26†	83 ± 28*
Dyspnea, Borg scale	6.1 ± 3.2	5.9 ± 3.3	5.3 ± 2.1	6.0 ± 2.4*‡
Leg discomfort, Borg scale	6.8 ± 3.2	6.4 ± 3.2	6.1 ± 2.1	5.8 ± 2.3
Reason for stopping exercise, %:				
Dyspnea	10	25	5	40*
Leg discomfort	65	50	40	10
Dyspnea + legs	20	25	45	45
Other	5	0	10	5
$V_{E,}$ L/min (% MVV)	95.0 ± 30.9 (73 ± 3)	95.8 ± 29.7 (74 ± 10)	55.6 ± 16.0 (69 ± 17)	58.6 ± 16.1 (73 ± 19)
Heart rate, beats/min (%predicted max)	157 ± 15 (90 ± 20)	157 ± 13 (90 ± 16)	136 ± 19† (82 ± 11†)	133 ± 20 (81 ± 12)
$P_{ET}CO_2$, mm Hg	32.2 ± 4.8	40.5 ± 6.3*	33.6 ± 4.5	41.3 ± 5.2*
$SpO_{2,}$ %	94.5 ± 2.9	93.5 ± 3.4	94.5 ± 2.1	93.6 ± 2.6
F_b, breaths/min	42 ± 9	39 ± 7*	35 ± 9	35 ± 7
V_T, L	2.26 ± 0.65	2.47 ± 0.76*	1.62 ± 0.41	1.73 ± 0.51*
V_T/IC, %	76 ± 11	83 ± 8*	68 ± 11	72 ± 13
IC, L	3.02 ± 0.85	2.96 ± 0.79	2.42 ± 0.50	2.42 ± 0.56
ΔIC peak-rest, L	0.10 ± 0.51	0.18 ± 0.52	-0.30 ± 0.43†	-0.21 ± 0.35
IRV, L	0.76 ± 0.42	0.50 ± 0.24*	0.78 ± 0.32	0.69 ± 0.39
EILV, L (% predicted TLC)	5.12 ± 0.89 (88 ± 6)	5.35 ± 0.93* (92 ± 4*)	5.16 ± 0.84 (90 ± 7)	5.26 ± 0.90 (91 ± 8)
EELV, L (% predicted TLC)	2.85 ± 0.59 (50± 12)	2.88 ± 0.55 (50 ± 12)	3.54 ± 0.64† (62 ± 8)†	3.53 ± 0.63 (62 ± 8)
T_I, sec	0.72 ± 0.14	0.75 ± 0.14	0.84 ± 0.20	0.83 ± 0.17
T_E, sec	0.77 ± 0.17	0.82 ± 0.17	0.98 ± 0.22	0.98 ± 0.23
T_I/T_{TOT}	0.49 ± 0.02	0.48 ± 0.03	0.46 ± 0.04	0.46 ± 0.05
V_T/T_I, L/sec	3.23 ± 1.04	3.31 ± 0.99	2.00 ± 0.54	2.12 ± 0.54
V_T/T_E, L/sec	3.07 ± 1.01	3.09 ± 1.02	1.70 ± 0.48	1.82 ± 0.54

Values are means ± SD.
*p<0.05 DS vs. CTRL within-group; †p<0.05 COPD vs. Healthy for CTRL test.
‡ p<0.05 between-group difference in DS-CTRL change by repeated measures ANOVA.
Abbreviations: V_E = minute ventilation; MVV = maximal voluntary ventilation; PETCO2; SpO2; F_b = breathing frequency; V_T = tidal volume; IC = inspiratory capacity; IRV = inspiratory reserve volume; EILV = end-inspiratory lung volume; TLC = total lung capacity; EELV = end-expiratory lung volume; T_I = inspiratory duration; T_E = expiratory duration; T_I/T_{TOT} = inspiratory duty cycle; V_T/T_I = mean inspiratory flow rate; V_T/T_E = mean expiratory flow rate.

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FIGURE LEGENDS

Figure 1. Minute ventilation and end-tidal carbon dioxide tension ($P_{ET}CO_2$) are shown relative to work rate during incremental cycle exercise in the mild COPD and healthy control groups during unloaded control (CTRL) and added dead space (DS) loading. Values are means ± SEM. *p<0.05 DS vs. CTRL at a given work rate or at end-exercise.

Figure 2. Relationships between minute ventilation and $P_{ET}CO_2$ are shown in the mild COPD and healthy during exercise under unloaded control (CTRL) and added dead space (DS) conditions. Dashed lines represent the ventilatory response to added DS at progressive work rates and at the peak of incremental exercise. Response slopes at equivalent work rates and at peak exercise are similar between groups; peak response slopes were significantly (p<0.05) lower than slopes at the earlier work rates within each group.

Figure 3. Tidal volume, breathing frequency (F_b), inspiratory reserve volume (IRV), and inspiratory capacity (IC) are shown relative to work rate during incremental cycle exercise in the mild COPD and healthy control groups during unloaded control (CTRL) and added dead space (DS) loading. The shaded area represents the minimal IRV reached in all tests. Values are means ± SEM. *p<0.05 DS vs. CTRL at a given work rate or at end-exercise.

Figure 4. Dyspnea intensity is shown relative to either work rate or minute ventilation during incremental cycle exercise in the mild COPD and healthy control groups during unloaded control (CTRL) and added dead space (DS) loading. At a standardized work rate of 60W, the mean DS-induced increase in dyspnea intensity was 1.8 Borg units in mild COPD compared with only 0.2 Borg units in health (p<0.05); this difference occurred despite a comparable increase in

ventilation in both groups. Values are means ± SEM. *p<0.05 DS vs. CTRL at a given work rate or at end-exercise.

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Fig 1

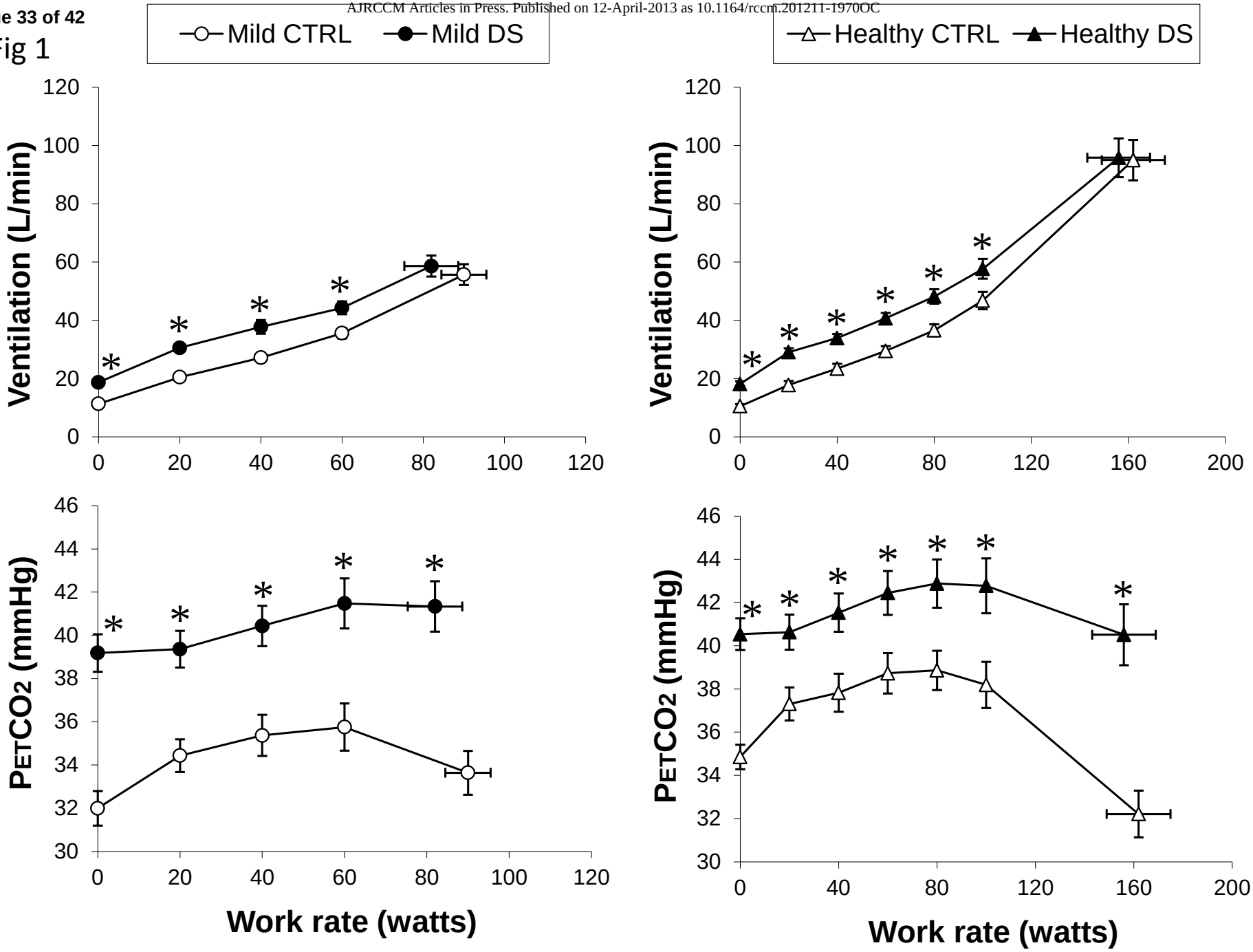

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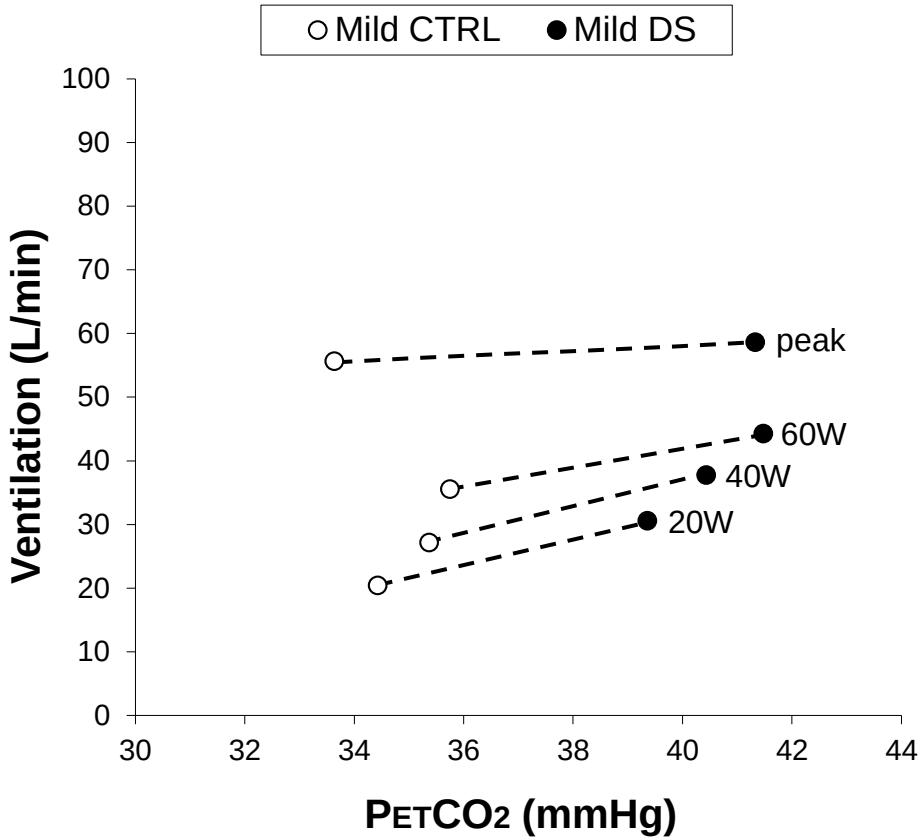
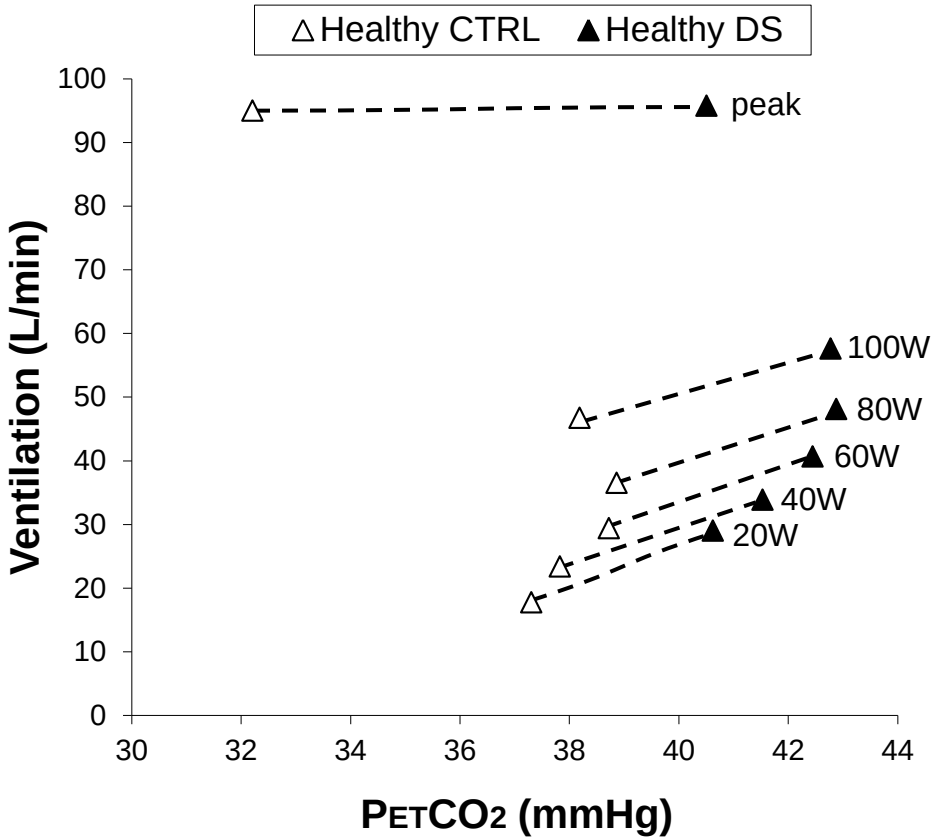
Fig 2





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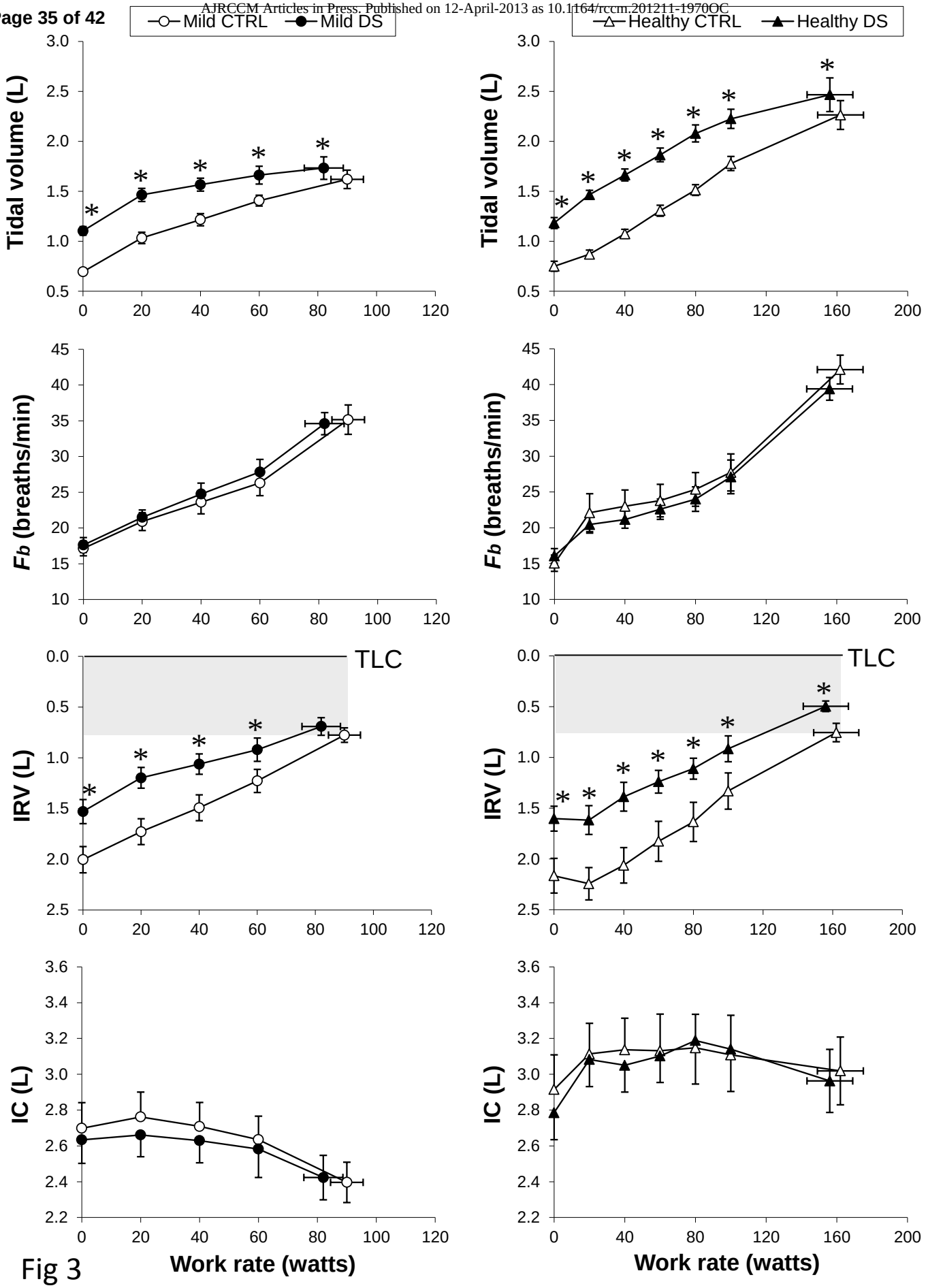

Fig 3

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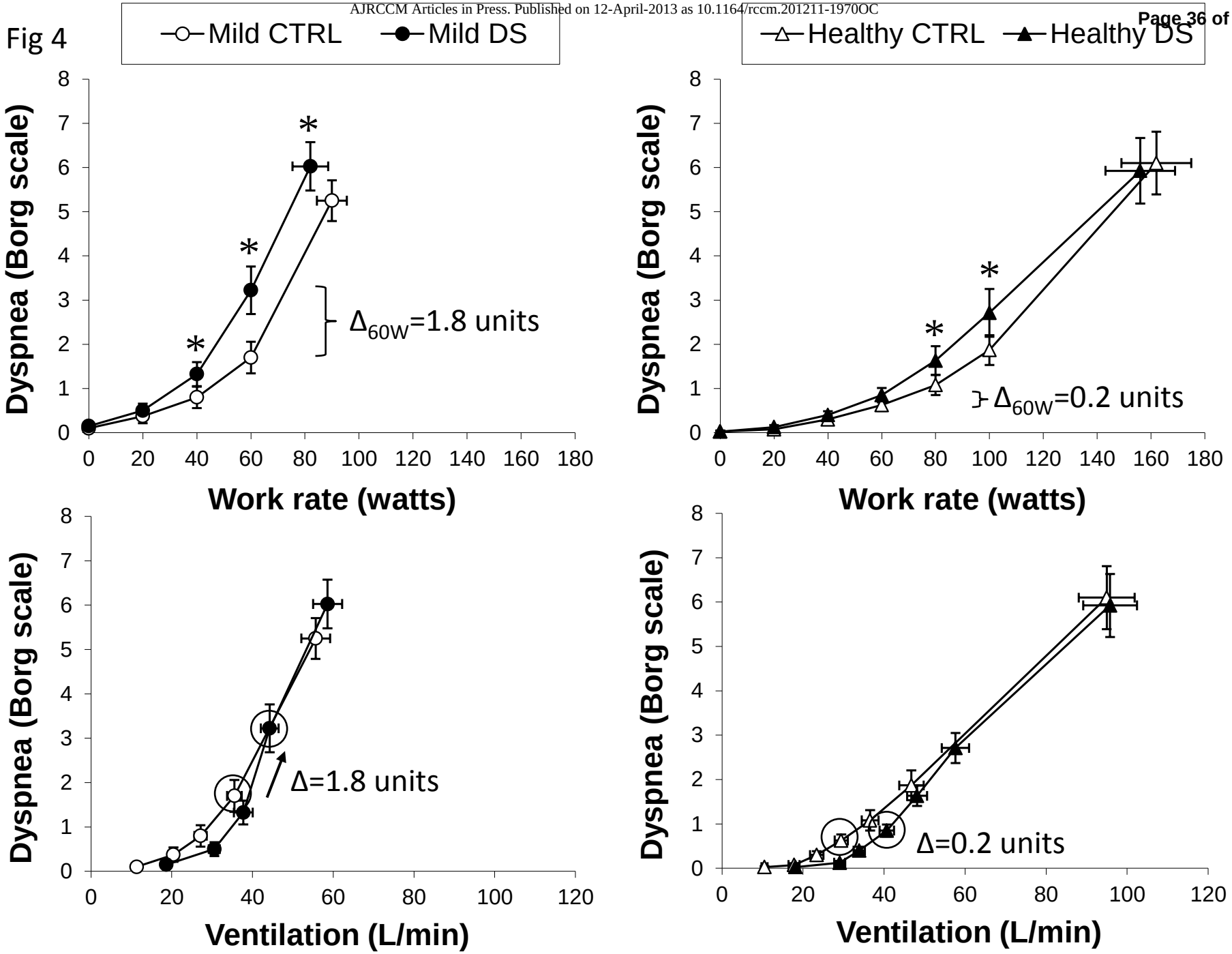
Fig 4



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Do Respiratory Mechanical Factors Limit Exercise in Mild COPD?

Roberto Chin, Jordan Guenette, Sicheng Cheng, Natya Raghavan, Naparat Amornputtisathaporn, Arturo Cortés-Télles, Katherine Webb, Denis O'Donnell

ONLINE DATA SUPPLEMENT

RESULTS

Subjects

Subjects with COPD had a significant smoking history (range, 10–108 pack-years): 15 were ex-smokers and 5 remained current smokers. In the healthy group, there were no current smokers and only 2 subjects had a prior smoking history of only 2 and 2.5 pack-years and had stopped smoking for ≥20 years. Thirteen of the 20 COPD subjects had a previous diagnosis of COPD; 9 out of the 13 had the diagnosis within the previous 5 years. Ten subjects with COPD used a respiratory medication on a regular basis (n=4 short-acting β_2-agonist, n=2 short-acting anticholinergic, n=7 long-acting anticholinergic, n=6 inhaled corticosteroid/long-acting β_2-agonist combination, n=2 inhaled corticosteroid only) and 2 subjects used a short-acting β_2-agonist bronchodilator as needed only. Comorbidities in the COPD group included well-controlled: hypertension (n=12), type 2 diabetes mellitus (n=5), hypercholesterolemia (n=3), osteoarthritis (n=2), and sleep apnea (n=1). Comorbidities in the healthy group included well-controlled: hypertension (n=4), osteoarthritis (n=4), hypercholesterolemia (n=1) and diabetes mellitus (n=1). The presence of osteoarthritis did not affect the ability to perform cycle exercise in any subject.

Pulmonary Function

Pulmonary function test results are reported in Table 1 of the manuscript. Subjects with COPD had significant expiratory airflow limitation that satisfied the GOLD stage I criteria for COPD;

the majority (17 out of 20) subjects also had a post-bronchodilator FEV_1/FVC ratio less than their predicted lower-limit of normal (LLN) while the remaining 3 subjects were all <1.5% above their LLN (NHANES III reference values). All healthy subjects had a post-bronchodilator FEV_1/FVC ratio greater than 0.7 and greater than their predicted LLN. Although the COPD group had significantly greater static lung volumes (FRC and RV) than the healthy group, only 6 subjects with COPD had FRC values greater than 120% predicted. Compared to health, the COPD group had significant reductions in D_LCO and maximal voluntary ventilation (MVV), and a significantly increased specific airway resistance. Closing volume was normal in both groups but N_2 slope was significantly increased in COPD compared with healthy subjects. In the COPD compared with healthy group, measurements obtained by impulse oscillometry showed significant increases in R5 and X5, frequency dependence of resistance (R5-20), and resonant frequency; all markers of distal airway obstruction.

Symptom-limited Incremental Cycle Exercise

Selected ventilatory and metabolic responses to incremental cycle exercise testing are shown in Figure E1. Compared to health, the COPD group had significantly reduced peak work rate and VO_2. At peak exercise, the COPD group also had a significantly lower minute ventilation (V_E) compared to the healthy group (56 vs. 95 L/min, $p<0.0005$); however, the ventilatory reserve at peak exercise was not significantly different between COPD and health (69 vs. 73 %MVV, respectively). V_E was higher at a given work rate in the COPD group compared with health, reaching statistical significance at 60 watts where the mean difference between groups was 6.2±0.7 L/min ($p<0.05$). At rest and at submaximal work rates during exercise, the ventilatory equivalent for CO_2 was greater and the end-tidal CO_2 ($P_{ET}CO_2$) was lower in the COPD group

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compared with the healthy group; however, both measurements were similar across groups at peak exercise.

In COPD compared to health, IC was similar at rest and early in exercise but became significantly smaller at 60W and at peak exercise (Figure E1). The magnitude of change in IC from rest to peak exercise was -0.30±0.43 L in the COPD group and +0.09±0.52 L in the healthy group ($p<0.05$): 85% of the COPD group and only 45% of the healthy group hyperinflated at the peak of exercise. Inspiratory reserve volume (IRV) was also reduced during submaximal exercise work rates in the COPD group compared with the healthy group, indicating that they were breathing closer to their total lung capacity. However, the COPD group reached a similarly reduced IRV at end-exercise (at a significantly lower peak work rate and V_E) than the healthy group. The peak tidal volume (V_T) response to exercise was curtailed in COPD compared with health and was accompanied by a relatively more rapid breathing pattern (Figure E1).

Although the distribution of reasons for stopping exercise was not significantly different across groups, 50% of COPD subjects stopped because of breathing discomfort, either alone or in combination with leg discomfort, while leg discomfort was the dominant reason for stopping in the healthy group. Intensity ratings of dyspnea and leg discomfort were not different between groups at peak exercise (Figure E2). Dyspnea intensity at a given work rate during exercise was greater in COPD than in health, reaching statistical significance ($p<0.01$) at 60 watts. Mean dyspnea-V_E plots showed a steeper rise in intensity ratings relationship as V_E increased during exercise in COPD compared with health (Figure E2). Leg discomfort was significantly ($p<0.05$) greater in the COPD group throughout exercise (Figure E2).

FIGURE LEGENDS

Figure E1. Responses to incremental cycle exercise in mild COPD and in age- and sex-matched healthy normal subjects. The shaded area represents the minimal inspiratory reserve volume IRV). *p<0.05 COPD versus healthy group at standardized work rates or at peak exercise. *Abbreviations*: V_E, minute ventilation; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide; IC, inspiratory capacity; SpO_2, oxygen saturation; *F*b, breathing frequency; VCO_2, carbon dioxide production; VO_2, oxygen consumption.

Figure E2. Symptom responses to incremental cycle exercise in mild COPD and in age- and sex-matched healthy normal subjects. *p<0.05 COPD versus healthy group at standardized work rate.

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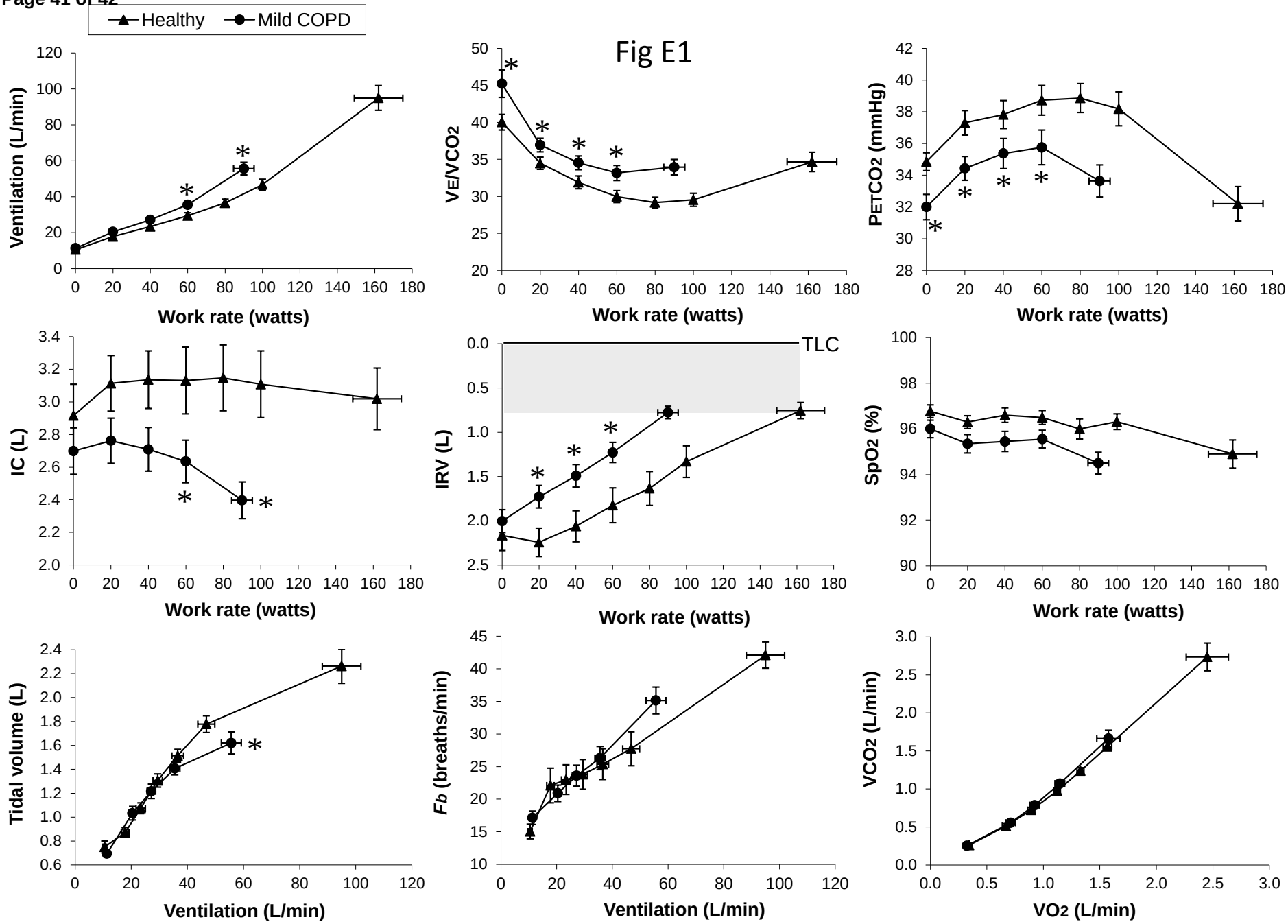
Fig E1



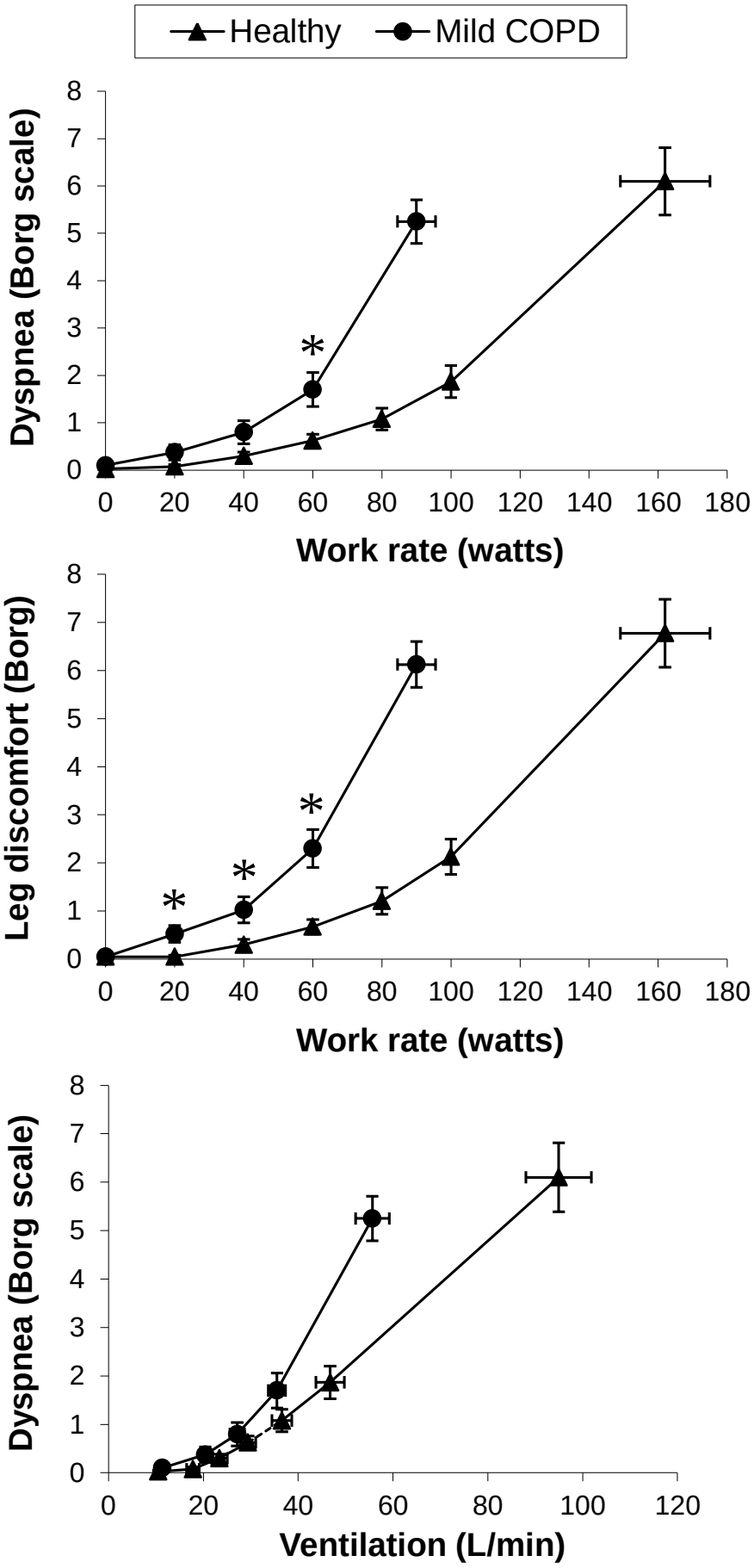

Healthy
Mild COPD
Dyspnea (Borg scale)
Work rate (watts)
Leg discomfort (Borg)
Work rate (watts)
Dyspnea (Borg scale)
Ventilation (L/min)

Fig E2