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CT and physiologic determinants of dyspnea and exercise capacity during the six-minute walk test in mild COPD

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Summary
Objectives: We aimed to explore physiological responses to the six-minute walk test (6MWT) and assess computed tomographic (CT) features of the lungs and thigh muscle in order to determine contributors to dyspnea intensity and exercise limitation in dyspneic and non-dyspneic subjects with GOLD-1 COPD and controls.
Methods: We compared Borg dyspnea ratings, ventilatory responses to 6MWT, and CT-measures of emphysema, airway lumen caliber, and cross-sectional area of the thigh muscle ($RTM_{CT\text{-}CSA}$) in 19 dyspneic, 22 non-dyspneic, and 30 control subjects.
Results: Dyspneic subjects walked less and experienced greater exertional breathlessness than non-dyspneic (105 m less and 2.4 Borg points more, respectively) and control subjects (94 m less and 2.6 Borg points more, respectively ($P < 005$ for all comparisons). At rest, dyspneic subjects had significant greater expiratory airflow obstruction, air trapping, ventilation/perfusion mismatch, burden of emphysema, narrower airway lumen, and lower $RTM_{CT\text{-}CSA}$ than comparison subjects. During walking dyspneic subjects had a decreased inspiratory capacity

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(IC) along with high ventilatory demand. Dyspneic subjects exhibited higher end-exercise tidal expiratory flow limitation and oxygen saturation drop than comparison subjects. In regression analysis, dyspnea intensity was best explained by ΔIC and forced expiratory volume in 1 s %predicted. $RTM_{CT\text{-}CSA}$ and ΔIC were independent determinants of distance walked.
Conclusions: Among subjects with *mild* COPD, those with daily-life dyspnea have worse exercise outcomes; distinct lung and thigh muscle morphologic features; and different pulmonary physiologic characteristics at rest and exercise. ΔIC was the main contributor to dyspnea intensity and ΔIC and thigh muscle wasting were determinants of exercise capacity.

Introduction

Dyspnea is a cardinal symptom of chronic obstructive pulmonary disease (COPD).[1] It predicts survival,[2] is part of a mortality index for COPD,[3] is used to select patients for therapy,[4] and was included in the new Global Initiative for Obstructive Lung Disease (GOLD) classification scheme for the disease.[1] COPD subjects with dyspnea usually experience exercise limitation and often seek medical care.[5] Low exercise capacity is associated with poorer quality of life[6] and low levels of daily physical activity are linked to increased hospitalization rate and mortality.[7] While determinants of exertional dyspnea and exercise limitation have long been recognized in COPD subjects with moderate-to-severe airway obstruction,[8–13] there is scarce data in subjects with a *milder* disease.

Ofir et al.[14] showed that symptomatic subjects with *mild* COPD during cycling had reduced exercise capacity and ventilatory abnormalities including dynamic hyperinflation (DH) and that DH was linked to exertional dyspnea. DH has also been observed during the six-minute walk test (6MWT) and associated with exertional dyspnea in moderate-to-severe COPD.[9,15] Whether DH is associated with both dyspnea and exercise performance during walking in subjects with *mild* disease has not been determined.

Computed tomography (CT) is increasingly used to assess lung emphysema and morphology of the airways and locomotor muscles. A high burden of emphysema on CT scan predicts poor exercise capacity[16] and quadriceps muscle wasting is associated with lower physical activity in daily life in subjects with a wide spectrum of COPD.[17] Whether these morphologic abnormalities of the lung and thigh muscle are related to dyspnea intensity and exercise impairment and their potential underlying mechanisms in *mild* COPD remain to be explored. Understanding function–structure relationships within the lungs can help to improve the understanding of dyspnea during exercise and thus advance patient care.

We hypothesize that compared to smoker controls and non-dyspneic subjects with mild COPD, daily-life dyspneic subjects with mild COPD during self-paced exercise: 1) develop dynamic hyperinflation and increase ventilatory demand, which lead to greater dyspnea perception and lower exercise performance and; 2) have higher burden of emphysema, narrower airways lumen and greater thigh muscle wasting on CT scans which are associated with greater dyspnea intensity and lower exercise capacity.

In order to assess these hypotheses, we evaluated metabolic, pulmonary, and cardiac responses to the 6MWT; determine contributors to exertional dyspnea and exercise limitation; and relate these outcomes and its underlying mechanisms with CT features of the lung and thigh muscles in subjects with *mild* COPD and controls. Preliminary results of this study have been presented in the form of an abstract.[18]

Methods

Details on inclusion/exclusion criteria and lung function, exercise, and CT imaging assessment as well as calculations for exercise parameters are on the Online Supplement.

Subject selection

Subjects are from a COPD longitudinal study, PELE (*Proyecto de Evaluación Longitudinal de la Enfermedad Pulmonar Obstructiva Crónica*). Briefly, the goal of the PELE study was to assess the clinical, physiological, and morphological determinants of the decline in exercise capacity in smokers with COPD. This report is a cross-sectional analysis including *all* Global Initiative for Obstructive Lung Disease (GOLD)[19] 1 COPD subjects and smoker controls ($N = 30$). COPD subjects were further divided into two groups: dyspneic (defined with a modified Medical Research Council[20] [mMRC] score ≥ 1; [D-COPD], $N = 19$) and non-dyspneic (ND-COPD, $N = 22$). The study was approved by the institutional review board of the Catholic University of Chile, University of Chile, and Brigham and Women's Hospital (protocol #2012P000302). Written informed consent was obtained from all participants.

Study design

A 3-visit baseline assessment was performed within a week. The first visit included demographic and medical history data collection with a structured questionnaire and two training 6MWTs.[21] In the second visit, pulmonary function assessment and two additional 6MWTs using portable equipment were performed. The final visit included CT imaging evaluation.

Lung function assessment

Subjects underwent spirometric testing before and after 200 μg of albuterol as well as maximal voluntary ventilation (MVV), single-breath diffusing lung capacity for carbon monoxide (DL_{CO}), and lung volumes following international guidelines.[22–24] Spirometric, $DL_{CO,}$ and lung volumes measurements were standardized as percentages of predicted values by using prediction equations.[25–27]

Six-minute walk testing

Subjects performed two additional 6MWTs with a portable telemetric system.[28–30] Oxygen consumption ($V'O_2$), carbon dioxide production ($V'CO_2$), minute ventilation ($V'E$), respiratory exchange ratio (RER; $V'CO_2/V'O_2$), end-tidal carbon dioxide partial pressure (PET_{CO_2}), heart rate (HR), arterial oxygen saturation (SpO_2), O_2 pulse ($V'O_2/HR$),[31] tidal volume (V_T), inspiratory (T_I) and expiratory time (T_E), mean tidal inspiratory (V_T/T_I) and expiratory (V_T/T_E) flow, inspiratory capacity[30] (IC), and Borg dyspnea ratings[32] were measured. ΔIC from rest was used to reflect the change in end-expiratory lung volume and therefore dynamic hyperinflation. For each subject the greatest of both distance walked was selected for subsequent analysis.

Tidal flow-volume loops

Both flow and volume were recorded during the 6MWTs with a portable system. End-exercise tidal flow-volume curves were made and situated within their respective maximal flow-volume loops. The presence and degree of expiratory flow limitation (EFL) was calculated as the percentage of tidal volume ($\%V_T$) that overlaps the maximal flow-volume envelope.[33]

CT imaging

A volumetric CT scan examination of the chest and the thigh muscle was performed. Emphysema was defined as percent of low attenuation areas less than −960 Hounsfield units (% LAA-960HU).[34] CT-based, single-slice airway measurements were collected in the right upper lobe apical bronchus (RB1) and right lower lobe posterior basal bronchus (RB10) as previously described.[16,35] The 5th airway generation luminal area (Ai) of RB1 and RB10 is reported. CT cross-sectional area (CSA) of the right thigh muscle ($RTM_{CT\text{-}CSA}$) was measured following a described method.[36]

Statistical analysis

Baseline variables were compared by ANOVA with adjustment for multiple comparisons, Kruskal–Wallis, and chi square tests according to the variable type and distribution. Group responses at time points during walking were compared via repeated ANOVA with Tukey–Kramer adjustment for multiple comparisons. The relationships of Borg ratings and distance walked to physiologic/morphologic variables were assessed via Spearman correlation. Separate regression analyses for Borg rating at min 6 and distance walked were performed. Since Borg rating was highly skewed it was log transformed. Analysis was performed with SAS 9.2 (Cary, NC).

Results

Table 1 shows subjects' clinical, lung function, and CT data. D-COPD subjects were more likely to be older and had greater airflow obstruction, air trapping, and ventilation/perfusion (V/Q) mismatch along with a lower PaO_2 than ND-COPD subjects or controls. D-COPD subjects had significantly higher %LAA-960, smaller airway Ai, and lower $RTM_{CT\text{-}CSA}$ on CT scans than subjects of comparison groups. After adjustment for age and gender the differences in Ai and $RTM_{CT\text{-}CSA}$ across groups persisted (Online Table 1). Among dyspneic subjects, 13 were receiving short-acting or long-acting bronchodilators and 9 inhaled corticosteroids. Comparison subject groups were no receiving any respiratory medication.

Exercise data

Exercise data is shown in Table 2. D-COPD subjects walked less than ND-COPD subjects and controls (476 ± 75 vs. 581 ± 70 vs. 570 ± 70 m, respectively). Also dyspneic subjects reported higher Borg ratings than comparison subjects from minute 2 and thereafter reporting 2.6 more points at the end of the test (Fig. 1A). D-COPD subjects had greater exertional dyspnea at any $V'E$ and greater dyspnea/$V'E$ slopes than comparison subjects from min 2 to 6 (Fig. 1B). In dyspneic subjects, while the rise in $V'O_2$ and $V'CO_2$ were significantly lower than comparison subjects at min 4 and thereafter, ventilatory equivalents for O_2 ($V'E/V'O_2$) and CO_2 ($V'E/V'CO_2$) were higher than comparison subjects (Fig. 2A–C). D-COPD subjects also had a significant decline in SpO_2 compared to other subject groups (Fig. 2D). At the end of exercise subjects had a greater degree of tidal EFL (73.8 ± 16.1%) than ND-COPD (13.5 ± 14.6%) and control subjects (4.1 ± 7.8%; for both comparisons $P < 0.05$) (Fig. 3). IC% predicted decreased 11.4 ± 6.6% (−260 mL) from rest to min 6 in D-COPD subjects compared to an increase of 3.0 ± 2.6% (80 mL) in ND-COPD subjects and 3.8 ± 5.2% (90 mL) in controls (for both IC% predicted comparisons $P < 0.05$) (Fig. 4). There were no significant differences in RER and PET_{CO_2} between groups.

Determinants of dyspnea intensity and exercise capacity

In the full cohort, greater Borg ratings at min 6 were associated with decreasing IC% predicted ($r = -0.54$, $P < 0.0001$) (Fig. 5) and greater degree of EFL ($\%V_T$) ($r = 0.53$, $P < 0.001$). While Borg dyspnea score also correlated with FEV_1% predicted ($r = -0.35$, $P = 0.003$), $RTM_{CT\text{-}CSA}$ ($r = -0.32$, $P = 0.007$), SpO_2 at min 6 ($r = -0.31$, $P = 0.009$), $V'E/V'CO_2$ at min 6 ($r = 0.34$; $P = 0.004$), and $V'E/V'O_2$ at min 6 ($r = 0.29$; $P = 0.015$), it was marginally correlated with $V'E$, % MVV at min 6 ($r = 0.23$; $P = 0.054$). Stepwise regression chose ΔIC and FEV_1% predicted to best describe Borg ratings ($R^2 = 0.36$; P model <0.0001). Similar results were observed when EFL replaced ΔIC% predicted in the model. EFL and ΔIC % predicted were highly correlated each other and when we included both in a model to explain dyspnea in exertion, only ΔIC% predicted remained as independent predictor.

The highest correlates of distance walked were $RTM_{CT\text{-}CSA}$ ($r = 0.62$), ΔO_2 pulse% predicted ($r = 0.58$), ΔIC% predicted ($r = 0.50$), and EFL ($\%V_T$) ($r = -0.46$) ($P < 0.0001$ for all correlations) (Fig. 6). In a regression model including the three highest correlates, age, FEV_1% predicted, gender, and BMI, all the variables remained as independent determinants of distance walked. This model explained 77% of the variance. When ΔIC% predicted is

Table 1 Anthropometric, clinical, lung function, and CT data in dyspneic and non-dyspneic subjects with *mild* COPD and smoker controls at baseline.

	Smoker control	Non-dyspneic COPD	Dyspneic COPD
N	30	22	19
Gender, M/F	13/17	11/11	8/11
Age, years	63 ± 8	61 ± 10	69 ± 8[a,b]
Pack-years smoked	26 ± 18	38 ± 18	50 ± 23[a]
Current smoking, yes/no	16/14	12/10	7/12
Time quitting smoking, years	18.9 ± 10.4	14.2 ± 9.9	18.3 ± 11.3
BMI, kg/m^2	28 ± 4	26 ± 4	27 ± 3
Modified MRC score	0	0	1 (1–2)[a,b]
FEV_1, L	2.7 ± 0.6	2.7 ± 0.8	2.1 ± 0.5[a,b]
FEV_1, % predicted	100 (96–111)	92 (84–109)	86 (83–95)[a]
FVC, L	3.7 ± 0.8	4.2 ± 1	3.7 ± 1.1
FVC, % predicted	113 ± 16	120 ± 13	119 ± 15
FEV_1/FVC, %	75 (72–111)	68 (62–69)	59 (54–66)[a,b]
DL_{CO}/V_A , ml CO/min/mmHg/L	4.4 ± 0.7	4.2 ± 0.6	3.4 ± 0.8[a,b]
DL_{CO}/V_A, % predicted	124 ± 21	118 ± 16	99 ± 24[a,b]
PaO_2, mmHg	83 ± 7	82 ± 7	73 ± 8[a,b]
$PaCO_2$, mmHg	39 ± 2	37 ± 3	38 ± 3
TLC, L	5.5 ± 1.0	6.4 ± 1.4	6.0 ± 1.5
TLC, % predicted	103 ± 12	115 ± 11	114 ± 12[a]
RV, L	1.9 ± 0.4	2.2 ± 0.6	2.3 ± 0.6[a]
RV, % predicted	90 ± 16	107 ± 23	106 ± 19[a]
RV/TLC, %	34 ± 5	35 ± 6	39 ± 8[a]
$V'E$, L/min	10 ± 2.3	10.8 ± 2.9	11.6 ± 2.3
V_T, L	0.60 (0.53–0.71)	0.73 (0.57–0.80)	0.70 (0.57–0.83)
V_T, % predicted VC	19 (16–23)	21 (17–24)	22 (18–26)
F, breaths/min	15 (14–19)	15 (14–17)	18 (14–20)
IC, L	2.52 ± 0.48	2.60 ± 0.65	2.48 ± 0.60
IC, % predicted	93 ± 15	93 ± 15	99 ± 10
$RTM_{CT\text{-}CSA}$, cm^2	75.5 ± 17	78.4 ± 18	57.6 ± 16[a,b]
% LAA-960HU, %	4.0 (2.7–6.2)	5.3 (3.5–7.3)	9.1 (7.0–16.4)[a,b]
5th generation Ai of RB1, mm^2	6.7 ± 2.9	6.5 ± 3.8	4.1 ± 1.6[a]
5th generation Ai of RB10, mm^2	12.4 ± 8.2	8.2 ± 4.6	6.4 ± 2.4[a]

Values are expressed as frequency, mean ± standard deviation or median (interquantile range).
Abbreviations: M, Male; F, Female; BMI, Body Mass Index; MRC, Medical Research Council; FEV_1, Forced Expiratory Volume in 1 Second; FEV_1/FVC, Ratio of Forced Expiratory Volume in 1 s to Forced Vital Capacity; DL_{CO}/V_A, Ratio of Diffusing Lung Capacity for Carbon Monoxide/Alveolar Volume; PaO_2, Arterial Oxygen Tension; $PaCO_2$, Arterial Carbon Dioxide Tension; TLC, Total Lung Capacity; RV, Residual Volume; RV/TLC Ratio of Residual Volume to Total Lung Capacity; $V'E$, Minute Ventilation; VT, Tidal Volume; VC, Vital Capacity; F, Respiratory Rate; IC, Inspiratory Capacity; $RTM_{CT\text{-}CSA}$, Cross-sectional Area of the Right Thigh Muscle by Computed Tomography; %LAA-960 HU, Percent of Low-attenuation Areas Less than −960 Hounsfield Units; Ai, Airway Luminal Area; RB1, Right Upper Lobe Apical Bronchus; RB10, Right Lower Lobe Posterior Basal Bronchus.
[a] $P < 0.05$ vs. controls.
[b] $P < 0.05$ vs. Non-dyspneic COPD group.

replaced by EFL (%V_T) results were similar but gender is marginally significant ($P = 0.054$) and the model R^2 is 0.73. In a more parsimonious model that excluded age, gender, and BMI, distance walked was best explained by the combination of $RTM_{CT\text{-}CSA,}$ ΔIC% predicted, and ΔO_2 pulse% predicted ($R^2 = 0.59$). The same explanatory variables remained when EFL (%V_T) replaces ΔIC% predicted.

Relationships between CT measures of emphysema, airway narrowing, and physiologic variables

While %LAA-960 was not correlated with either Borg ratings ($r = 0.19$, $P = 0.1$) or distance walked ($r = -0.13$, $P = 0.3$), the 5th-airway generation Ai of the RB1 had an inverse relationship with dyspnea intensity ($r = -0.25$, $P = 0.03$). Ai of both RB1 ($r = 0.32$, $P = 0.007$) and RB10 ($r = 0.34$, $P = 0.003$) had a direct relationship with exercise performance. %LAA-960 was directly correlated with the degree of EFL (%V_T) ($r = 0.43$, $P = 0.0002$) and inversely related to IC% predicted ($r = -0.39$, $P = 0.0007$). Ai was associated with both EFL (RB1, $r = -0.38$, $P = 0.001$; RB10, $r = -0.47$, $P < 0.0001$) and IC% predicted (RB1, $r = 0.33$, $P = 0.005$; RB10, $r = 0.26$, $P = 0.03$).

Discussion

In this study we examined physiological responses to 6MWT and CT data in subjects with *mild* COPD and controls. We

Table 2 End-exercise metabolic, ventilatory and cardiovascular responses to the six-min walk test in dyspneic and non-dyspneic subjects with *mild* COPD and smoker controls.

	Smoker control	Non-dyspneic COPD	Dyspneic COPD
Distance walked, m	570 ± 70	581 ± 70	476 ± 75[a,b]
Distance walked, % predicted	94 ± 8	92 ± 11	83 ± 9[a,b]
Dyspnea, Borg units	1.3 ± 1.0	1.5 ± 1.2	3.9 ± 2.3[a,b]
$V'O_2$, L/min	1519 ± 441	1487 ± 426	1102 ± 301[a,b]
$V'O_2$, % predicted	109 ± 21	101 ± 21	86 ± 21[a,b]
$V'CO_2$, L/min	1414 ± 442	1378 ± 406	991 ± 302[a,b]
$V'O_2$, mL/kg/min	21 ± 5	21 ± 4	16 ± 4[a,b]
RER	0.93 ± 0.07	0.93 ± 0.04	0.89 ± 0.05
$V'E$, L/min	49 ± 16	48 ± 15	39 ± 10[a]
$V'E$, % MVV	42 ± 10	43 ± 11	48 ± 16
$V'E/V'O_2$	32 ± 4	32 ± 4	36 ± 6[a,b]
$V'E/V'CO_2$	35 ± 4	35 ± 4	40 ± 7[a,b]
$\Delta V'E/V'CO_2$ from rest, %	−25 ± 13	−29 ± 18	−26 ± 12
PET_{CO_2} mm Hg	38.5 ± 3.7	37.5 ± 3.5	36.1 ± 4.3
SpO_2, %	96 ± 2	96 ± 2	91 ± 7[a,b]
ΔSpO_2 from rest, %	−0.7 ± 1.3	−1.4 ± 2.9	−4.9 ± 6.8[a,b]
EFL, % of V_T overlapping maximal flow-volume curve	4.1 ± 7.8	13.5 ± 14.6	73.8 ± 16.1[a,b]
F, breaths/min	30 ± 3	28 ± 5	29 ± 6
V_T, L	1.63 ± 0.4	1.73 ± 0.5	1.41 ± 0.5
V_T, % predicted VC	50 ± 9	50 ± 9	45 ± 9
ΔV_T, % predicted VC from rest	162 ± 59	154 ± 84	107 ± 55[a]
T_I, s	0.73 ± 0.13	0.80 ± 0.16	0.77 ± 0.21
T_E, s	1.31 ± 0.21	1.42 ± 0.24	1.40 ± 0.30
V_T/T_I, L/s	2.28 ± 0.70	2.22 ± 0.71	1.86 ± 0.52
V_T/T_E, L/s	1.29 ± 0.44	1.24 ± 0.38	1.0 ± 0.27[a]
IC, L	2.61 ± 0.5	2.68 ± 0.7	2.22 ± 0.6[a]
IC, % predicted	96 ± 14	96 ± 16	88 ± 14
ΔIC, % predicted from rest	3.8 ± 5.2	3.0 ± 2.6	−11.4 ± 6.6[a,b]
HR, beats/min	133 ± 17	129 ± 15	118 ± 18[a]
HR, % predicted	85 ± 11	82 ± 10	77 ± 11[a]
O_2 pulse, ml/beat	11.4 ± 3.0	11.5 ± 3.0	9.5 ± 2.9
O_2 pulse, % predicted	109 ± 19	104 ± 23	94 ± 21
ΔO_2, % predicted from rest	248 ± 84	235 ± 86	170 ± 78[a,b]

The values correspond to the min 6 or the change from rest to min 6 and are expressed as mean ± standard deviation.
Abbreviations: $V'O_2$, Oxygen Consumption; $V'CO_2$, Carbon Dioxide Production; RER, Respiratory Exchange Ratio. $V'E$, Minute Ventilation; MVV, Maximal Voluntary Ventilation; PET_{CO_2}, End-tidal Carbon Dioxide Partial Pressure; SpO_2, Arterial Oxygen Saturation by Pulse Oximeter; EFL, Expiratory Flow-limitation; F, Respiratory Rate; V_T, Tidal Volume; VC, Vital Capacity; T_I, Tidal Inspiratory Time; T_E, Tidal Expiratory Time; V_T/T_I, Mean Tidal Inspiratory Flow; V_T/T_E, Mean Tidal Expiratory Flow; IC, Inspiratory Capacity; HR, Heart Rate; O_2, Oxygen; Δ, Change from Rest to min 6.
[a] $P < 0.05$ vs. controls.
[b] $P < 0.05$ vs. Non-dyspneic COPD group.

found that compared to non-dyspneic COPD and control subjects, dyspneic COPD subjects in daily life had the following findings: (a) lower exercise performance and higher Borg ratings; b) greater emphysema, lower airway luminal area, and thigh muscle wasting on CT scan; and c) increased ventilatory demand, dynamic hyperinflation, and arterial oxygen desaturation during exercise, which were related to greater dyspnea perception. These findings provide support to the inclusion of dyspnea in the new GOLD classification scheme[1] as it clearly separates GOLD stage 1 COPD subjects with distinct physiologic and morphologic features as well as exercise outcomes.

Subjects with *mild* COPD who experienced dyspnea in daily activities (mMRC 1—2) had a clinically meaningful reduction in exercise performance and experienced more dyspnea during walking (at least 94 m less and 2.6 points more than comparison subjects, respectively). These differences in distance walked and Borg ratings are higher than a minimal important difference suggested for these outcomes (for walking, 54—80 m[37]; for Borg scale, 1 point[38]). Our findings confirm prior data observed during cycling exercise in a similar population[14] and extend them by relating morphologic characteristics of the lung and thigh muscle on CT scan with these outcomes. While subjects with the greatest airway lumen narrowing experienced the greatest dyspnea intensity and the lowest exercise performance, those with greatest thigh muscle wasting also walked the least. Additionally, CT measures of

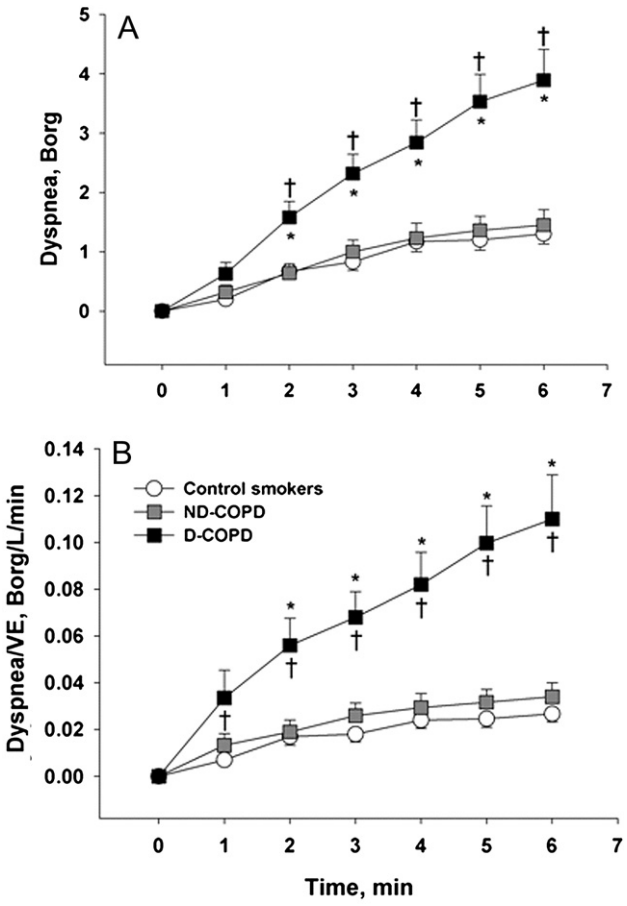

Figure 1 A. Borg dyspnea ratings and B. dyspnea/VE over time during the six-minute walk are shown. Data are shown as mean ± SEM for dyspneic (■) and non-dyspneic (□) GOLD 1 COPD subjects and smoker controls (○). †$P < 0.05$ vs. controls; *$P < 0.05$ vs. Non-dyspneic COPD group.

emphysema and airway narrowing may be the structural basis of expiratory flow limitation and dynamic hyperinflation we observed in our subjects. We think that these observations are not explained by poor effort during walking or age differences across study groups. Standardized encouragement was given to the subjects during the 6MWT. The dyspneic group reached 77% of maximum heart rate, similar to that observed in normals in a multicenter study.[39] Mean dyspnea ratings and mean walking speed (1.36 ± 0.21 m/s) were similar to those described in patients with more advanced disease.[40] The comparable subjects' walking speed between our and a prior study[40] suggests that our subjects likely walked at their maximum sustainable speed. Additionally, the analyses were adjusted by age. We identified three potential contributors to exertional dyspnea and exercise capacity in these subjects: abnormalities of resting and dynamic ventilatory mechanics; reduced peripheral muscle mass; and inappropriate cardiovascular response.

Our data demonstrate that during walking the ventilatory demand in dyspneic subjects was increased suggested by higher $V'E/V'CO_2$ and $V'E/V'O_2$ ratios. Potential explanations for this finding from our data are larger ventilation–perfusion (V/Q) inequalities (reflected by lower DL_{CO}/V_A). As a result, these patients showed lower PaO_2 at rest along with higher drop in SpO_2 at the end of the walking. Further, we found that subjects with the greatest burden of emphysema on CT scan had both the lowest DL_{CO}/V_A ($r = -0.50$; $P < 0.0001$) at rest and SpO_2 at the end of walking ($r = -0.25$; $P = 0.04$) supporting structure–function relationships for the V/Q imbalance and pulmonary gas exchange in *mild* COPD. Our findings confirm prior observations of V/Q mismatch at rest[41] and during cycling[14] in *mild* COPD. Unlike cycling, in the self-paced walking the gas exchange abnormalities of the lungs were enough to cause a modest but significant decline in oxygen arterial saturation at min 6 among dyspneic subjects. The increased ventilatory demand likely led to greater dyspnea and exercise limitation. In this study, significant associations between dyspnea ratings, $V'E/V'CO_2$, and $V'E/V'O_2$ ratios were found. Consistent with prior investigation,[14] subjects with the highest ventilatory demand (assessed by $V'E$ as % MVV) tended to report the greater dyspnea intensity ($r = 0.23$, $P = 0.054$). Finally, subjects with the lowest SpO_2, and thus the largest V/Q mismatch and ventilatory demand, had the greatest Borg ratings at the end of walking.

In this study we also found that dyspneic subjects had significant ventilatory constraints during walking as they exhibited a marked expiratory flow limitation during tidal breathing at end-exercise. It is of note that this ventilatory limitation manifested despite an apparent preserved ventilatory reserve as assessed by the end-exercise $V'E$ (% MVV). This finding is consistent with early observations among patients with mild-to-moderate COPD.[42] During walking our subjects had to face a decreased IC (as % predicted) along with an increase in end-expiratory lung volume (0.26 ± 0.1 L). Additionally, dyspneic subjects had higher resting ventilatory mechanical loads suggested by greater airway obstruction and air trapping. Thus, their steeper dyspnea/$V'E$ slopes were the combined result of greater resting ventilatory mechanical loads and exercise-induced hyperinflation. The decline in IC was approximately a half of that during incremental cycling (0.54 L).[14] Two reasons may account for the lower decrease in IC: a) the short duration of the 6MWT likely does not allow developing a greater degree of DH; b) the subjects' walking speed was probably at their critical level, and consequently they were exercising at or below the ventilatory threshold. This is supported by the fact that no dyspneic patients reached a RER >1.0 and both average ΔIC and $V'E$ (as % MVV) were comparable to those observed at the ventilatory threshold during cycling in a similar population (0.28 L and 51%, respectively).[14] In dyspneic subjects the reduction in IC tended to limit the V_T response. Subjects with the lowest V_T (as % VC) expansion had the greatest reduction in IC% predicted ($r = 0.32$, $P = 0.007$). Supporting this assumption, the lower V_T expansion in dyspneic subjects was likely due to decreased V_T/T_I ($P = 0.08$ vs. controls), since T_I did not differ significantly from that of comparison subjects. We have previously found that a reduced mean inspiratory flow is likely the response to increased inspiratory loads.[43] The mechanical restriction we observed largely explained exertional dyspnea and reduced exercise performance in our subjects. We found that both IC% predicted and EFL were the highest correlates of Borg ratings and were independent predictors of dyspnea in exertion in separate

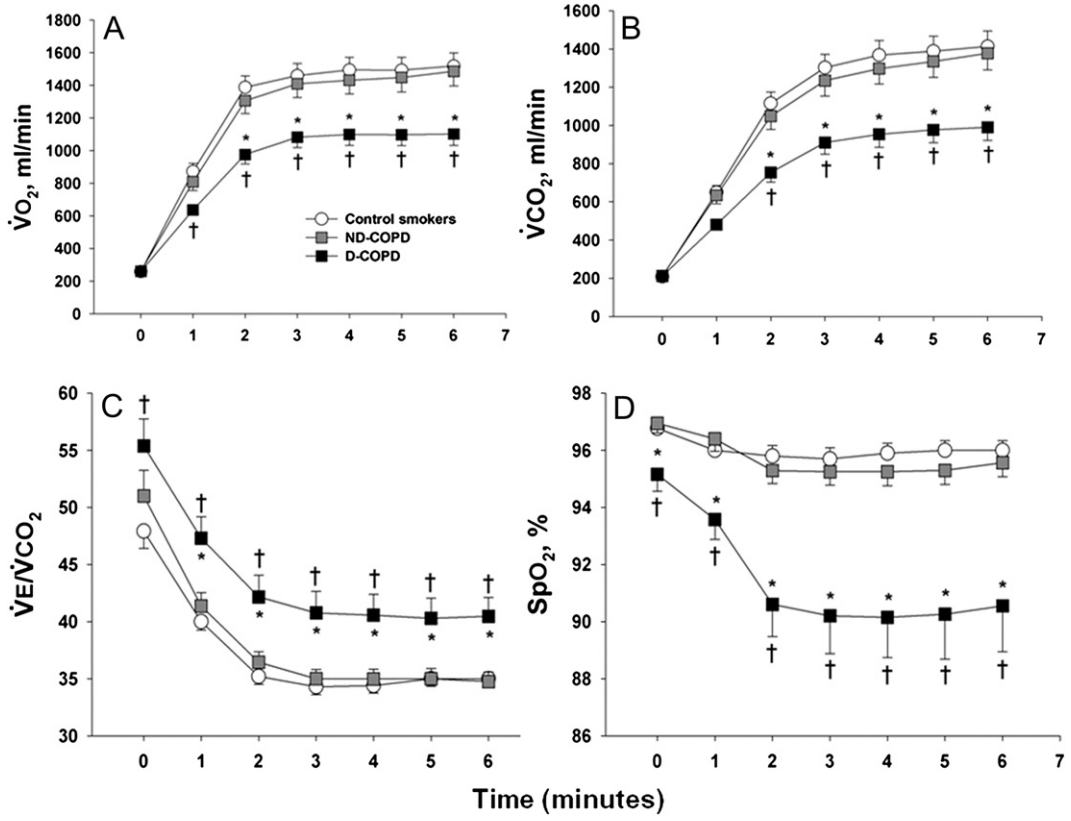

Figure 2 A. Oxygen consumption ($V'O_2$), B. Carbon dioxide production ($V'CO_2$), C. Ventilatory equivalent for carbon dioxide ($V'E/V'CO_2$), and D. Oxygen saturation by pulse oximeter (SpO_2) responses to the six-minute walk test are depicted. Data are shown as mean ± SEM for dyspneic (■) and non-dyspneic (□) GOLD 1 COPD subjects and smoker controls (○). $^{\dagger}P < 0.05$ vs. controls; $^{*}P < 0.05$ vs. Non-dyspneic COPD group.

multivariate models. Additionally, a greater airflow obstruction at baseline was also an independent predictor of increased exertional dyspnea and reduced exercise performance. The relationship between airflow obstruction and 6MWT was consistent with observations made by Mak et al.[44] Similarly, both IC% predicted and EFL again were independent determinants of exercise capacity in separate models.

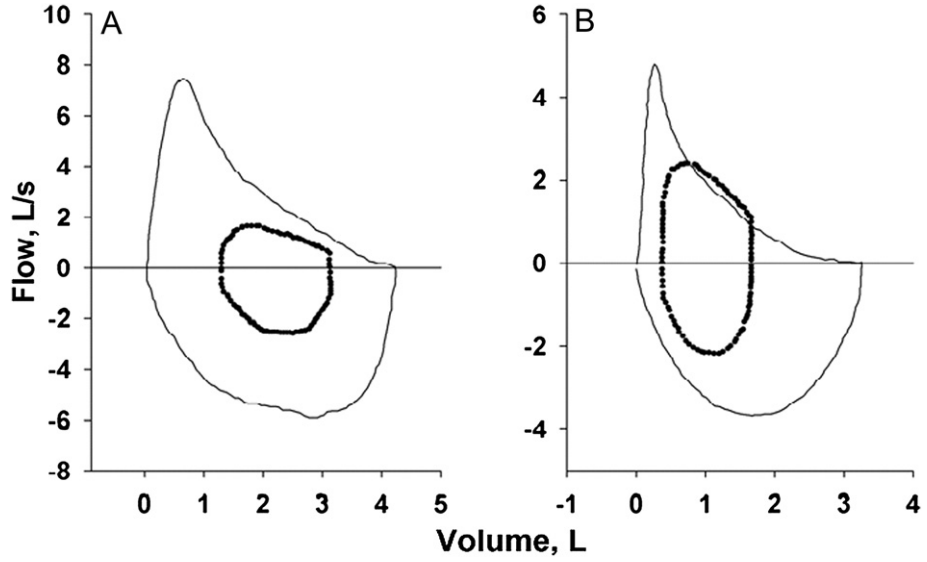

Figure 3 End-exercise tidal flow-volume loops (dotted-line) placed within their maximal flow-volume curves at rest are shown. A smoker control subject (A) with no tidal expiratory flow limitation (no overlap between curves) and a dyspneic-COPD subject (B) with tidal expiratory flow limitation (EFL) over >70% of the V_T are depicted. EFL is represented by the tidal flow-volume loop overlapping the maximal flow-volume curve.

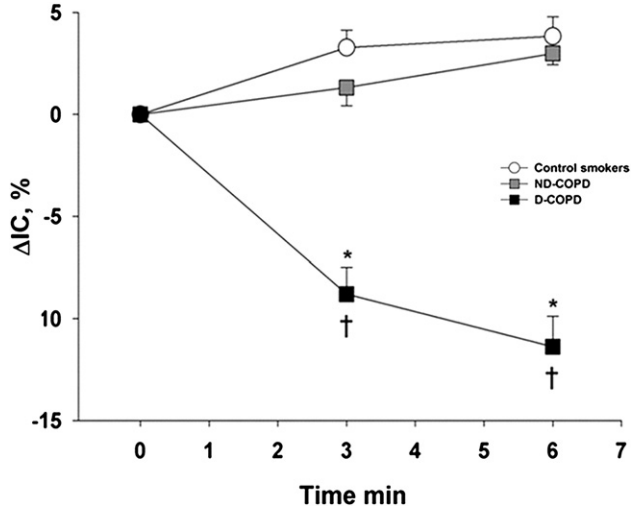

Figure 4 Inspiratory capacity (ΔIC)% predicted response to the six-minute walk test is shown. Data are shown as mean ± SEM for dyspneic (■) and non-dyspneic (□) GOLD 1 COPD subjects and smoker controls (○). $^{\dagger}P < 0.05$ vs. controls; $^{*}P < 0.05$ vs. Non-dyspneic COPD group.

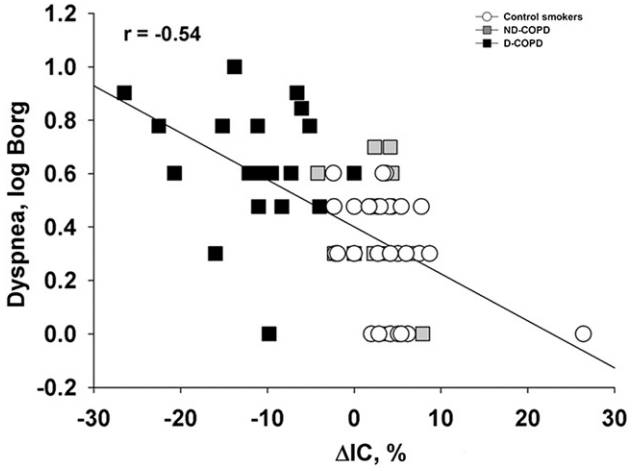

Figure 5 Scatter plot of log Borg dyspnea ratings at min 6 to Δinspiratory capacity (IC)% predicted from rest is shown. Data points represent dyspneic (■) and non-dyspneic (□) GOLD 1 COPD subjects and smoker controls (○).

CT assessment of the lungs demonstrated that subjects with the narrowest airway lumen measured as Ai and those with the greatest burden of emphysema on CT scan had the greatest EFL (as % VT) and decrease in IC% predicted. These relationships suggest that these CT anatomical changes reflecting increased airway resistance and elastic recoil loss (emphysema) may be the morphological basis of expiratory flow limitation and its mechanical consequence, dynamic hyperinflation. Also subjects with the greatest airway narrowing on CT scan reported greater dyspnea intensity and walked the least.

We also observed that those patients with lower $RTM_{CT\text{-}CSA}$ experienced greater dyspnea intensity and lower exercise performance. This morphologic assessment of the thigh muscle was an independent explanatory factor for distance walked in regression analysis. Muscle wasting might prone to leg fatigue. A recent study showed that COPD subjects who experienced leg fatigue during cycling obtained the greatest increase in six-minute walking distance after training,[45] which suggests that thigh muscle wasting might be amenable to intervention. Based on recent investigation,[17] we speculate that the thigh muscle loss in dyspneic subjects with *mild* COPD may result from avoiding daily symptom-limited exercising. Further replication in a larger cohort of subjects with *mild* COPD undergoing direct assessment of muscle strength is warranted.

An unexpected finding in this study was that dyspneic subjects had an attenuated increase in oxygen pulse than either non-dyspneic COPD or control subjects and that ΔO_2 pulse was an independent determinant of distance walked. Recent studies have confirmed an association between the degree of lung hyperinflation and a reduction in O_2 pulse, a crude non-invasive measure of stroke volume during exercise, in subjects with moderate-to-severe COPD.[46–48] Consistent with these studies, our results indicate a significant association between concurrent IC% predicted and O_2 pulse at end-exercise ($r = 0.32$, $P = 0.007$). It should be noted, however, that the reduced O_2 pulse could merely reflect the lower $V'O_2$ achieved by the dyspneic patients. Further studies with direct assessment of the cardiac

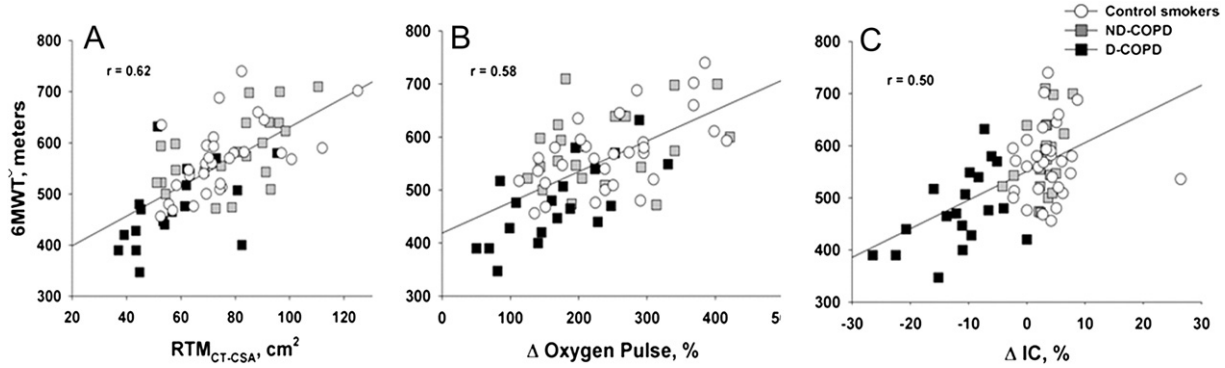

Figure 6 Scatter plot of six-minute walk distance (6MWT) to A. cross sectional area of the right thigh muscle by computed tomography ($RTM_{CT\text{-}CSA}$), B. ΔO_2 pulse % predicted from rest and C. Δinspiratory capacity (IC)% predicted from rest are shown. Data points represent dyspneic (■) and non-dyspneic (□) GOLD 1 COPD subjects and smoker controls (○).

function may reveal the potential contribution of cardiac dysfunction to exercise capacity in *mild* COPD.

Several limitations should be noted. Our subjects were recruited from clinics and may not be representative of the whole population with *mild* COPD. Thus, caution should be exercised to generalize these findings. We did not assess the psychological profile of our subjects, which may explain differences in dyspnea perception among study groups. We did not directly measure cardiac function and used a non-invasive measure of stroke volume, O_2 pulse. Thus, the potential role of cardiac dysfunction due to hyperinflation on exercise impairment is rather a hypothesis-generating finding. We did not include a muscle strength assessment and relied on an objective measure of CT thigh muscle cross-sectional area (CSA). Thus, the potential mechanism linking the thigh muscle wasting and exertional dyspnea remain to be determined. Other radiation-free imaging modalities such as MRI[49] and ultrasound[50] have emerged to assess CSA of peripheral muscles. However, the former technique is expensive and not widely available and the latter is operator-dependent and requires training.

This study in subjects with *mild* COPD (GOLD stage 1) shows that those with dyspnea in daily life had reduced exercise capacity and exertional dyspnea along with distinct morphologic features including greater emphysema, airway lumen narrowing, and peripheral muscle wasting on CT scan. They also had increased ventilatory demands, dynamic hyperinflation, and arterial oxygen desaturation during exercise, which were linked to dyspnea in exertion as well as to emphysema and airway narrowing. These differences in exercise outcomes as well as in morphologic and physiologic features of the lung and thigh muscle between GOLD 1 COPD subjects with and without dyspnea in daily life provide support to include the assessment of breathlessness in the new GOLD classification scheme for this disease.[1]

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2012.12.011.

Conflicts of interest statement

Dr. Alejandro A. Díaz, Arturo Morales, Juan C Díaz, Cristóbal Ramos, Julieta Klaassen, Fernando Saldías, Carlos Aravena, Rodrigo Díaz, Carmen Lisboa, George R. Washko, and Orlando Díaz have no conflicts of interest to disclose.

The study sponsor had no role in the study design and collection, analysis, and interpretation of data., collection, analysis, and interpretation of data.

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