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RESEARCH ARTICLE

Never-smokers with occupational COPD have better exercise capacities and ventilatory efficiency than matched smokers with COPD

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Soumagne T, Guillien A, Roche N, Dalphin JC, Degano B. Never-smokers with occupational COPD have better exercise capacities and ventilatory efficiency than matched smokers with COPD. *J Appl Physiol* 129: 1257–1266, 2020. First published October 1, 2020; doi:10.1152/jappphysiol.00306.2020.—Chronic obstructive pulmonary disease (COPD) in never-smokers exposed to organic dusts is still poorly characterized. Therapeutic strategies in COPD are only evaluated in smoking-related COPD. Understanding how never-smokers with COPD behave during exercise is an important prerequisite for optimal management. The objective of this study was to compare physiological parameters measured during exercise between never-smokers with COPD exposed to organic dusts and patients with smoking-related COPD matched for age, sex, and severity of airway obstruction. Healthy control subjects were also studied. Dyspnea (Borg scale), exercise tolerance, and ventilatory constraints were assessed during incremental cycle cardiopulmonary exercise testing in COPD patients at mild to moderate stages [22 exposed to organic dusts: postbronchodilator forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC) z score -2.44 ± 0.72 and FEV₁ z score -1.45 ± 0.78 ; 22 with smoking-related COPD: FEV₁/FVC z score -2.45 ± 0.61 and FEV₁ z score -1.43 ± 0.69] and 44 healthy control subjects (including 22 never-smokers). Despite the occurrence of similar significant dynamic hyperinflation, never-smoker COPD patients exposed to organic dusts had lower dyspnea ratings than those with smoking-related COPD. They also had better ventilatory efficiency, higher peak oxygen consumption and peak power output than smoking-related COPD patients, all these parameters being similar to control subjects. Differences in exercise capacity between the two COPD groups were mainly driven by better ventilatory efficiency stemming from preserved diffusion capacity. Never-smokers exposed to organic dusts with mild to moderate COPD have better exercise capacities, better ventilatory efficiency, and better diffusion capacity than matched patients with smoking-related COPD.

NEW & NOTEWORTHY It is unknown whether or not never-smokers with chronic obstructive pulmonary disease (COPD) behave like their smoking counterparts during exercise. This is the first study showing that never-smokers with mild to moderate COPD [defined by a postbronchodilator forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC) < lower limit of normal] have preserved exercise capacities. They also have lower exertional dyspnea than patients with smoking-related COPD. This suggests that the two COPD groups should not be managed in the same way.

chronic obstructive pulmonary disease; exercise tolerance; nonsmokers

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide (29). Although tobacco smoking is the main risk factor for COPD, it is now admitted that up to 30% of patients with COPD have never smoked (27, 34). Risk factors for COPD in never-smokers include occupational or environmental dust exposure (4, 14, 27). Development of COPD following the chronic inhalation of environmental dusts seems to be mainly driven by an inflammatory reaction that occurs in a subset of exposed subjects (2, 9, 24). COPD in these patients has been associated with some Th2 phenotype markers and is considered to depend on individuals' susceptibility rather than on the magnitude and/or the characteristics of exposure (30, 38).

COPD in never-smokers is still poorly characterized. Nevertheless, there is increasing evidence for differences in clinical, radiological, and physiological presentations between COPD secondary to tobacco smoking and COPD that develops in never-smokers (3, 4, 34, 37). As an example, never-smokers with COPD are less likely to have emphysema, and their single-breath lung diffusion for carbon monoxide (DL_{CO}) is less impaired than that of patients with COPD secondary to tobacco smoking (5, 34). Whether or not these differences translate into differences in physiological characteristics measured at exercise is unknown.

Even at mild stages of the disease, patients with smoking-related COPD have reduced exercise capacity and higher exertional dyspnea measured during symptom-limited, incremental cycle ergometer cardiopulmonary exercise testing (CPET) (21). In these patients, ventilatory abnormalities during CPET include higher ventilatory demand, significant dynamic lung hyperinflation, and a relatively rapid and shallow breathing pattern (21, 32). Compared with matched healthy subjects, patients with smoking-related mild COPD have poorer perceived health status, higher chronic activity-related dyspnea, and reduced activity levels (20, 21, 32). Whether or not never-smokers with COPD behave like their smoking COPD counterparts in terms of impairment at exercise remains unknown. In addition, almost all large trials of pharmacotherapy for COPD aiming at improving exercise-related symptoms and physiological impairments

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have excluded patients who have no history of tobacco smoking (27). Increasing our knowledge of exercise behavior in never-smokers with COPD is therefore a prerequisite that will guide therapeutic strategies in these patients. To do this, we compared the exercise physiology between never-smokers with occupational COPD due to organic dust exposure, patients with smoking-related COPD (all at mild to moderate stages, matched for severity of airway obstruction), and healthy control subjects.

METHODS

Subjects and study design. COPD patients and control subjects were recruited through a regional COPD screening program (the BALISTIC Study; ClinicalTrials.gov Identifier: NCT02540408), as previously described (8, 31). For the present analysis, we identified four groups: patients with smoking-related COPD; never-smokers with occupational COPD secondary to organic dust exposure; ever-smokers with normal spirometry; and never-smokers exposed to organic dusts with normal spirometry. Never-smokers were individuals who had never smoked in their lifetime (dairy farmers, i.e., all chronically exposed to organic dusts), whereas ever-smokers (either current or former smokers) were individuals who had smoked >15 pack-yr. Among the subjects included in the BALISTIC study, we identified pairs of ever-smokers and never-smokers with COPD matched for age (± 10 yr) and sex. These two groups were also pair-matched with ever-smokers and never-smokers with normal spirometry for age (± 10 yr), sex, and postbronchodilator (post-BD) forced expiratory volume in 1 s (FEV₁)% ($\pm 10\%$).

Patients with COPD had 1) a medical history compatible with the disease (i.e., persistent respiratory symptoms, including dyspnea, cough, and/or sputum production, and a significant exposure to noxious particles or gases); 2) persistent airflow limitation defined as a post-BD FEV₁-to-forced vital capacity (FVC) ratio < 5th centile lower limit of normal according to the last GLI-2012 equations; and 3) a FEV₁ > 50% of predicted value according to the GLI-2012 equations (25, 29). Control subjects had normal spirometry. Exclusion criteria for COPD and control subjects were 1) a history of any medical conditions that could cause or contribute to breathlessness (i.e., a respiratory disease other than COPD and/or a cardiovascular disease) and/or 2) any other disorder that could interfere with exercise testing (21, 32). In particular, patients with asthma (either self-reported or confirmed by a doctor) were carefully excluded from the present analysis.

Subjects were in stable condition (for COPD patients, no exacerbation during the previous 6 wk) and were not taking any oral or inhaled anti-inflammatory drugs, including corticosteroids. COPD patients were asked to interrupt short- and long-acting bronchodilators 72 h before the visit, if required.

Ethical approval was received from the local Ethics Committee (CPP Est; P-2011-119), and written informed consent was obtained from all subjects.

Procedures. Subjects attended a single visit beginning early in the morning. They underwent pulmonary function testing before bronchodilator and 30 min after bronchodilator administration, as previously described (32). Symptom-limited incremental cycle ergometer cardiopulmonary exercise testing (CPET) was performed on the same day, at least 6 h after the bronchodilator test and at least 4 h after a meal.

Routine spirometry, constant-volume body plethysmography, and single-breath lung diffusion for carbon monoxide (DL_{CO}) (Platinum Elite; MGC Diagnostics Corporation, St. Paul, MN) were performed in accordance with recommended techniques (12, 13, 40). Symptom-limited incremental CPET was performed on an electronically braked cycle ergometer (Ergometrics 900; Ergoline, Bitz, Germany), as previously described (32). Briefly, after a steady-state resting period, a 3-min warm-up was conducted at ~20% of individually estimated maximal work load, and the load was increased every minute such that CPET duration was between 8 and 12 min (22). Tests were terminated

at the point of symptom limitation (peak exercise). Physiological data were obtained breath by breath (MGC-CPX System; MGC Diagnostics Corporation) and were expressed as 30-s averages, according to current recommendations (22). Blood gases were measured from samples drawn from the arterialized earlobe, and measurements were corrected to estimate arterial oxygen partial pressure (1). Subjects rated the magnitude of their perceived breathing and leg discomfort by pointing to a number on the 10-point Borg scale. Changes in end-expiratory lung volume were estimated from inspiratory capacity (IC) measurements at rest, at the end of each 1-min increment of exercise, and at peak exercise. Dynamic hyperinflation was defined as a decrease of >150 mL in IC compared with resting levels at any time point during exercise (20).

The ventilatory equivalent for carbon dioxide [minute ventilation (\dot{V}_E)-to-carbon dioxide output (\dot{V}_{CO_2}) ratio] plotted against work rate (WR) and its nadir were used as surrogate markers of ventilatory efficiency. Dead space (V_D)-to-tidal volume (V_T) ratio was calculated by the Enghoff equation using arterialized CO₂ partial pressure (PcapCO₂) at maximal exercise (26). In the relationship between V_T and \dot{V}_E , there is an inflection point beyond which almost no further change in V_T occurs despite a continued increase in \dot{V}_E (18). This inflection in the V_T response marks the point where dyspnea sharply increases because of mechanical constraints on V_T expansion (18). This inflection point was determined by two trained observers (B.D. and T.S.) for each patient by analyzing individual plots of \dot{V}_E vs. V_T (15).

Statistical analysis. A sample size of 22 subjects in each group was estimated to provide 90% power to detect a 1-point difference between never-smokers with COPD and ever-smokers with COPD in dyspnea intensity (Borg scale) measured at a standardized work rate (WR) during incremental cycle exercise based on an SD = 1 unit, $\alpha = 0.05$, and a two-tailed test of significance (21, 32). Matching procedures were performed with the *matchcc* macro in SAS.

Between-group comparisons of subjects' characteristics were performed with two-factor (smoking and disease) analysis of variance (ANOVA) followed by Tukey multiple comparisons tests for continuous variables. Comparisons of categorical data between groups were performed with Fisher's exact test. Repeated-measures ANOVA was performed to evaluate differences between groups for

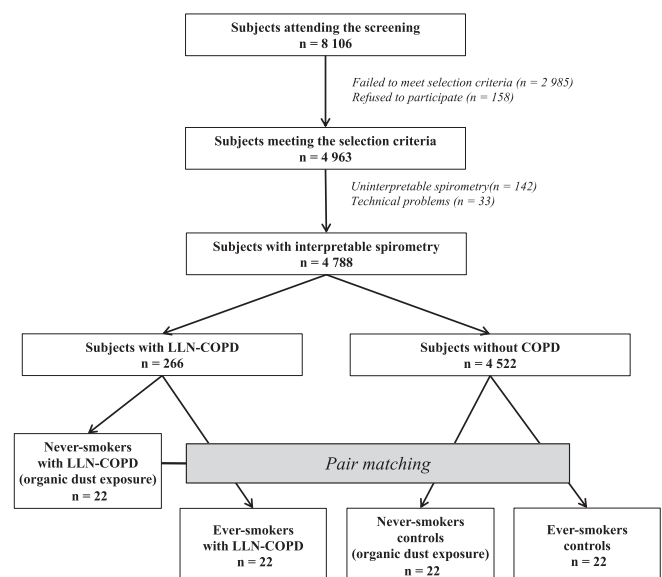


Fig. 1. Flowchart of participants included in the study. Subjects were recruited through a screening program in 2 branches of the social security. Common inclusion criteria in the screening programs were men or women aged 40–74 yr with no history of chronic respiratory disease including asthma and hypersensitivity pneumonitis. COPD, chronic obstructive lung disease; LLN, lower limit of normal.

quantitative measurements made at different time points and/or intensities during exercise. The Scheffé test was applied to evaluate pairwise comparisons when a significant difference was found by ANOVA. Pearson's r assessed association between continuous variables. All reported P values were two sided, with a significance level set at $P < 0.05$.

In addition, to identify factors associated with ventilatory efficiency, a multivariate linear regression analysis with backward stepwise selection was performed. All variables associated with ventilatory efficiency in univariate analysis with a P value < 0.20 were included.

Statistical analysis was performed with R version 3.5.0, RStudio version 1.1.453 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Subject characteristics. A total of 88 subjects (22 in each group) were included (Fig. 1). By design, all groups had similar sex distribution and age (Table 1). Comorbidities were

similar except for dyslipidemia, which was more frequent in smokers (Table 2). Among the 88 study subjects, only 1 patient with COPD was taking long-term bronchodilators at the time of screening and none was taking inhaled corticosteroids (Table 2).

The two groups of patients with COPD had a similar burden of symptoms, that is, chronic activity-related dyspnea [modified Medical Research Council scale (mMRC)], chronic cough, and chronic sputum production, but ever-smokers with COPD had a baseline dyspnea index (BDI) and COPD assessment test (CAT) that were poorer than for never-smokers (Table 1).

Pulmonary function. By design, post-BD FEV₁ and FEV₁/FVC were similar in the two groups with COPD (Table 1). The maximal midexpiratory flow (FEF_{25–75}) was significantly lower (mean z score < -1.64) in the two groups with COPD compared with control subjects. Lung volumes measured at rest were similar in the two groups of patients with COPD. The major difference between the two COPD groups was that never-smokers with COPD had preserved DL_{CO} (mean z score $>$

Table 1. Characteristics, respiratory symptoms, and pulmonary function in subjects with COPD and healthy control subjects

	Never-Smokers		Ever-Smokers		P Value		
	COPD ($n = 22$)	Control ($n = 22$)	COPD ($n = 22$)	Control ($n = 22$)	Interaction	COPD vs. control	Never-smokers vs. ever-smokers
Demographics							
Male, n (%)	20 (91)	20 (91)	20 (91)	20 (91)		1	
Age, yr	56.4 \pm 8.3	58.5 \pm 7.8	58.8 \pm 7.3	59.0 \pm 7.8	0.55	0.50	0.40
Body mass index, kg/m ²	26.1 \pm 4.2	26.6 \pm 2.9	25.3 \pm 3.8	27.1 \pm 3.7	0.41	0.15	0.90
Current smokers, %			8 (36)#	14 (64)			
Tobacco, pack-yr			36.0 \pm 18.8	28.7 \pm 13.7			
Symptoms							
Chronic cough, n (%)	10 (45)	4 (18)	8 (36)	4 (18)		0.12	
Chronic sputum, n (%)	10 (45)	4 (18)	9 (41)	4 (18)		0.09	
mMRC dyspnea scale (0–4)	0.24 \pm 0.44	0.14 \pm 0.35	0.55 \pm 0.80	0.36 \pm 0.90	0.78	0.32	0.07
BDI dyspnea scale (0–12)	11.3 \pm 1.04*	11.6 \pm 1.0	10.1 \pm 2.1#	11.3 \pm 1.5	0.15	0.02	0.02
SGRQ	14.6 \pm 10.9	6.1 \pm 5.4	18.1 \pm 15.4†	10.7 \pm 10.2	0.67	0.002	0.06
CAT score (0–40)	8.3 \pm 4.8*		11.9 \pm 6.1				
Pulmonary function tests							
Post-BD FEV ₁ , L (z score)	2.78 \pm 0.68 (−1.45 \pm 0.78)#†	3.66 \pm 0.65 (0.55 \pm 0.79)	2.65 \pm 0.54 (−1.43 \pm 0.69)#†	3.67 \pm 0.65 (0.59 \pm 0.83)	0.63	<0.0001	0.66
Post-BD FEV ₁ /FVC, % (z score)	59.8 \pm 7.1 (−2.44 \pm 0.72)#†	78.7 \pm 4.5 (0.11 \pm 0.68)	59.2 \pm 5.2 (−2.45 \pm 0.61)#†	79.1 \pm 3.4 (0.16 \pm 0.51)	0.69	<0.0001	0.93
Pre-BD pulmonary function							
FEV ₁ , L (z score)	2.56 \pm 0.63 (−1.87 \pm 0.72)#†	3.55 \pm 0.62 (0.31 \pm 0.65)	2.46 \pm 0.48 (−1.79 \pm 0.68)#†	3.56 \pm 0.62 (0.37 \pm 0.79)	0.68	<0.0001	0.75
FVC, L (z score)	4.48 \pm 0.93 (0.01 \pm 0.91)	4.72 \pm 0.74 (0.57 \pm 0.57)	4.27 \pm 0.81 (−0.06 \pm 0.79)	4.65 \pm 0.87 (0.47 \pm 0.89)	0.71	0.09	0.44
FRC, L (z score)	3.91 \pm 0.86 (0.82 \pm 1.43)	3.78 \pm 0.64 (0.58 \pm 0.91)	3.86 \pm 0.95 (0.73 \pm 1.50)	3.73 \pm 0.98 (0.47 \pm 1.48)	0.99	0.50	0.79
IC, L	3.54 \pm 0.61	3.57 \pm 0.70	3.33 \pm 0.81	3.54 \pm 0.60	0.56	0.44	0.43
FEF _{25–75} , L (z score)	1.17 \pm 0.48 (−2.28 \pm 0.49)#†	2.83 \pm 0.95 (−0.16 \pm 0.73)	1.09 \pm 0.32 (−2.20 \pm 0.49)#†	3.07 \pm 0.83 (0.11 \pm 0.73)	0.29	<0.0001	0.59
RV, L (z score)	2.82 \pm 0.54 (1.42 \pm 1.60)	2.49 \pm 0.44 (0.48 \pm 0.96)	2.79 \pm 0.73 (1.22 \pm 1.82)	2.48 \pm 0.47 (0.42 \pm 1.17)	0.95	0.01	0.84
TLC, L (z score)	7.44 \pm 0.84 (1.08 \pm 0.89)	7.35 \pm 1.02 (0.97 \pm 0.82)	7.19 \pm 1.19 (0.85 \pm 1.27)	7.27 \pm 1.05 (0.86 \pm 1.09)	0.69	0.96	0.45
DL _{CO} , mmol/min/kPa (z score)	8.45 \pm 2.24 (−0.43 \pm 1.22)*#	9.96 \pm 2.36 (0.72 \pm 1.08)	6.64 \pm 1.67 (−1.69 \pm 1.22)#†	8.66 \pm 2.00 (−0.15 \pm 1.33)	0.57	0.0001	0.0008
Kco, mmol/min/kPa/L (z score)	1.31 \pm 0.27*# (−0.73 \pm 1.14)*#	1.47 \pm 0.24 (0.07 \pm 1.00)	1.09 \pm 0.23 (−1.75 \pm 1.15)#†	1.33 \pm 0.22 (−0.54 \pm 1.07)	0.42	0.0002	0.0009

Values are means \pm SD. Significant P values are in bold. BD, bronchodilator; BDI, baseline dyspnea index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; DL_{CO}, lung diffusion for carbon monoxide; FEF_{25–75}, maximal midexpiratory flows; FEV₁, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity (z score was omitted because SDs of theoretical values are not available); Kco, carbon monoxide transfer coefficient; mMRC, modified Medical Research Council scale; RV, residual volume; SGRQ, St. George's Respiratory Questionnaire; TLC, total lung capacity; z score, standardized residual. * $P < 0.05$ vs. ever-smokers with COPD, # $P < 0.05$ vs. never-smoker control subjects, † $P < 0.05$ vs. ever-smoker control subjects.

Table 2. Comorbidities and use of medication among subjects with COPD

	Never-Smokers		Ever-Smokers		P Value
	COPD (n = 22)	Control (n = 22)	COPD (n = 22)	Control (n = 22)	
Comorbidities					
High blood pressure, n (%)	2 (9)	3 (14)	7 (32)	5 (23)	0.27
Diabetes, n (%)	0	0	3 (14)	1 (5)	0.19
Dyslipidemia, n (%)	2 (9)*	3 (14)	10 (45)	7 (32)	0.02
Osteoporosis, n (%)	0	0	2 (9)	0	0.24
Obstructive sleep apnea syndrome, n (%)	2 (9)	1 (5)	4 (18)	1 (5)	0.51
Gastroesophageal reflux, n (%)	0	0	2 (9)	0	0.24
Use of pulmonary medication, n (%)	1 (5)	0	1 (5)	0	1
Short-acting β_2 agonists, n (%)	0	0	0	0	
Long-acting β_2 agonists (LABA), n (%)	0	0	1 (5)	0	0.99
Combined LABA and inhaled corticosteroids, n (%)	0	0	0	0	
Short-acting anticholinergics, n (%)	1 (5)	0	0	0	0.99
Long-acting anticholinergics, n (%)	0	0	1 (5)	0	0.99
Theophylline, n (%)	0	0	0	0	
Inhaled corticosteroids, n (%)	0	0	0	0	

−1.64) whereas ever-smokers with COPD had altered DL_{CO} ($P < 0.05$ between the 2 groups).

Symptom-limited incremental cycle exercise. Comparisons between the two COPD groups showed that despite similar airflow obstruction at rest and similar heart rate (HR) and respiratory exchange ratio (RER) at peak exercise, ever-smokers had significantly lower peak work rate (WR) and peak oxygen consumption ($\dot{V}O_2$) than never-smokers (Table 3 and Fig. 2). Of note, never-smokers with COPD and their healthy counterparts without COPD had similar peak WR and peak $\dot{V}O_2$ (Table 3).

Regarding dynamic hyperinflation, the two groups with COPD had a greater reduction in IC during exercise than their healthy counterparts (Fig. 3), dynamic hyperinflation being found in 14 never-smokers with COPD (64%) and in 13 ever-smokers with COPD (59%). The main difference between the two COPD groups was that dynamic hyperinflation occurred for a lower WR in ever-smokers than in never-smokers. Respiratory rate (f)/minute ventilation (\dot{V}_E) slope as well as f/WR slope were greater in ever-smokers with COPD than in the other three groups. Dyspnea/WR slope

Table 3. Measurements at peak symptom-limited incremental cycle exercise

	Never-Smokers		Ever-Smokers		P Value		
	COPD (n = 22)	Control (n = 22)	COPD (n = 22)	Control (n = 22)	Interaction	COPD vs. control	Never-smokers vs. ever-smokers
Dyspnea, Borg scale	7.8 ± 2.2	8.4 ± 2.3	7.9 ± 2.1	9.0 ± 1.5	0.68	0.12	0.52
Leg discomfort, Borg scale	8.0 ± 2.1	8.2 ± 2.3	9.0 ± 1.5	8.5 ± 2.2	0.54	0.81	0.21
Reason for exercise discontinuation							
Leg discomfort	9 (41)	16 (73)	15 (68)	14 (64)			
Breathing discomfort	7 (32)	4 (18)	4 (18)	8 (36)			
Work rate, W (% pred)	173 ± 36 (89 ± 14)*	185 ± 51 (97 ± 20)	145 ± 44 (78 ± 20)#†	174 ± 38 (92 ± 18)	0.36	0.03	0.04
$\dot{V}O_2$, L/min (% predicted)	2.22 ± 0.46 (97 ± 15)*	2.47 ± 0.62 (110 ± 21)	1.91 ± 0.48 (87 ± 19)#†	2.30 ± 0.53 (104 ± 23)	0.52	0.006	0.03
RER	1.12 ± 0.09	1.13 ± 0.09	1.14 ± 0.09	1.16 ± 0.07	0.76	0.43	0.28
HR, % predicted maximum	98.6 ± 7.9	99.5 ± 9.0	95.3 ± 9.8	99.0 ± 9.0	0.48	0.23	0.32
O ₂ pulse, mL O ₂ /beat	13.6 ± 2.6	15.3 ± 3.3	12.3 ± 2.4#†	14.5 ± 3.4	0.6	0.004	0.081
PcapO ₂ , kPa	11.09 ± 1.13	11.71 ± 0.91	10.92 ± 1.30#†	11.93 ± 1.01	0.42	0.0009	0.91
PcapCO ₂ , kPa	4.59 ± 0.56	4.66 ± 0.52	4.84 ± 0.54	4.63 ± 0.59	0.25	0.55	0.36
\dot{V}_E , L/min (% estimated MVV)	85.9 ± 19.2 (99.3 ± 22.1)	93.7 ± 26.0 (75.3 ± 15.9)	76.8 ± 18.2 (89.5 ± 15.0)#†	93.1 ± 21.1 (75.5 ± 16.1)	0.36	0.01	0.29
f, breaths/min	35.8 ± 7.1	36.0 ± 8.1	36.9 ± 6.3	35.6 ± 5.9	0.61	0.72	0.79
V _T , L	2.44 ± 0.46*	2.60 ± 0.46	2.11 ± 0.46#†	2.63 ± 0.49	0.08	0.001	0.01
IC, L	3.35 ± 0.61	3.48 ± 0.55	3.08 ± 0.68†	3.57 ± 0.65	0.19	0.03	0.53
IRV, L	0.89 ± 0.37	0.88 ± 0.32	0.96 ± 0.45	0.95 ± 0.38	0.98	0.92	0.38
$\dot{V}_E/\dot{V}O_2$	39.2 ± 7.3	37.9 ± 5.3	41.1 ± 6.9	41.1 ± 7.0	0.65	0.64	0.08
$\dot{V}_E/\dot{V}CO_2$	34.6 ± 4.7	33.4 ± 3.7	36.1 ± 5.0	35.3 ± 5.1	0.79	0.32	0.09
V _D /V _T	0.23 ± 0.11	.23 ± 0.09	0.28 ± 0.08	0.27 ± 0.07	0.86	0.86	0.01

Values are means ± SD. Significant P values are in bold. COPD, chronic obstructive pulmonary disease; f, respiratory rate; HR, heart rate; IC, inspiratory capacity; IRV, inspiratory reserve volume; MVV, maximal voluntary ventilation; PcapCO₂, arterialized CO₂ partial pressure; PcapO₂, arterialized O₂ partial pressure; RER, respiratory exchange ratio; V_D, dead volume; \dot{V}_E , minute ventilation; $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalents for oxygen and carbon dioxide, respectively; $\dot{V}O_2$, oxygen uptake; V_T, tidal volume. * $P < 0.05$ vs. ever-smokers with COPD, # $P < 0.05$ vs. never-smoker control subjects, † $P < 0.05$ vs. ever-smoker control subjects.

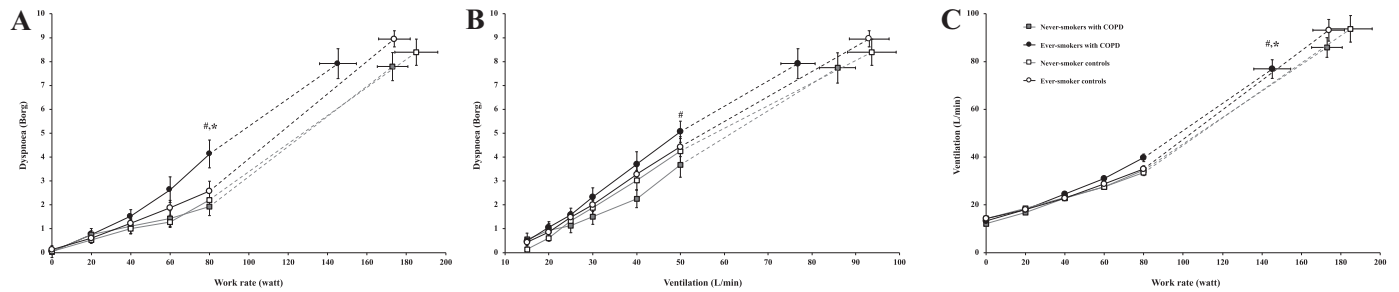


Fig. 2. Exertional dyspnea intensity during incremental cycle exercise testing is shown relative to work rate (A) and minute ventilation (B). Dyspnea-to-work rate and dyspnea-to-minute ventilation slopes were significantly different between ever-smokers with chronic obstructive lung disease (COPD) and never-smokers with COPD (repeated-measures analysis of variance). Of note, the relationship between work rate and minute ventilation was superimposed in all the groups (C). Values are means \pm SE. # $P < 0.05$ vs. never-smokers with COPD, * $P < 0.05$ vs. control subjects at a standardized work rate (Scheffé's test).

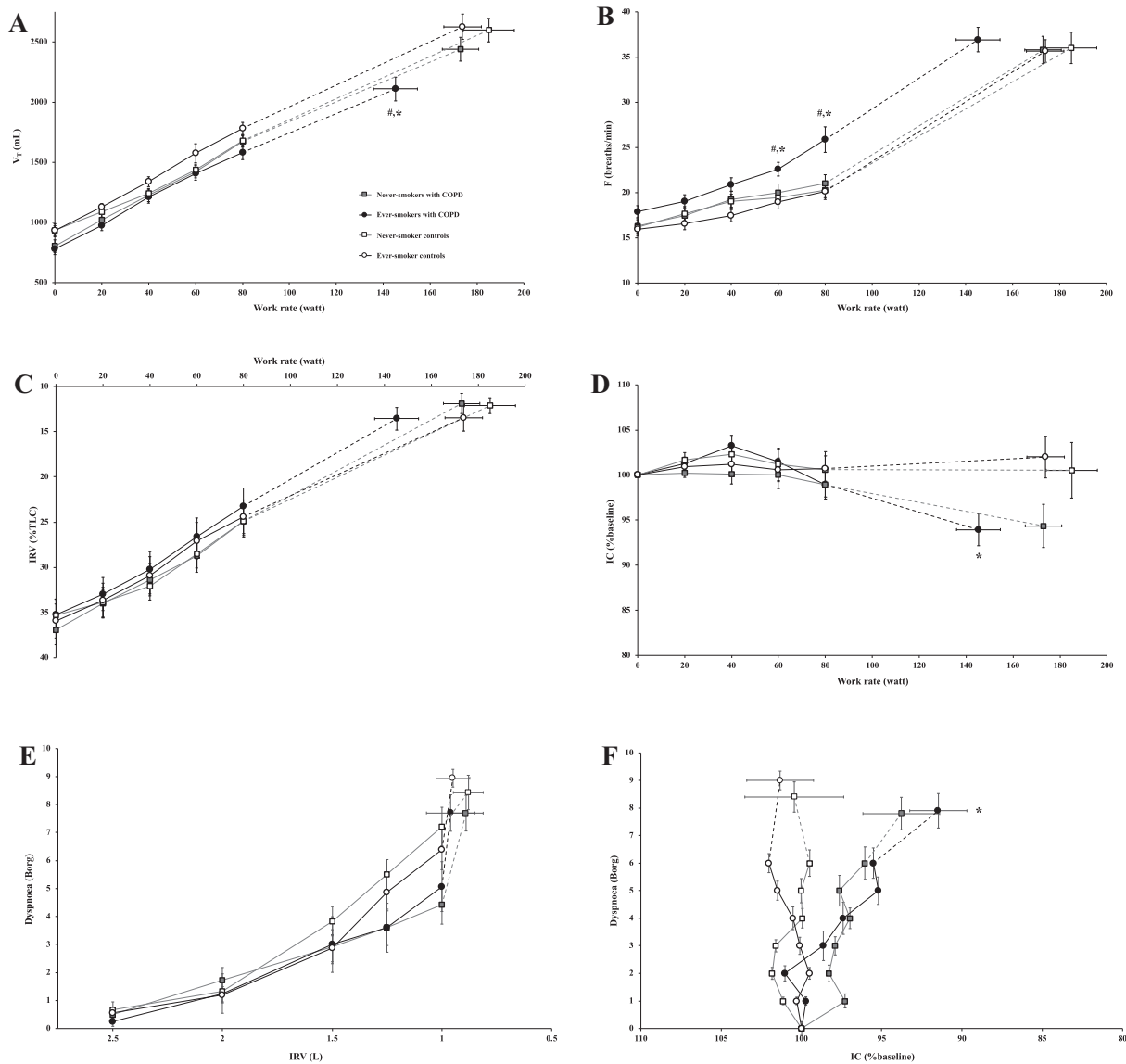


Fig. 3. A–D: tidal volume (V_T ; A), breathing frequency (F; B), inspiratory reserve volume [IRV, expressed as % of total lung capacity (TLC); C], and inspiratory capacity (IC, expressed as % of the value measured at rest during the exercise test; D) plotted in relation to work rate. E and F: dyspnea plotted in relation to IRV (E) and IC (expressed as % of the value measured at rest during the exercise test; F). Values are means \pm SE. # $P < 0.05$ vs. never-smokers with chronic obstructive lung disease (COPD), * $P < 0.05$ vs. control subjects at a standardized work rate (Scheffé's test).

Table 4. Measurements at the highest common work rate achieved by all study patients (80 W)

	Never-Smokers		Ever-Smokers		P Value		
	COPD (n = 22)	Control (n = 22)	COPD (n = 22)	Control (n = 22)	Interaction	COPD vs. control	Never-smokers vs. ever-smokers
Dyspnea, Borg scale	1.9 ± 1.4*	2.2 ± 1.5	4.1 ± 1.8#†	2.6 ± 1.8	0.04	0.15	0.004
Leg discomfort, Borg scale	2.6 ± 1.7*	2.6 ± 1.4	5.1 ± 2.9#†	3.0 ± 1.8	0.04	0.049	0.007
$\dot{V}O_2$, L/min (% predicted)	1.17 ± 0.09 (52 ± 9)	1.21 ± 0.11 (55 ± 10)	1.20 ± 0.13 (56 ± 10)	1.18 ± 0.13 (54 ± 9)	0.19	0.55	0.94
RER	0.93 ± 0.08	0.89 ± 0.08	0.96 ± 0.10	0.93 ± 0.09	0.79	0.07	0.06
HR, % predicted maximum	69.3 ± 9.5	68.1 ± 9.6	74.0 ± 9.1	72.2 ± 12.0	0.88	0.49	0.05
O ₂ pulse, mL O ₂ /beat	10.4 ± 1.4	11.2 ± 1.7	10.2 ± 1.3	10.4 ± 1.8	0.45	0.14	0.11
SpO ₂ , %	97.0 ± 1.5	97.8 ± 0.9	97.1 ± 1.4	97.8 ± 1.1	0.23	0.16	0.45
$\dot{V}E$, L/min (% estimated MVV)	34.5 ± 6.0 (42.8 ± 19.5)*	33.5 ± 5.7 (28.2 ± 8.9)	39.7 ± 7.5 (49.0 ± 18.3)#†	35.1 ± 5.8 (29.2 ± 7.9)	0.18	0.04	0.01
f, breaths/min	21.0 ± 4.5*	20.2 ± 3.8	25.9 ± 6.6#†	20.1 ± 4.2	0.02	0.003	0.03
V _T , L	1.67 ± 0.22	1.68 ± 0.22	1.58 ± 0.28†	1.78 ± 0.24	0.06	0.048	0.91
IC, L	3.53 ± 0.64	3.51 ± 0.63	3.28 ± 0.85	3.53 ± 0.57	0.39	0.46	0.47
IRV, L	1.86 ± 0.60	1.83 ± 0.63	1.70 ± 0.84	1.75 ± 0.56	0.77	0.94	0.42
$\dot{V}E/\dot{V}O_2$	29.7 ± 5.6*	27.6 ± 3.2	33.3 ± 6.7#†	29.8 ± 5.0	0.53	0.01	0.01
$\dot{V}E/\dot{V}CO_2$	31.8 ± 4.3*	31.0 ± 2.8	34.5 ± 4.7#†	31.9 ± 3.4	0.27	0.04	0.03

Values are means ± SD. Significant *P* values are in bold. COPD, chronic obstructive pulmonary disease; f, respiratory rate; HR, heart rate; IC, inspiratory capacity; IRV, inspiratory reserve volume; MVV, maximal voluntary ventilation; RER, respiratory exchange ratio; SpO₂, oxygen saturation; $\dot{V}E$, minute ventilation; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalents for carbon dioxide; $\dot{V}O_2$, oxygen uptake; V_T, tidal volume. **P* < 0.05 vs. ever-smokers with COPD, #*P* < 0.05 vs. never-smoker control subjects, †*P* < 0.05 vs. ever-smoker control subjects.

was also significantly greater in ever-smokers with COPD compared with the other three groups. In particular, Borg scale rating at 80 W was higher by >1 unit in ever-smokers with COPD than in the other three groups (Fig. 2 and Table 4). Moreover, Borg scale ratings as a function of $\dot{V}E$ were similar in never-smokers with COPD and control subjects, whereas they were increased in ever-smokers with COPD (Fig. 2 and Table 5). Finally, the V_T/ $\dot{V}E$ inflection point occurred at lower V_T and $\dot{V}E$ in ever-smokers with COPD than in the other three groups (Fig. 4).

Regarding ventilatory efficiency, $\dot{V}E/\dot{V}CO_2$ nadir was modestly but significantly higher (i.e., poorer) in ever-smokers with COPD than in never-smokers with COPD (32.8 ± 3.9 vs. 30.3 ± 4.1, respectively; *P* < 0.05) (Fig. 5), and the V_D-to-V_T ratio also tended to be higher (i.e., poorer) in ever-smokers with COPD than in never-smokers with COPD (*P* = 0.06; Table 3). Of note, never-smokers with COPD and their healthy counterparts had similar $\dot{V}E/\dot{V}CO_2$ nadir and V_D-to-V_T ratio. In addition, the $\dot{V}E$ -

$\dot{V}CO_2$ intercept and $\dot{V}E$ - $\dot{V}CO_2$ slope were not significantly different among patients with COPD and control subjects (Fig. 5).

Functional correlates of ventilatory efficiency and dyspnea. Correlations were calculated on the entire population (*n* = 88). Lower DL_{CO} z score was associated with higher $\dot{V}E/\dot{V}CO_2$ nadir (*r* = −0.62, *P* < 0.001) and higher V_D/V_T at peak exercise (*r* = −0.36, *P* < 0.05) (Fig. 6). There was no correlation between IC (% baseline) measured at peak exercise and ventilatory inefficiency. However, there was a significant correlation between IC (% baseline) measured at 80 W (the highest work rate achieved by all patients) and $\dot{V}E/\dot{V}CO_2$ nadir (*r* = −0.48; *P* < 0.01). In multivariate analysis, DL_{CO} z score (*β* = −0.98, *P* < 0.001) and IC (% baseline) measured at 80 W (*β* = −1.75, *P* < 0.01) were independently associated with ventilatory efficiency.

Correlations with dyspnea intensity (Borg scale) measured at 80 W were DL_{CO} z score (*r* = −0.35), rate of uptake of CO from alveolar gas (K_{CO}) z score (*r* = −0.24), and $\dot{V}E/\dot{V}CO_2$ nadir (*r* = 0.27) (all *P* < 0.05).

Table 5. Measurements at highest common ventilation rate (50 L/min)

	Never-Smokers		Ever-Smokers		P Value		
	COPD (n = 22)	Control (n = 22)	COPD (n = 22)	Control (n = 22)	Interaction	COPD vs. control	Never-smokers vs. ever-smokers
Dyspnea, Borg scale	3.7 ± 1.9	4.3 ± 2.1	5.1 ± 1.5	4.4 ± 1.8	0.23	0.97	0.12
Leg discomfort, Borg scale	4.4 ± 2.3	4.9 ± 1.9	5.8 ± 2.7	4.9 ± 2.1	0.28	0.81	0.20
$\dot{V}O_2$, L/min (% predicted)	1.59 ± 0.25 (70 ± 11)	1.72 ± 0.23 (77 ± 6)	1.49 ± 0.25 (69 ± 13)	1.62 ± 0.22 (74 ± 13)	0.99	0.05	0.06
RER	1.03 ± 0.06	0.99 ± 0.09	1.03 ± 0.08	1.01 ± 0.08	0.69	0.14	0.59
HR, % predicted maximum	80.9 ± 8.2	80.5 ± 10.3	82.7 ± 8.0	82.6 ± 9.7	0.96	0.9	0.33
O ₂ pulse, mL O ₂ /beat	12.1 ± 2.1	13.4 ± 2.2	11.2 ± 1.8	12.4 ± 2.4	0.95	0.06	0.07
f, breaths/min	23.8 ± 4.8*	23.4 ± 3.9	27.9 ± 5.4#†	23.7 ± 3.5	0.06	0.02	0.03
IRV, L	1.20 ± 0.48	1.32 ± 0.44	1.33 ± 0.64	1.41 ± 0.49	0.85	0.39	0.37
IC, L	3.40 ± 0.62	3.53 ± 0.57	3.20 ± 0.78	3.54 ± 0.59	0.46	0.11	0.53
V _T , L	2.18 ± 0.42*	2.19 ± 0.35	1.86 ± 0.33#†	2.16 ± 0.33	0.07	0.04	0.03

Values are means ± SD. Significant *P* values are in bold. COPD, chronic obstructive pulmonary disease; f, respiratory rate; HR, heart rate; IC, inspiratory capacity; IRV, inspiratory reserve volume; RER, respiratory exchange ratio; $\dot{V}O_2$, oxygen uptake; V_T, tidal volume. **P* < 0.05 vs. ever-smokers with COPD, #*P* < 0.05 vs. never-smoker control subjects, †*P* < 0.05 vs. ever-smoker control subjects.

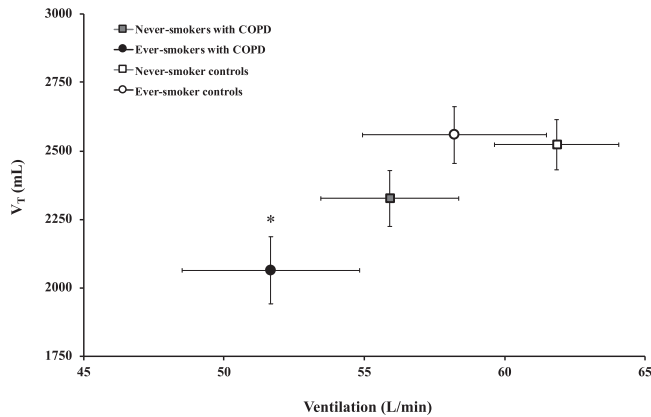


Fig. 4. On evaluation of individual plots of minute ventilation (\dot{V}_E) vs. tidal volume (V_T) (Hey plots), the group of asymptomatic subjects with airway obstruction had an inflection point of the relationship between V_T and \dot{V}_E between those of control subjects and those of never-smokers with chronic obstructive lung disease (COPD) with controls. By contrast, the inflection point occurred at a lower V_T for a lower \dot{V}_E in ever-smokers with COPD compared with control subjects ($P < 0.05$). Graphs represent mean \pm SE values. * $P < 0.05$ vs. control subjects.

DISCUSSION

This is the first study comparing responses to exercise between never-smokers with occupational COPD and individuals with

smoking-related COPD, all at mild to moderate stages. The main findings are that despite having similar airway obstruction, 1) never-smokers with occupational COPD have better exercise capacity and exercise tolerance than individuals with smoking-related COPD; 2) these two COPD groups developed similar dynamic hyperinflation, but hyperinflation occurred at a higher work rate in never-smokers with occupational COPD; and 3) better ventilatory efficiency and less dyspnea in never-smokers with COPD is explained at least in part by a preserved DL_{CO} .

In patients with mild COPD secondary to tobacco smoking, the respiratory system reaches its physiological limit at lower peak work rate and ventilation than in smokers without pulmonary disease (7). This limitation is attributed at least in part to dynamic hyperinflation leading to mechanical constraint of the respiratory system during exercise (19). In the presence of airway obstruction, dynamic hyperinflation is mainly due to the inability of patients to empty their lungs because of too short a time available for expiration when frequency of breathing increases during exercise (20). In patients with smoking-related COPD, poor ventilatory efficiency leads to an increased ventilatory demand for a given exercise power, thus contributing to increase frequency of breathing and dynamic hyperinflation (19). In these patients, more extensive emphysema and lower DL_{CO} are two independent factors associated with ventilatory inefficiency during exercise and poor exercise tolerance (10, 16). Our observation that despite having similar dynamic

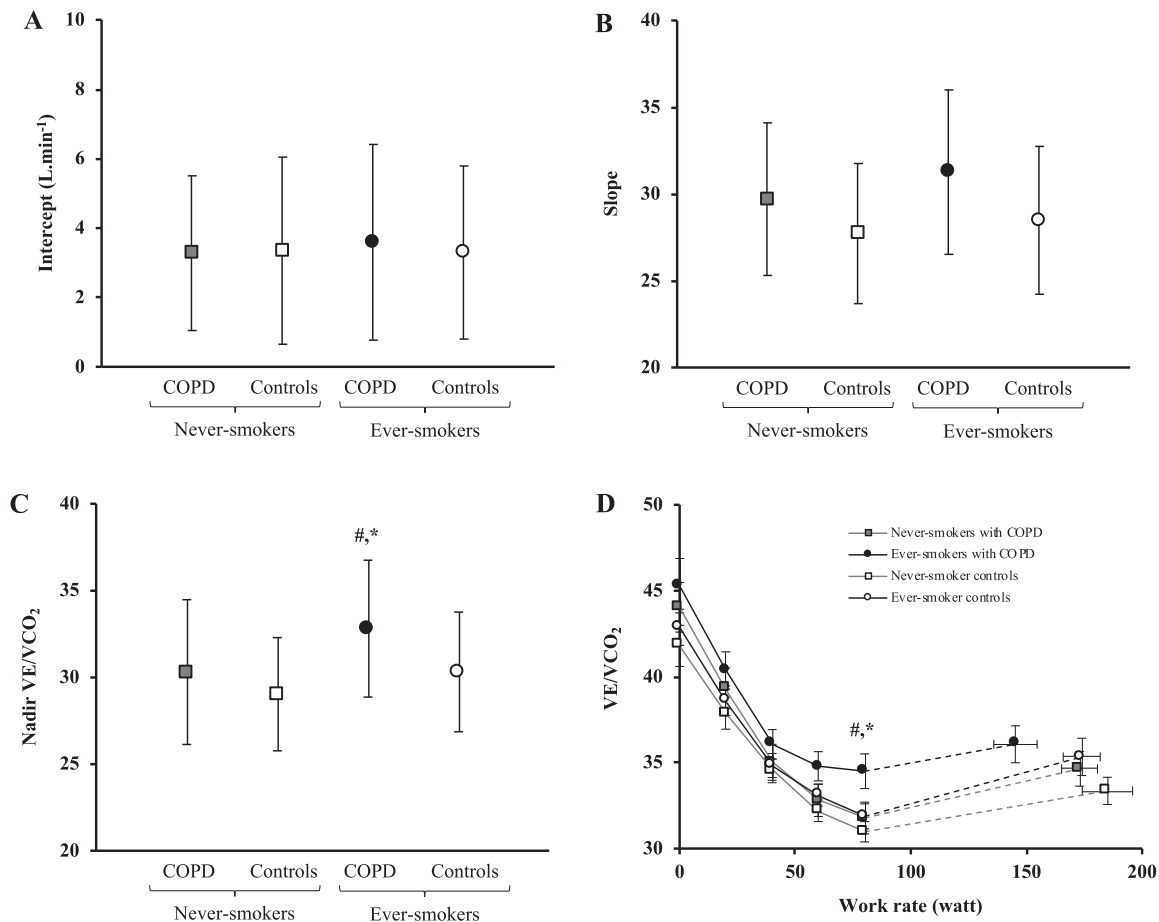


Fig. 5. A–C: ventilation [minute ventilation (\dot{V}_E)]–carbon dioxide output (\dot{V}_{CO_2}) intercept (A), \dot{V}_E – \dot{V}_{CO_2} slope (B), and \dot{V}_E/\dot{V}_{CO_2} nadir (C). D: \dot{V}_E/\dot{V}_{CO_2} plotted in relation to work rate. Values are means \pm SE. # $P < 0.05$ vs. never-smokers with chronic obstructive lung disease (COPD), * $P < 0.05$ vs. control subjects.

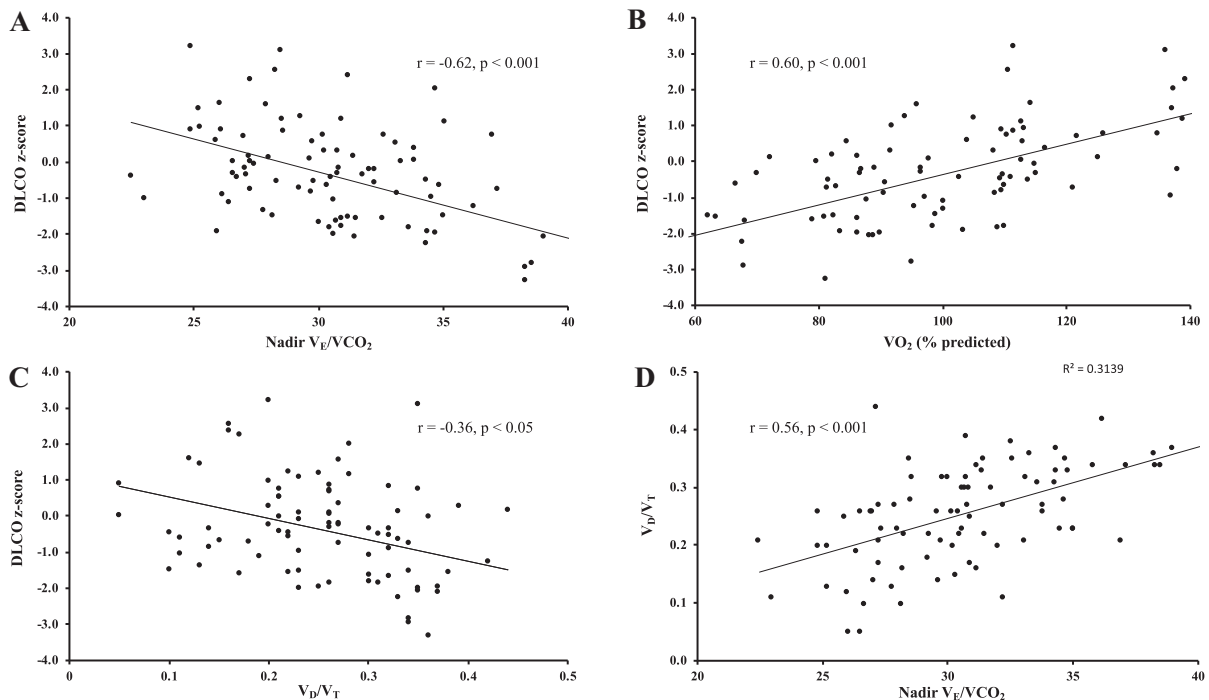


Fig. 6. Correlates of lower lung diffusion for carbon monoxide (DL_{CO}) and higher ventilatory efficiency [ventilation (\dot{V}_E)/carbon dioxide output (\dot{V}_{CO_2}) nadir; A], lower peak oxygen uptake (\dot{V}_{O_2}) (B), and higher dead space (V_D)-to-tidal volume (V_T) ratio (C). D: correlates of higher \dot{V}_E/\dot{V}_{CO_2} ventilatory efficiency and higher V_D/V_T .

hyperinflation nonsmoking patients with occupational mild to moderate COPD have better exercise capacity and tolerance compared with their counterparts with smoking-related COPD deserves several comments. First, nonsmokers with occupational COPD had a frequency of breathing that was significantly lower at a given exercise power than their smoker counterparts. Despite similar airway obstruction, patients with occupational COPD had therefore a longer time available for expiration (and thus less hyperinflation) at a given exercise power. At peak exercise, both COPD groups had similar frequency of breathing (and similar hyperinflation), but peak power was significantly higher in nonsmokers. Second, nonsmokers with COPD had preserved ventilatory efficiency as assessed by \dot{V}_E -to- \dot{V}_{CO_2} ratio and had therefore a “normal” ventilatory demand for a given exercise power. This “normal” ventilatory demand is likely to explain in part why patients with occupational COPD had similar breathing frequency at a given work rate compared with the

healthy control subjects. Although we did not quantify emphysema by computed tomography (CT) scan, our comparison of two groups of mild-to-moderate COPD patients with strictly similar airway obstruction and resting lung volumes also suggests that preserved DL_{CO} (and thus presumably less extensive emphysema) was the main driver of preserved ventilatory efficiency and lower exertional dyspnea in nonsmokers. Using another approach that consisted of analyzing a large group of unselected patients with COPD across the severity spectrum of the disease, Elbehairy et al. (11) also found that low resting DL_{CO} was associated with increased intensity of exertional dyspnea and lower exercise capacity, independently of the degree of airflow obstruction and resting hyperinflation. Our present results add valuable knowledge, as we demonstrate that patients with occupational mild to moderate COPD and preserved DL_{CO} had exertional dyspnea and exercise capacity strictly similar to healthy control subjects.

Table 6. Measurement at ventilatory threshold

	Never-Smokers		Ever-Smokers		P Value		
	COPD (n = 22)	Control (n = 22)	COPD (n = 22)	Control (n = 22)	Interaction	COPD vs. control	Never-smokers vs. ever-smokers
Work rate, % predicted	53 ± 12	62 ± 10	44 ± 11#†	55 ± 14	0.85	0.001	0.001
HR, % predicted maximum	75 ± 9	78 ± 8	74 ± 8	78 ± 9	0.86	0.07	0.76
\dot{V}_{O_2} , L/min	1.43 ± 0.34	1.66 ± 0.35	1.22 ± 0.26#†	1.46 ± 0.37	0.95	0.001	0.005
RER	0.97 ± 0.05	0.97 ± 0.06	0.96 ± 0.08	0.96 ± 0.06	0.80	0.91	0.38
f, breaths/min	22.8 ± 5.4	22.7 ± 3.9	23.8 ± 2.9	21.2 ± 3.7	0.17	0.11	0.76
\dot{V}_E , L/min	42.8 ± 10.6	47.1 ± 9.2	38.2 ± 6.0	42.7 ± 10.7	0.95	0.03	0.03

Values are means ± SD. Significant P values are in bold. COPD, chronic obstructive pulmonary disease; f, respiratory rate; HR, heart rate; RER, respiratory exchange ratio; \dot{V}_E , minute ventilation; \dot{V}_{O_2} , oxygen uptake. #P < 0.05 vs. never-smoker control subjects, †P < 0.05 vs. ever-smoker control subjects.

A potential link between preserved DL_{CO} and ventilatory efficiency may be preserved pulmonary capillary blood volume and, therefore, normal diffusion capacity during exercise (36). It has been suggested that pulmonary and systemic endothelial and/or microvascular abnormalities may coexist in smokers with low DL_{CO} (39). As systemic vascular dysfunction in patients with COPD secondary to organic dust exposure is less frequent than in patients with COPD due to tobacco smoking (33), it is plausible that pulmonary vascular dysfunction is also less frequent.

Although COPD in never-smokers is now recognized, optimal therapeutic management of COPD in never-smokers is poorly studied. A proportion as high as 20–30% of patients diagnosed with COPD have never smoked (17, 34). Indoor and outdoor air pollutants as well as occupational hazards, including exposure to organic dusts, have been associated with an increased risk of COPD (4). Although to a lesser extent than in ever-smokers, COPD has been associated with a reduction in life expectancy in never-smokers (28, 37). Despite this burden, therapeutic COPD trials have systematically excluded patients who have never smoked, and the role of COPD medications (in particular bronchodilators) and their benefit in never-smoking COPD remains therefore to be explored. Exposing the physiological traits of COPD in never-smokers, as attempted in the present study, might help to answer these questions. Further studies are needed to determine the need for long-acting bronchodilators in never-smokers with COPD at mild stages.

Strengths and limitations of the study. Our study population was carefully selected to control as far as possible for confounders that could interfere with the results. Our two groups of COPD patients were carefully matched for age, sex, FEV₁, and FEV₁/FVC, as these factors can influence dyspnea (23). We also excluded subjects with cardiac comorbidities. This is important, because chronic heart failure and COPD frequently coexist (35), and dynamic hyperinflation during exercise has been reported in patients with chronic heart failure and normal spirometry (6). In our study, significant cardiac impairment was unlikely to have contributed to dyspnea and/or to dynamic hyperinflation since heart rate responses, O₂ pulse at peak exercise, and blood pressure measurements were similar in both COPD groups.

There are some limitations in our study. First, we did not record any information on usual physical activity. However, work rate, $\dot{V}O_2$, heart rate, and breath frequency at ventilatory threshold were similar in both groups (Table 6), suggesting that deconditioning, if any, was also similar. Second, high-resolution CT (HRCT) was not available, and we were unable to evaluate the extent of emphysema. Third, the fact that patients only exposed to organic dusts were labeled “never-smokers” may be open to discussion. However, organic dust exposure is one of the first causes of COPD in never-smokers, and patients have already been labeled in this way in previous studies (34).

Conclusions. Although they develop dynamic hyperinflation at peak exercise, never-smokers with mild to moderate COPD have preserved exercise capacities and lower exertional dyspnea than smoking-related COPD patients matched for severity of airflow limitation. These differences may be in part driven by a better ventilatory efficiency stemming from a preserved diffusion capacity. This suggests that the two COPD groups should not be managed the same way, in particular regarding prescription of bronchodilators. Also, this reinforces the need to

establish phenotypical differences among COPD patients. Further studies are needed to define appropriate COPD management in never-smokers.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

T.S. and B.D. conceived and designed research; T.S. and B.D. performed experiments; T.S. and A.G. analyzed data; T.S., N.R., and B.D. interpreted results of experiments; T.S. prepared figures; T.S. drafted manuscript; T.S., A.G., N.R., J.C.D., and B.D. edited and revised manuscript; T.S., A.G., N.R., J.C.D., and B.D. approved final version of manuscript.

REFERENCES

1. Aguilaniu B, Maitre J, Diab S, Perrault H, Péronnet F. Detection of disturbances in pulmonary gas exchanges during exercise from arterialized ear-lobe PO₂. *Respir Physiol Neurobiol* 177: 30–35, 2011. doi:10.1016/j.resp.2011.03.005.
2. Basinas I, Sigsgaard T, Erlandsen M, Andersen NT, Takai H, Heederik D, Omland Ø, Kromhout H, Schlünssen V. Exposure-affecting factors of dairy farmers' exposure to inhalable dust and endotoxin. *Ann Occup Hyg* 58: 707–723, 2014. doi:10.1093/annhyg/meu024.
3. Behrendt CE. Mild and moderate-to-severe COPD in nonsmokers: distinct demographic profiles. *Chest* 128: 1239–1244, 2005. doi:10.1378/chest.128.3.1239.
4. Blanc PD, Annesi-Maesano I, Balmes JR, Cummings KJ, Fishwick D, Miedinger D, Murgia N, Naidoo RN, Reynolds CJ, Sigsgaard T, Torén K, Vinnikov D, Redlich CA. The occupational burden of nonmalignant respiratory diseases. An Official American Thoracic Society and European Respiratory Society Statement. *Am J Respir Crit Care Med* 199: 1312–1334, 2019. doi:10.1164/rccm.201904-0717ST.
5. Camp PG, Ramirez-Venegas A, Sansores RH, Alva LF, McDougall JE, Sin DD, Paré PD, Müller NL, Silva CI, Rojas CE, Coxson HO. COPD phenotypes in biomass smoke- versus tobacco smoke-exposed Mexican women. *Eur Respir J* 43: 725–734, 2014. doi:10.1183/09031936.00206112.
6. Chiari S, Torregiani C, Boni E, Bassini S, Vizzardi E, Tantucci C. Dynamic pulmonary hyperinflation occurs without expiratory flow limitation in chronic heart failure during exercise. *Respir Physiol Neurobiol* 189: 34–41, 2013. doi:10.1016/j.resp.2013.06.017.
7. Chin RC, Guenette JA, Cheng S, Raghavan N, Amornputtisathaporn N, Cortés-Télles A, Webb KA, O'Donnell DE. Does the respiratory system limit exercise in mild chronic obstructive pulmonary disease? *Am J Respir Crit Care Med* 187: 1315–1323, 2013. doi:10.1164/rccm.201211-1970OC.
8. Degano B, Bouhaddi M, Laplante JJ, Botebol M, Annesi-Maesano I, Marescaux A, Roux P, Thaon I, Wolf JP, Regnard J, Dalphin JC. [COPD in dairy farmers: screening, characterization and constitution of a cohort. The BALISTIC study]. *Rev Mal Respir* 29: 1149–1156, 2012. doi:10.1016/j.rmr.2012.08.007.
9. Eduard W, Pearce N, Douwes J. Chronic bronchitis, COPD, and lung function in farmers: the role of biological agents. *Chest* 136: 716–725, 2009. doi:10.1378/chest.08-2192.
10. Elbehairy AF, Faisal A, Guenette JA, Jensen D, Webb KA, Ahmed R, Nader JA, O'Donnell DE; Canadian Respiratory Research Network (CRRN). Resting physiological correlates of reduced exercise capacity in

- smokers with mild airway obstruction. *COPD* 14: 267–275, 2017. doi:10.1080/15412555.2017.1281901.
11. Elbehairy AF, O'Donnell CD, Abd Elhameed A, Vincent SG, Milne KM, James MD, Webb KA, Neder JA, O'Donnell DE; Canadian Respiratory Research Network. Low resting diffusion capacity, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. *J Appl Physiol* (1985) 127: 1107–1116, 2019. doi:10.1152/jappphysiol.00341.2019.
 12. Graham BL, Brusasco V, Burgos F, Cooper BG, Jensen R, Kendrick A, MacIntyre NR, Thompson BR, Wanger J. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J* 49: 1600016, 2017 [Erratum in *Eur Respir J* 52: 1650016, 2018]. doi:10.1183/13993003.00016-2016.
 13. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, Hallstrand TS, Kaminsky DA, McCarthy K, McCormack MC, Oropez CE, Rosenfeld M, Stanojevic S, Swanney MP, Thompson BR. Standardization of spirometry 2019 update. An Official American Thoracic Society and European Respiratory Society technical statement. *Am J Respir Crit Care Med* 200: e70–e88, 2019. doi:10.1164/rccm.201908-1590ST.
 14. Guillien A, Soumagne T, Dalphin JC, Degano B. COPD, airflow limitation and chronic bronchitis in farmers: a systematic review and meta-analysis. *Occup Environ Med* 76: 58–68, 2019. doi:10.1136/oemed-2018-105310.
 15. Hey EN, Lloyd BB, Cunningham DJ, Jukes MG, Bolton DP. Effects of various respiratory stimuli on the depth and frequency of breathing in man. *Respir Physiol* 1: 193–205, 1966. doi:10.1016/0034-5687(66)90016-8.
 16. Jones JH, Zelt JT, Hirai DM, Diniz CV, Zaza A, O'Donnell DE, Neder JA. Emphysema on thoracic CT and exercise ventilatory inefficiency in mild-to-moderate COPD. *COPD* 14: 210–218, 2017. doi:10.1080/15412555.2016.1253670.
 17. Lamprecht B, McBurnie MA, Vollmer WM, Gudmundsson G, Welte T, Nizankowska-Mogilnicka E, Studnicka M, Bateman E, Anto JM, Burney P, Mannino DM, Buist SA; BOLD Collaborative Research Group. COPD in never smokers: results from the population-based burden of obstructive lung disease study. *Chest* 139: 752–763, 2011. doi:10.1378/chest.10-1253.
 18. Laveneziana P, Webb KA, Ora J, Wadell K, O'Donnell DE. Evolution of dyspnea during exercise in chronic obstructive pulmonary disease: impact of critical volume constraints. *Am J Respir Crit Care Med* 184: 1367–1373, 2011. doi:10.1164/rccm.201106-1128OC.
 19. Neder JA, Arbex FF, Alencar MC, O'Donnell CD, Cory J, Webb KA, O'Donnell DE. Exercise ventilatory inefficiency in mild to end-stage COPD. *Eur Respir J* 45: 377–387, 2015. doi:10.1183/09031936.00135514.
 20. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 164: 770–777, 2001. doi:10.1164/ajrccm.164.5.2012122.
 21. Ofir D, Laveneziana P, Webb KA, Lam YM, O'Donnell DE. Mechanisms of dyspnea during cycle exercise in symptomatic patients with GOLD stage I chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 177: 622–629, 2008. doi:10.1164/rccm.200707-1064OC.
 22. Palange P, Ward SA, Carlsen KH, Casaburi R, Gallagher CG, Gosselink R, O'Donnell DE, Puente-Maestu L, Schols AM, Singh S, Whipp BJ; ERS Task Force. Recommendations on the use of exercise testing in clinical practice. *Eur Respir J* 29: 185–209, 2007. doi:10.1183/09031936.00046906.
 23. Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, Calverley PM, Gift AG, Harver A, Lareau SC, Mahler DA, Meek PM, O'Donnell DE; American Thoracic Society Committee on Dyspnea. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 185: 435–452, 2012. doi:10.1164/rccm.201111-2042ST.
 24. Poole JA, Romberger DJ. Immunological and inflammatory responses to organic dust in agriculture. *Curr Opin Allergy Clin Immunol* 12: 126–132, 2012. doi:10.1097/ACI.0b013e3283511d0e.
 25. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J, Stocks J; ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 40: 1324–1343, 2012. doi:10.1183/09031936.00080312.
 26. Robertson HT. Dead space: the physiology of wasted ventilation. *Eur Respir J* 45: 1704–1716, 2015 [Erratum in *Eur Respir J* 46: 1226, 2015]. doi:10.1183/09031936.00137614.
 27. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *Lancet* 374: 733–743, 2009. doi:10.1016/S0140-6736(09)61303-9.
 28. Shavelle RM, Paculdo DR, Kush SJ, Mannino DM, Strauss DJ. Life expectancy and years of life lost in chronic obstructive pulmonary disease: findings from the NHANES III Follow-up Study. *Int J Chron Obstruct Pulmon Dis* 4: 137–148, 2009. doi:10.2147/COPD.S5237.
 29. Singh D, Agustí A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Criner GJ, Frith P, Halpin DM, Han M, López Varela MV, Martínez F, Montes de Oca M, Papi A, Pavord ID, Roche N, Sin DD, Stockley R, Vestbo J, Wedzicha JA, Vogelmeier C. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. *Eur Respir J* 53: 1900164, 2019. doi:10.1183/13993003.00164-2019.
 30. Soumagne T, Degano B, Guillien A, Annesi-Maesano I, Andujar P, Hue S, Adotevi O, Jouneau S, Botebol M, Laplante JJ, Roche N, Dalphin JC. Characterization of chronic obstructive pulmonary disease in dairy farmers. *Environ Res* 188: 109847, 2020. doi:10.1016/j.envres.2020.109847.
 31. Soumagne T, Guillien A, Roux P, Laplante JJ, Botebol M, Laurent L, Roche N, Dalphin JC, Degano B. Quantitative and qualitative evaluation of spirometry for COPD screening in general practice. *Respir Med Res* 77: 31–36, 2020. doi:10.1016/j.resmer.2019.07.004.
 32. Soumagne T, Laveneziana P, Veil-Picard M, Guillien A, Claudé F, Puyraveau M, Annesi-Maesano I, Roche N, Dalphin JC, Degano B. Asymptomatic subjects with airway obstruction have significant impairment at exercise. *Thorax* 71: 804–811, 2016. doi:10.1136/thoraxjnl-2015-207953.
 33. Soumagne T, Roche N, Guillien A, Bouhaddi M, Rocchi S, Hue S, Claudé F, Bizard L, Andujar P, Dalphin JC, Degano B. Cardiovascular risk in COPD: deciphering the contribution of tobacco smoking. *Chest* 157: 834–845, 2020. doi:10.1016/j.chest.2019.11.002.
 34. Tan WC, Sin DD, Bourbeau J, Hernandez P, Chapman KR, Cowie R, Fitzgerald JM, Marciniuk DD, Maltais F, Buist AS, Road J, Hogg JC, Kirby M, Coxson H, Hague C, Leipsic J, O'Donnell DE, Aaron SD; CanCOLD Collaborative Research Group. Characteristics of COPD in never-smokers and ever-smokers in the general population: results from the CanCOLD study. *Thorax* 70: 822–829, 2015. doi:10.1136/thoraxjnl-2015-206938.
 35. Tavazzi L, Swedberg K, Komajda M, Böhm M, Borer JS, Lainscak M, Robertson M, Ford I; SHIFT Investigators. Clinical profiles and outcomes in patients with chronic heart failure and chronic obstructive pulmonary disease: an efficacy and safety analysis of SHIFT study. *Int J Cardiol* 170: 182–188, 2013. doi:10.1016/j.ijcard.2013.10.068.
 36. Tedjasaputra V, van Diepen S, Phillips DB, Wong EY, Bhutani M, Michaelchuk WW, Bryan TL, Stickland MK. Pulmonary capillary blood volume response to exercise is diminished in mild chronic obstructive pulmonary disease. *Respir Med* 145: 57–65, 2018. doi:10.1016/j.rmed.2018.10.015.
 37. Thomsen M, Nordestgaard BG, Vestbo J, Lange P. Characteristics and outcomes of chronic obstructive pulmonary disease in never smokers in Denmark: a prospective population study. *Lancet Respir Med* 1: 543–550, 2013. doi:10.1016/S2213-2600(13)70137-1.
 38. Veil-Picard M, Soumagne T, Vongthilath R, Annesi-Maesano I, Guillien A, Laurent L, Andujar P, Roche N, Jouneau S, Cypriani B, Laplante JJ, Degano B, Dalphin JC. Is atopy a risk indicator of chronic obstructive pulmonary disease in dairy farmers? *Respir Res* 20: 124, 2019. doi:10.1186/s12931-019-1082-2.
 39. Walter Barbosa G, Neder JA, Utida K, O'Donnell DE, de Tarso Müller P. Impaired exercise ventilatory efficiency in smokers with low transfer factor but normal spirometry. *Eur Respir J* 49: 1602511, 2017. doi:10.1183/13993003.02511-2016.
 40. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Casaburi R, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson D, Macintyre N, McKay R, Miller MR, Navajas D, Pellegrino R, Viegi G. Standardisation of the measurement of lung volumes. *Eur Respir J* 26: 511–522, 2005. doi:10.1183/09031936.05.00035005.