CrossMark

Mechanisms of exertional dyspnoea in symptomatic smokers without COPD

Amany F. Elbehairy^{1,2}, Jordan A. Guenette³, Azmy Faisal^{1,4}, Casey E. Ciavaglia¹, Katherine A. Webb¹, Dennis Jensen⁵, Andrew H. Ramsook³, J. Alberto Neder¹ and Denis E. O'Donnell¹ on behalf of the Canadian Respiratory Research Network

Affiliations: ¹Respiratory Investigation Unit, Department of Medicine, Queen's University and Kingston General Hospital, Kingston, ON, Canada. ²Dept of Chest Diseases, Faculty of Medicine, Alexandria University, Alexandria, Egypt. ³Dept of Physical Therapy and UBC Centre for Heart Lung Innovation, University of British Columbia and St. Paul's Hospital, Vancouver, BC, Canada. ⁴Faculty of Physical Education for Men, Alexandria University, Alexandria, Egypt. ⁵Dept of Kinesiology & Physical Education, McGill University, Montreal, QC, Canada.

Correspondence: Denis O'Donnell, 102 Stuart Street, Kingston, Ontario, Canada K7L 2V6.
E-mail: odonnell@queensu.ca

ABSTRACT Dyspnoea and activity limitation can occur in smokers who do not meet spirometric criteria for chronic obstructive pulmonary disease (COPD) but the underlying mechanisms are unknown.

Detailed pulmonary function tests and sensory-mechanical relationships during incremental exercise with respiratory pressure measurements and diaphragmatic electromyography (EMG_{di}) were compared in 20 smokers without spirometric COPD and 20 age-matched healthy controls.

Smokers (mean±SD post-bronchodilator forced expiratory volume in 1 s (FEV₁)/forced vital capacity 75±4%, mean±SD FEV₁ 104±14% predicted) had greater activity-related dyspnoea, poorer health status and lower physical activity than controls. Smokers had peripheral airway dysfunction: higher phase-III nitrogen slopes (3.8±1.8 *versus* 2.6±1.1%·L⁻¹) and airway resistance (difference between airway resistance measured at 5 Hz and 20 Hz 19±11 *versus* 12±7% at 5 Hz) than controls (*p*<0.05). Smokers had significantly (*p*<0.05) lower peak oxygen uptake (78±40 *versus* 107±45% predicted) and ventilation (61±26 *versus* 97±29 L·min⁻¹). Exercise ventilatory requirements, operating lung volumes and cardio-circulatory responses were similar. However, submaximal dyspnoea ratings, resistive and total work of breathing were increased in smokers compared with controls (*p*<0.05); diaphragmatic effort (transdiaphragmatic pressure/maximal transdiaphragmatic pressure) and fractional inspiratory neural drive to the diaphragm (EMG_{di}/maximal EMG_{di}) were also increased (*p*<0.05) mainly reflecting the reduced denominator.

Symptomatic smokers at risk for COPD had greater exertional dyspnoea and lower exercise tolerance compared with healthy controls in association with greater airways resistance, contractile diaphragmatic effort and fractional inspiratory neural drive to the diaphragm.

@ERSpublications

Exertional dyspnoea in smokers without COPD is linked to higher inspiratory neural drive to the crural diaphragm <http://ow.ly/e9Z7302uFM6>

Editorial comment in *Eur Respir J* 2016; 48: 604–607.

This article has supplementary material available from erj.ersjournals.com

Received: Jan 11 2016 | Accepted after revision: May 16 2016 | First published online: Aug 04 2016

Support statement: Ontario Thoracic Society; William Spear/Richard Start Endowment Fund, Queen's University; The Canadian Respiratory Research Network (CRRN). The CRRN is supported by grants from the Canadian Institutes of Health Research (CIHR) - Institute of Circulatory and Respiratory Health; Canadian Lung Association (CLA)/Canadian Thoracic Society (CTS); British Columbia Lung Association; and Industry Partners Boehringer Ingelheim Canada Ltd, AstraZeneca Canada Inc., and Novartis Canada Ltd. Jordan A. Guenette was supported by a Scholar Award from the Michael Smith Foundation for Health Research. Dennis Jensen was supported by a Chercheurs-Boursiers Junior 1 Salary Award from the Fonds de Recherche du Québec-Santé and by a William Dawson Research Scholars Award (McGill University). The funders had no role in the study design, data collection and analysis, or preparation of the manuscript. Funding information for this article has been deposited with the Open Funder Registry.

Conflict of Interest: Disclosures can be found alongside this article at erj.ersjournals.com

Copyright ©ERS 2016

Introduction

Smokers who do not meet spirometric criteria for chronic obstructive pulmonary disease (COPD) [1], but who report persistent respiratory symptoms (cough, sputum production or dyspnoea) have a higher risk of all-cause mortality and accelerated decline of lung function compared with healthy reference populations [2–4]. This sub-population has formerly been designated as Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 0 “at risk” for COPD [5]. Recent population studies have confirmed that current and former smokers without spirometric COPD have poorer perceived quality of life, greater respiratory symptoms (including exertional dyspnoea) and lower exercise tolerance when compared with healthy non-smokers [4, 6–8]. Accordingly, the main purpose of the current study was to better understand the nature and extent of physiological impairment and mechanisms of dyspnoea and exercise intolerance in smokers at risk for COPD.

It is well known that normal spirometry in cigarette smokers may obscure heterogeneous disease of the peripheral airways, lung parenchyma and its vasculature [9, 10]. Extensive small airway inflammation has been described in smokers who do not fit conventional diagnostic criteria for COPD [10]. Small airways (<2 mm in diameter) are believed to be an important site of increased airflow resistance in such individuals [11]. Small airway dysfunction is associated with delayed mechanical time constants for lung emptying within the lungs which can become further amplified by increasing breathing frequency and ventilation (e.g. during exercise). Thus, pulmonary gas trapping and dynamic lung hyperinflation during exercise may be early manifestations of peripheral airway dysfunction in some individuals [12]. It follows that the inspiratory muscles in smokers with small airway dysfunction may be faced with combined increases in resistive and elastic loading with potential negative sensory consequences. The current study is the first to use diaphragm electromyography (EMG_{di}) and manometry to explore mechanisms of dyspnoea in smokers without spirometrically defined COPD.

We reasoned that peripheral airway dysfunction in smokers is likely to develop insidiously over time, allowing compensatory physiological adaptations to emerge. Such strategies might include increased neural drive to the inspiratory muscles to maintain ventilation appropriate to metabolic demand when the respiratory system is stressed [13]. Our hypothesis was that, while these adaptations would help preserve near normal ventilatory responses to exercise (commensurate with metabolic demands), the attendant increased contractile respiratory muscle effort and fractional inspiratory neural drive to the diaphragm (relative to healthy non-smoking controls) would result in greater perceived respiratory discomfort and earlier exercise termination in smokers at risk for COPD. To test this hypothesis, we compared dyspnoea intensity, breathing pattern, ventilatory efficiency, inspiratory neural drive to the crural diaphragm (indirectly assessed by EMG_{di}) and dynamic respiratory mechanics in groups of symptomatic smokers at risk for COPD and age-matched healthy non-smokers during symptom-limited incremental exercise.

Materials and methods

Subjects

20 symptomatic current or ex-smokers without spirometric evidence of COPD (post-bronchodilator forced expiratory volume in 1 s (FEV₁) >80% predicted and FEV₁/forced vital capacity (FVC) >0.7 and more than the lower limit of normal [1, 14]) were selected during screening for COPD at the Respiratory Investigation Unit (Queen’s University and Kingston General Hospital, Kingston, ON, Canada). Smokers were determined to be symptomatic if they had cough/sputum and/or chronic activity-related dyspnoea (modified Medical Research Council dyspnoea scale ≥ 2 or COPD Assessment Test (CAT) score ≥ 10 or baseline dyspnoea index score ≤ 9) [15–17]. Other inclusion criteria were age ≥ 40 years and smoking history ≥ 20 pack-years. Exclusion criteria included: presence of asthma; other medical conditions that could contribute to dyspnoea or exercise limitation; contraindications to exercise testing; body mass index (BMI) <18.5 or ≥ 35 kg·m⁻². 20 age-matched, non-smoking healthy controls, recruited from the Respiratory Investigation Unit database registry, were used for comparison.

Study design

This cross-sectional study received ethical approval from the Queen’s University and Affiliated Teaching Hospitals Research Ethics Board (DMED-1319-10). After written informed consent, subjects completed two visits. Visit 1 included screening for eligibility, medical history, symptom and activity assessment questionnaires [15–19]; Charlson Comorbidity Index [20]; pre- and post-bronchodilator (400 µg salbutamol) pulmonary function tests; tests of small airway function (pre-bronchodilator); and an incremental cycle cardiopulmonary exercise test (CPET) for familiarisation. Visit 2 included spirometry followed by an incremental cycle CPET with EMG_{di} and respiratory pressure measurements. Subjects refrained from smoking ≥ 1 h before visits and avoided caffeine, heavy meals, alcohol and vigorous exercise ≥ 4 h before visits. Subjects were not tested if they had upper or lower respiratory tract infections within the previous 3 weeks and 3 months respectively.

Procedures

Detailed pulmonary function tests were performed using automated equipment (Vmax229d and Autobox V62); and MasterScreen impulse oscillometry (IOS); SensorMedics, Yorba Linda, CA) [21–26]. Tests of small airway function included single-breath nitrogen washout [26] and IOS [25]. CPETs were conducted on an electronically braked cycle ergometer (Ergoline 800s; SensorMedics) using a SensorMedics Vmax229d system according to clinical exercise testing guidelines [27] as previously described [13]. Tests consisted of steady-state rest followed by 20-Watt stepwise increases in work rate every 2 mins until symptom limitation. Measurements included: standard breath-by-breath cardiorespiratory and breathing pattern parameters; oxygen saturation by pulse oximetry (SpO_2); heart rate by 12-lead electrocardiography; dynamic operating lung volumes calculated from inspiratory capacity manoeuvres [28]; dyspnoea intensity measured by the modified 10-point Borg scale [29].

EMG_{di} and respiratory pressures

EMG_{di} and respiratory pressures were recorded continuously during exercise and analysed as previously described [13, 30]. A combined EMG_{di} electrode catheter with oesophageal and gastric balloons was inserted nasally and positioned as previously described [31]. The raw EMG_{di} signal was sampled at 2000 Hz (PowerLab, model ML880; ADInstruments, Castle Hill, Australia), band-pass filtered between 20 and 1000 Hz (Bioamplifier model RA-8; Guangzhou Yinghui Medical Equipment Co. Ltd, Guangzhou, China) and converted to a root mean square. The largest value from the five electrode pairs in each inspiration was used for the analysis. Maximal EMG_{di} (EMG_{di,max}) was determined during serial inspiratory capacity manoeuvres [32]; EMG_{di,max} measured in this way often produces greater values than during sniff manoeuvres, and has been shown to be highly reproducible and remains unchanged during ventilatory stimulation by exercise or hypercapnia (see online supplement). EMG_{di}/EMG_{di,max} was used as an index of inspiratory neural drive to the crural diaphragm based on a number of assumptions [31, 33, 34], that were discussed in the online supplement of our recent publication [33]. The oesophageal and gastric balloon catheters were connected to differential pressure transducers (model DP15-34; Validyne Engineering, Northridge, CA, USA) to obtain oesophageal (P_{oes}) and gastric pressures (P_{ga}); transdiaphragmatic pressure (P_{di}) was calculated as P_{ga} minus P_{oes} . The PowerLab system received continuous flow signal input from the Vmax229d system for offline analysis. Maximal inspiratory P_{di} ($P_{di,max}$) and inspiratory P_{oes} ($P_{i,max}$) were determined during inspiratory capacity manoeuvres. Tidal P_{oes} swings were expressed relative to the maximum inspiratory/expiratory excursion ($P_{oes,max}$); the latter measured as the difference between the most negative P_{oes} and the most positive P_{oes} acquired during maximal inspiratory capacity and FVC manoeuvres, respectively. $P_{oes}/P_{oes,max}$ and inspiratory $P_{di}/P_{di,max}$ were used as indices of respiratory muscle effort and diaphragmatic effort, respectively. Accepted formulae were used to calculate: total lung resistance; dynamic lung compliance (CL_{dyn}); total work of breathing as well as inspiratory elastic and resistive work; and the tension-time index of the inspiratory muscles (TTI_{oes}) and diaphragm (TTI_{di}). Details are provided in the online supplement.

Statistical analysis

A sample size of 20 was estimated to provide >80% power to detect a between-group difference in dyspnoea intensity at a standardised work rate during exercise of 1 Borg unit, based on a standard deviation of 1 unit, $\alpha=0.05$ and a two-tailed test of significance. Based on our previous experience in mild COPD patients [13], we estimated that sample sizes between 12 and 16 would be large enough to detect significant between-group differences in EMG_{di} and respiratory pressure measurements. Reasons for stopping exercise were compared between groups using the Fisher's exact test. Unpaired t-tests was used to compare differences in: 1) pulmonary function tests and measurements of small airway function; 2) dyspnoea intensity, cardiorespiratory, metabolic, gas exchange, operating lung volumes, EMG_{di} and respiratory pressures at rest, iso-work rates and peak exercise. A multivariable linear regression model was used to evaluate the relationship between dyspnoea intensity and relevant independent variables (*i.e.* EMG_{di}/EMG_{di,max}, inspiratory $P_{di}/P_{di,max}$) during exercise: group was included as a categorical effect, an interaction term was used to determine whether the relationship was similar across groups (independent variable $\times$ group), and subjects were treated as random effects to account for serial measurements (subject nested within group). Results are reported as mean $\pm$ SD unless otherwise specified. A p-value <0.05 was considered significant.

Results

Both groups had similar age, height, body mass and BMI (table 1). Smokers had worse activity-related dyspnoea and quality of life, lower habitual physical activity and higher CAT scores compared with controls (table 1). Smokers were not on any inhaled medications at the time of the study except for two subjects who occasionally used a short-acting β_2 -agonist. Smokers had a significant smoking history (range: 21–96 pack-years) and 70% were current smokers. Controls were never-smokers except for two subjects who had an insignificant smoking history (≤ 2 pack-years) and had stopped smoking >20 years before the study.

TABLE 1 Subject characteristics

	Smokers without COPD	Healthy controls
Male:female n	13:7	11:9
Age years	56±10	61±9
Height cm	168±8	167±10
Body mass kg	78.5±14.4	74.0±13.5
BMI kg·m ⁻²	27.7±4.8	26.5±2.8
Smoking history pack-years	43.4±19.9 [#]	0.2±0.5
Smoking status n		
Current	14	0
Never	0	18
Ex-smoker	6	2
BDI focal score (0–12)	9.0±1.2 [#]	11.5±0.7
Modified MRC dyspnoea scale (0–4)	0.7±0.6 [#]	0.05±0.2
CAT score (0–40)	12.1±7.1 [#]	2.6±2.8
Oxygen cost diagram (0–100) mm	74±14 [#]	92±8
CHAMPS kcal·week ⁻¹ for all activities	4466±4027 [#]	7498±4248
SGRQ total score	25.3±15.7 [#]	3.0±2.7
Charlson Comorbidity Index	1.8±1.9	1.7±0.9

Data are presented as mean±SD, unless otherwise stated. COPD: chronic obstructive pulmonary disease; BMI: body mass index; BDI: baseline dyspnoea index; MRC: Medical Research Council; CAT: COPD Assessment Test; CHAMPS: Community Healthy Activities Model Programme for Seniors questionnaire; SGRQ: St. George's Respiratory Questionnaire. [#]: p<0.05 smokers without COPD versus healthy controls group.

Pulmonary function and small airway function

Pulmonary function tests are summarised in table 2. Smokers had normal spirometry and plethysmographic lung volumes except for a slight but significant reduction in maximal mid-expiratory flow (FEF_{25–75%}) compared with controls. Smokers had evidence of peripheral airway dysfunction (higher differential change in airway resistance from 5 to 20 Hz and resonant frequency) and maldistribution of ventilation (higher phase-III nitrogen slope) compared with controls. The average diffusing capacity of the lung for carbon monoxide (DLCO) was within normal limits for both groups, although 25% of smokers had values <80% predicted. There were no significant differences in resting pulmonary function and IOS measurements between active and ex-smokers (all p>0.05).

Exercise responses, respiratory mechanics and diaphragmatic function

Measurements at peak exercise are summarised in tables 3 and 4. Peak work rate, oxygen uptake ($\dot{V}'\text{O}_2$), ventilation ($\dot{V}'\text{E}$) and heart rate were significantly lower in smokers compared with controls. There were no differences in ventilatory requirements, operating lung volumes, SpO₂ and cardio-circulatory responses during exercise between groups (figure 1, figure E1). $\dot{V}'\text{E}$ –carbon dioxide production ($\dot{V}'\text{CO}_2$) relationships expressed as slope (26.3±2.9 versus 26.6±3.2), intercept (3.7±1.7 versus 3.1±1.8) and nadir (28.7±3.3 versus 27.9±3.3) were not different in smokers versus controls (all p>0.05). Smokers with a $\dot{V}'\text{E}/\dot{V}'\text{CO}_2$ nadir above the median (n=10) had a lower peak $\dot{V}'\text{O}_2$ than those below the median (n=10): 56±24 versus 101±41% predicted, respectively (p=0.007) (figure E2). The anaerobic threshold occurred at a similar $\dot{V}'\text{O}_2$ in smokers and controls (1.4±0.5 versus 1.6±0.5 L·min⁻¹, p=0.1).

14 subjects in each group accepted insertion of the EMGdi pressure catheter. In both smokers and healthy controls, subject characteristics, pulmonary function and standard exercise test parameters were similar in each subgroup with EMGdi pressure measurements (n=14) compared with their respective total group (n=20). There was no between-group difference in inspiratory elastic work of breathing but total lung resistance and total and inspiratory resistive work of breathing were significantly higher for a given work rate and $\dot{V}'\text{E}$ during exercise in smokers compared with controls (figure 2, figure E3). EMGdi/EMGdi,max was greater in smokers at rest and for a given work rate during exercise compared with controls (figure 3). Looking at individual data, there were several smokers with tidal EMGdi values at rest and early in exercise that were higher than any seen in the control group. In addition, the majority of smokers had EMGdi,max values during their serial inspiratory capacity manoeuvres in the low range (*i.e.* <100 µV) in contrast to the control group where the majority had values in the higher range (*i.e.* >150 µV) (figure E4); EMGdi,max during the highest inspiratory capacity was lower in smokers versus controls (113±65 versus 165±56 µV, p=0.028). Thus, the higher EMGdi/EMGdi,max reflected differences in both the numerator (tidal EMGdi) and the denominator (EMGdi,max) which varied between smokers (figure 3). The EMGdi/EMGdi,max was higher in smokers versus controls regardless of how the denominator (EMGdi,max) was measured, *i.e.* during

TABLE 2 Resting pulmonary function

	Smokers without COPD	Healthy controls
Post-bronchodilator		
FEV ₁ L	3.01±0.7 (104±14 [#])	3.20±0.6 (121±11)
FEV ₁ /FVC %	75±4	77±5
Pre-bronchodilator		
FEV ₁ L	2.93±0.7 (101±13 [#])	3.04±0.6 (117±12)
FEV ₁ /FVC %	72.7±5.3 (100±7)	74.2±5.7 (104±8)
PEF L·s ⁻¹	7.9±1.9 (106±15 [#])	8.7±2.5 (125±24)
FEF _{25-75%} L·s ⁻¹	2.1±0.8 (70±20 [#])	2.4±0.9 (88±30)
SVC L	4.14±1.1 (103±15 [#])	4.25±0.9 (117±13)
IC L	2.98±0.8 (105±23)	2.95±0.8 (109±18)
FRC L	3.01±1.0 (94±27)	3.01±0.7 (98±25)
TLC L	5.99±1.3 (99±13)	5.96±1.0 (103±14)
RV L	1.86±0.5 (93±23)	1.72±0.5 (84±23)
D _{LCO} mL·min ⁻¹ ·mmHg ⁻¹	19.8±4.7 (92±25)	21.6±5.6 (104±17)
D _{LCO} /V _A mL·min ⁻¹ ·mmHg ⁻¹ ·L ⁻¹	3.7±0.6 [#] (99±16 [#])	4.2±0.7 (108±18)
sR _{aw} cmH ₂ O·s	6.9±2.6 (162±60)	5.4±2.0 (131±53)
MVV L·min ⁻¹	113±35	130±30
MIP cmH ₂ O	79±37 (92±35)	85±31 (106±27)
Closing volume L	0.39±0.2	0.40±0.2
N ₂ slope %·L ⁻¹	3.8±1.8 [#]	2.6±1.1
R5 cmH ₂ O·L ⁻¹ ·s ⁻¹	4.9±1.8	4.0±0.9
R5-20 %R5	19.4±11.5 [#]	12.5±7.1
X5 cmH ₂ O·L ⁻¹ ·s ⁻¹	-1.5±0.9 [#]	-0.9±0.4
F _{res} Hz	14.7±5.9 [#]	11.3±3.2

Data are presented as mean±SD or mean±SD (percentage of predicted normal values). COPD: chronic obstructive pulmonary disease; FEV₁: forced expired volume in 1 s; FVC: forced vital capacity; PEF: peak expiratory flow; FEF_{25-75%}: forced expiratory flow between 25 and 75% of forced vital capacity; SVC: slow vital capacity; IC: inspiratory capacity; FRC: functional residual capacity; TLC: total lung capacity; RV: residual volume; D_{LCO}: diffusing capacity of the lung for carbon monoxide; V_A: alveolar volume; sR_{aw}: specific airway resistance; MVV: maximum voluntary ventilation; MIP: maximum inspiratory mouth pressure measured from FRC; R5: airway resistance at 5 Hz during impulse oscillometry; R5-20: differential change in airway resistance between 5 and 20 Hz; X5: distal capacitive reactance at 5 Hz; F_{res}: resonant frequency. #: p<0.05 smokers without COPD versus healthy controls.

serial inspiratory capacity manoeuvres or during the highest value obtained during either inspiratory capacity or sniff manoeuvres throughout the test (figure E5). Inspiratory P_{di} was similar for a given work rate and $\dot{V}'_E$, while inspiratory $P_{di}/P_{di,max}$ was greater in smokers at rest and during exercise due to reduced $P_{di,max}$ (figure 3, figure E3). Poes-derived indices of global inspiratory muscle effort (inspiratory $P_{oes}/P_{i,max}$) and expiratory muscle activity (expiratory rise in P_{ga}) were not significantly different between groups (figure 3, figures E1 and E3). During submaximal exercise in all subjects, $EMG_{di}/EMG_{di,max}$ and inspiratory $P_{di}/P_{di,max}$ correlated with inspiratory resistive work ($R=0.343$, $p<0.001$ and $R=0.362$, $p<0.001$, respectively).

Throughout exercise, dyspnoea intensity at a given work rate was higher in smokers than controls: the mean difference at the highest equivalent work rate (80 W) was 1.9 Borg units (figure 4). Dyspnoea- $\dot{V}'_E$ slopes were also greater in smokers than controls: 0.108 ± 0.05 versus 0.067 ± 0.04 Borg units·L⁻¹·min⁻¹ ($p=0.008$) (figure 4). Dyspnoea ratings increased in direct proportion to increases in $EMG_{di}/EMG_{di,max}$ and inspiratory $P_{di}/P_{di,max}$ (figure 4). There was a strong relationship between dyspnoea intensity and both $EMG_{di}/EMG_{di,max}$ (partial $R^2=0.67$; $p<0.0005$) and inspiratory $P_{di}/P_{di,max}$ (partial $R^2=0.61$; $p<0.0005$); both relationships were similar across groups. Of note, intensity of leg discomfort was significantly higher during exercise in smokers than controls (figure E1).

Discussion

The novel finding of this study was that symptomatic smokers who did not meet spirometric criteria for COPD had greater inspiratory resistive work, $P_{di}/P_{di,max}$, $EMG_{di}/EMG_{di,max}$, and dyspnoea intensity ratings during exercise compared with healthy controls. The results partly support the hypothesis that adaptations to preserve appropriate ventilatory responses to exercise in the face of increased mechanical loading, negatively influence respiratory sensation and exercise performance in smokers at risk for COPD.

TABLE 3 Measurements at the peak of symptom-limited incremental cycle exercise

	Smokers without COPD	Healthy controls
Work rate W (% predicted)	118±46 [#] (65±19 [#])	166±55 (104±22)
$\dot{V}O_2$ L·min ⁻¹ (% predicted)	1.89±0.81 [#] (78±40 [#])	2.53±0.79 (107±45)
$\dot{V}E$ L·min ⁻¹ (% MVV)	61.4±25.9 [#] (55±19 [#])	96.9±29.3 (74±15)
V_T L	1.80±0.70 [#]	2.34±0.60
f_R breaths·min ⁻¹	33.8±5.4 [#]	41.4±9.3
T_I/T_{TOT}	0.47±0.03	0.48±0.02
IC L (% predicted)	2.90±0.71 (103±21)	2.94±0.81 (109±20)
Change in IC from rest L	-0.05±0.44	0.04±0.54
IRV L	1.10±0.59 [#]	0.61±0.32
EILV %TLC	81±11 [#]	90±5
P_{ETCO_2} mmHg	36.4±3.8 [#]	32.5±4.9
$\dot{V}E/\dot{V}CO_2$	31.3±4.1	34.4±5.8
SpO_2 %	95.8±2.2	95.3±2.7
Respiratory exchange ratio	1.05±0.1 [#]	1.13±0.1
Heart rate beats·min ⁻¹ (% predicted)	130±28 [#] (75±15 [#])	159±13 (94±7)
O_2 pulse mL·beat ⁻¹	14.3±4.5	15.9±5.1
Dyspnoea Borg units	5.3±2.9	5.6±3.1
Leg discomfort Borg units	7.3±2.7	6.5±3.1
Reason for stopping n		
Breathing discomfort	0	2
Leg discomfort	16	14
Both breathing and legs	4	4

Data are presented as mean±SD. COPD: chronic obstructive pulmonary disease; $\dot{V}O_2$: oxygen uptake; $\dot{V}E$: minute ventilation; V_T : tidal volume; f_R : respiratory frequency; T_I : inspiratory time; T_{TOT} : total breath duration; T_I/T_{TOT} : inspiratory duty cycle; IC: inspiratory capacity; IRV: inspiratory reserve volume; EILV: end-inspiratory lung volume; P_{ETCO_2} : partial pressure of end-tidal carbon dioxide; SpO_2 : arterial oxygen saturation measured by pulse oximetry; O_2 pulse: oxygen pulse. [#]: $p < 0.05$ smokers without COPD versus healthy controls.

Smokers had greater chronic activity-related dyspnoea, poorer perceived health status and lower self-reported daily physical activity compared with controls [4, 6–8]. In this context, such individuals had a lower mean symptom-limited peak $\dot{V}O_2$ by over 25% compared with controls and this reduction is

TABLE 4 Selected diaphragm electromyography and respiratory mechanical parameters at peak exercise

Variable	Smokers without COPD	Healthy controls
EMG _{di} μV	62±49 [#]	100±44
EMG _{di} /EMG _{di,max} %	63±18	65±16
Tidal P_{oes} swing cmH ₂ O	23.4±6.4 [#]	29.7±7.1
Tidal $P_{oes}/P_{oes,max}$ %	31±6 [#]	39±9
Inspiratory $P_{oes}/P_{i,max}$ %	45±9	51±12
Inspiratory $P_{di}/P_{di,max}$ %	70±17	75±15
$P_{di,insp,rise}$ cmH ₂ O	18.9±6.7 [#]	24.4±6.9
$P_{ga,exp,rise}$ cmH ₂ O	8.5±3.3	9.7±2.0
Total work of breathing J·min ⁻¹	99±53 [#]	186±104
Inspiratory elastic work J·min ⁻¹	60±32 [#]	112±61
Inspiratory resistive work J·min ⁻¹	34±20 [#]	65±38
Total lung resistance cmH ₂ O·L ⁻¹ ·s ⁻¹	2.6±0.9	2.3±0.5
CL_{dyn} mL·cmH ₂ O ⁻¹	185±49	203±57
TTI _{oes}	0.15±0.03 [#]	0.19±0.05
TTI _{di}	0.18±0.05 [#]	0.23±0.05

Data are presented as mean±SD. COPD: chronic obstructive pulmonary disease; EMG_{di}: diaphragmatic electromyography; EMG_{di,max}: maximal EMG_{di}; P_{oes} : oesophageal pressure; $P_{oes,max}$: maximal P_{oes} swing; $P_{i,max}$: maximal inspiratory P_{oes} ; P_{di} : transdiaphragmatic pressure; $P_{di,max}$: maximal P_{di} ; $P_{di,insp,rise}$: inspiratory rise in P_{di} ; $P_{ga,exp,rise}$: expiratory rise in gastric pressure; CL_{dyn} : dynamic lung compliance; TTI_{oes}: tension time index of the respiratory muscles; TTI_{di}: tension time index of the diaphragm. [#]: $p < 0.05$ smokers without COPD versus healthy controls.

FIGURE 1 Ventilatory, breathing pattern and operating lung volume responses to incremental cycle exercise in smokers without chronic obstructive pulmonary disease (COPD) and age-matched healthy controls. Data are presented as mean $\pm$ SEM. Dashed line in e indicates total lung capacity (TLC) for smokers at risk for COPD while the solid line is for controls. $V'E$: minute ventilation; $V'CO_2$: carbon dioxide production; $V'E/V'CO_2$: ventilatory equivalent for carbon dioxide; $PETCO_2$: end-tidal carbon dioxide; SpO_2 : oxygen saturation measured by pulse oximetry; TLC: total lung capacity; EELV: end-expiratory lung volume; EILV: end-inspiratory lung volume; f_R : respiratory frequency; V_T : tidal volume; IC: inspiratory capacity.

considered clinically significant [27]. The smokers stopped exercise primarily because of intolerable symptoms of severe dyspnoea and leg discomfort at a significantly lower peak work rate and $V'O_2$, a point where apparent cardiopulmonary reserve was present by traditional criteria [27].

Previous studies in mild COPD (established by spirometry) have confirmed heterogeneous physiological impairment of small airway and pulmonary microvascular function [12, 13, 35]. In the smoker group of the current study, decreased reactance (X_5), increased frequency dependence of dynamic resistance (R_{5-20}) and maldistribution of ventilation comprised the most consistent abnormalities. Notably, the post-bronchodilator

FIGURE 2 Elastic, total and resistive work of breathing and total lung resistance are shown during incremental cycle exercise in smokers without chronic obstructive pulmonary disease (COPD) and age-matched healthy controls. Data are presented as mean $\pm$ SEM. *: $p < 0.05$ smokers without COPD versus healthy controls at rest and at standardised work rates. WOB: work of breathing.

FEV₁/FVC ratio, lung volumes and DLCO were within the normal range and not significantly different from age-matched healthy controls.

During incremental exercise, the increase in ventilation in tandem with metabolic demand was similar in both groups (figure 1). On average, measures of ventilatory efficiency (V'_E/V'_{CO_2} nadir, $V'_E-V'_{CO_2}$ slope and intercept) in smokers were not different from those of healthy controls. These results are in contrast to those of several previous studies in patients with mild airway obstruction meeting GOLD stage 1 criteria for COPD where ventilatory efficiency was consistently lower than healthy controls [12, 13, 35]. However, considerable variability in this measurement was evident among smokers in the current study. Moreover, there was an inverse relationship between the V'_E/V'_{CO_2} nadir and peak $V'O_2$ (figure E2).

Ventilation and breathing pattern were similar in smokers and controls throughout much of exercise (figure 1). Since operating lung volumes, CL_{dyn} and elastic work were similar in smokers and controls during exercise, the small increases in total work of breathing in smokers compared with controls mainly reflected the increased resistive work (figure 2).

Fractional inspiratory neural drive to the diaphragm was increased both at rest and during exercise in smokers compared with controls (figure 3). The data reveal that both compensatory increases in inspiratory EMG_{di} to overcome increased airways resistance and lower maximal voluntary diaphragm activation and force generation during inspiratory capacity manoeuvres (singly or in combination) account for the higher fractional inspiratory neural drive to the diaphragm in smokers (figure E4). It is also plausible that, in some smokers, increased chemo-stimulation as a result of higher physiological dead space (increased V'_E/V'_{CO_2} , figure E2) may have contributed to a higher inspiratory EMG_{di} during tidal breathing [35].

The lower EMG_{di,max} and $P_{di,max}$ during both inspiratory capacity and sniff manoeuvres in smokers was unexpected and could not be explained by between-group differences in motivational effort during the inspiratory capacity manoeuvres since peak negative inspiratory P_{oes} was similar in both groups. Accordingly,

FIGURE 3 Diaphragm electromyography (EMG_{di}), transdiaphragmatic pressure (P_{di}) and oesophageal pressure (P_{oes}) are shown during incremental cycle exercise in smokers without chronic obstructive pulmonary disease (COPD) and age-matched healthy controls. Dynamic maximal measurements during inspiratory capacity (IC) manoeuvres are also shown. Data are presented as mean $\pm$ SEM. *: $p < 0.05$ smokers without COPD versus healthy controls at rest, at standardised work rates or at peak exercise. Insp: inspiratory; Exp: expiratory.

the lower EMG_{di,max} and P_{di,max} in smokers likely reflects reduced contribution of the diaphragm to overall pressure generation during maximal inhalation to TLC. Indeed, the lower P_{di,max} ($P_{ga,max} - P_{oes,max}$) can be mathematically explained by relatively lower intra-abdominal pressures ($P_{ga,max}$) since $P_{oes,max}$ was similar. This is compatible with a relatively greater contribution of the rib-cage and accessory muscles to maximal negative pressure generation during inspiratory capacity manoeuvres in smokers.

This is a novel observation and the precise mechanisms are unclear. We speculate that this may represent a strategy to limit maximal voluntary activation of the mechanically stressed diaphragm to minimise respiratory discomfort. Alternatively or in addition, isolated diaphragm weakness due to inflammatory

FIGURE 4 Exertional dyspnoea intensity is shown relative to a) work rate, b) ventilation, c) diaphragm electromyography relative to maximum ($EMG_{di}/EMG_{di,max}$) and d) inspiratory transdiaphragmatic pressure relative to maximum ($P_{di}/P_{di,max}$). Square symbols represent the points at the highest equivalent work rate (80W): the mean difference (Δ) in dyspnoea intensity at 80W between smokers without chronic obstructive pulmonary disease (COPD) and age-matched healthy controls was 1.9 Borg units ($p=0.009$). Data are presented as mean $\pm$ SEM. *: $p<0.05$ smokers without COPD versus healthy controls at rest and at standardised work rates. #: $p<0.05$ dyspnoea/ventilation slopes in smokers without COPD versus healthy controls.

injury from smoking has been described on the basis of muscle biopsy findings in patients with COPD (including GOLD stage 1). However the average $P_{di,max}$ for the group was ~ 60 cmH₂O which is in the lower range of normal based on previous studies making this mechanism less likely [36].

This is the first study to examine mechanisms of exertional dyspnoea in symptomatic smokers with minor spirometric abnormalities. Dyspnoea intensity ratings during exercise increased in association with the increasing diaphragmatic contractile effort and $EMG_{di}/EMG_{di,max}$ (figure 4). Since the dyspnoea- $P_{di}/P_{di,max}$ and dyspnoea- $EMG_{di}/EMG_{di,max}$ relationships during exercise were similar in both groups, the higher intensity ratings at a standardised work rate in smokers reflected higher diaphragmatic effort and electrical activation (both relative to maximum) (figure 4). The results are consistent with the frequent observation in multiple studies that dyspnoea intensity during exercise in health and in pulmonary diseases generally correlates well with physiological ratios that fundamentally reflect demand/capacity imbalance (e.g. $V'E/\text{maximum ventilatory capacity}$, $P_{oes}/P_{oes,max}$, tidal volume/inspiratory capacity, $EMG_{di}/EMG_{di,max}$) [13, 28, 33, 37, 38]. The results of the current study once more underline the importance of considering “the capacity denominator” when examining the origins of perceived respiratory discomfort during exercise. Our results are in accordance with current neurophysiological constructs that emphasise the association between increasing dyspnoea and awareness of increased efferent activity from bulbopontine and cortical motor centres in the brain to the inspiratory muscles [39, 40].

Severe to very severe leg discomfort also contributed to exercise intolerance in the smoker group and was selected as the dominant exercise-limiting symptom by both groups. Previous studies in GOLD 1 COPD have also shown that perceived leg discomfort is often the main sensory locus of exercise limitation although the

underlying mechanisms are not fully understood [12, 13, 35, 41]. Our smoker group reported lower habitual physical activity than controls but definitive evidence of skeletal muscle deconditioning in conjunction with lower cardiorespiratory fitness is lacking. In the presence of peripheral muscle weakness, greater motor command output and perceived effort (relative to maximum) would be required for a given force generation by these muscles during exercise [42]. However, this hypothesis was not formally tested in the current study.

Limitations

Not all subjects consented to EMGdi and respiratory pressure measurements due to the invasiveness of this procedure. However, the subgroup sample size (n=14) was sufficient to uncover consistent differences in the relevant sensory and physiological parameters of interest between smokers and healthy controls. We selected current and former smokers with respiratory symptoms for study inclusion, so our results cannot be generalised to asymptomatic smokers. We obtained EMG measurements of the crural diaphragm only and cannot comment on concomitant electrical activation or activity of the ribcage and accessory muscles engaged in supporting ventilation during exercise.

Conclusions and implications

Our results showed that symptomatic smokers at risk for COPD with evidence of small airway dysfunction successfully met the ventilatory requirements of incremental exercise. However, they did so at the cost of greater perceived dyspnoea at relatively low work rates due partly to the effects of increased mechanical loading. The increased fractional inspiratory neural drive to the diaphragm in smokers was multifactorial and reflected not only the effects of increased mechanical impedance but also (and more importantly) lower maximal voluntary activation and force generation of the diaphragm. Regardless of the nature of the underlying physiological impairment in individual smokers, higher dyspnoea intensity ratings at a given work rate compared with controls were associated with higher contractile diaphragmatic effort and fractional inspiratory neural drive to the diaphragm.

The results add to the accumulating evidence that exclusive reliance on spirometry to assess respiratory impairment related to smoking may obscure clinically significant physiological derangements in some symptomatic individuals. Careful interrogation of the heterogeneous physiological impairment in symptomatic smokers without overt COPD (in conjunction with biological and imaging markers) should facilitate more precise phenotyping and ultimately, individualised targeted therapies.

Acknowledgements

Authors' contributions: All authors played a role in the content and writing of the manuscript. In addition: Denis E. O'Donnell was the principal investigator and contributed the original idea for the study; Denis E. O'Donnell and Katherine A. Webb had input into the study design and conduct of study; Katherine A. Webb, Jordan A. Guenette, Casey E. Ciavaglia and Amany F. Elbehairy collected the data; Amany F. Elbehairy, Jordan A. Guenette, Casey E. Ciavaglia, Katherine A. Webb, Azmy Faisal and Andrew H. Ramscook performed data analysis and prepared it for presentation.

References

- 1 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2014. www.goldcopd.org. Date last accessed: May 15, 2015.
- 2 Stavem K, Sandvik L, Erikssen J. Can Global Initiative for Chronic Obstructive Lung Disease stage 0 provide prognostic information on long-term mortality in men? *Chest* 2006; 130: 318–325.
- 3 Mannino DM. GOLD stage 0 COPD: is it real? Does it matter? *Chest* 2006; 130: 309–310.
- 4 Vestbo J, Lange P. Can GOLD Stage 0 provide information of prognostic value in chronic obstructive pulmonary disease? *Am J Respir Crit Care Med* 2002; 166: 329–332.
- 5 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2001. www.goldcopd.org Date last accessed: June 15, 2015.
- 6 Furlanetto KC, Mantoani LC, Bisca G, *et al.* Reduction of physical activity in daily life and its determinants in smokers without airflow obstruction. *Respirology* 2014; 19: 369–375.
- 7 Vozoris NT, O'Donnell DE. Smoking, activity level and exercise test outcomes in a young population sample without cardiopulmonary disease. *J Sports Med Phys Fitness* 2015; 55: 787–796.
- 8 Regan EA, Lynch DA, Curran-Everett D, *et al.* Clinical and radiologic disease in smokers with normal spirometry. *JAMA Intern Med* 2015; 175: 1539–1549.
- 9 Clark KD, Wardrobe-Wong N, Elliott JJ, *et al.* Patterns of lung disease in a “normal” smoking population: are emphysema and airflow obstruction found together? *Chest* 2001; 120: 743–747.
- 10 Gordon C, Gudi K, Krause A, *et al.* Circulating endothelial microparticles as a measure of early lung destruction in cigarette smokers. *Am J Respir Crit Care Med* 2011; 184: 224–232.
- 11 Hogg JC, Macklem PT, Thurlbeck WM. Site and nature of airway obstruction in chronic obstructive lung disease. *N Engl J Med* 1968; 278: 1355–1360.
- 12 Ofir D, Laveneziana P, Webb KA, *et al.* Mechanisms of dyspnea during cycle exercise in symptomatic patients with GOLD stage I chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008; 177: 622–629.
- 13 Guenette JA, Chin RC, Cheng S, *et al.* Mechanisms of exercise intolerance in global initiative for chronic obstructive lung disease grade I COPD. *Eur Respir J* 2014; 44: 1177–1187.
- 14 Gutierrez C, Ghezzi RH, Abboud RT, *et al.* Reference values of pulmonary function tests for Canadian Caucasians. *Can Respir J* 2004; 11: 414–424.

- 15 Brooks SM, ATS Task Group on Screening for Respiratory Disease in Occupational Settings. Surveillance for respiratory hazards in the occupational setting. *Am Rev Respir Dis* 1982; 126: 952–956.
- 16 Jones PW, Harding G, Berry P, *et al.* Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009; 34: 648–654.
- 17 Mahler DA, Weinberg DH, Wells CK, *et al.* The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 1984; 85: 751–758.
- 18 Jones PW, Quirk FH, Baveystock CM, *et al.* A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992; 145: 1321–1327.
- 19 Stewart AL, Mills KM, King AC, *et al.* CHAMPS physical activity questionnaire for older adults: outcomes for interventions. *Med Sci Sports Exerc* 2001; 33: 1126–1141.
- 20 Charlson ME, Pompei P, Ales KL, *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373–383.
- 21 Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
- 22 Wanger J, Clausen JL, Coates A, *et al.* Standardisation of the measurement of lung volumes. *Eur Respir J* 2005; 26: 511–522.
- 23 MacIntyre N, Crapo RO, Viegi G, *et al.* Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005; 26: 720–735.
- 24 American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002; 166: 518–624.
- 25 Oostveen E, MacLeod D, Lorino H, *et al.* The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *Eur Respir J* 2003; 22: 1026–1041.
- 26 Buist AS, Ross BB. Quantitative analysis of the alveolar plateau in the diagnosis of early airway obstruction. *Am Rev Respir Dis* 1973; 108: 1078–1087.
- 27 American Thoracic Society; American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003; 167: 211–277.
- 28 O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 770–777.
- 29 Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982; 14: 377–381.
- 30 Ciavaglia CE, Guenette JA, Langer D, *et al.* Differences in respiratory muscle activity during cycling and walking do not influence dyspnea perception in obese patients with COPD. *J Appl Physiol* 2014; 117: 1292–1301.
- 31 Luo YM, Moxham J, Polkey MI. Diaphragm electromyography using an oesophageal catheter: Current concepts. *Clin Sci (Lond)* 2008; 115: 233–244.
- 32 Sinderby C, Beck J, Spahija J, *et al.* Voluntary activation of the human diaphragm in health and disease. *J Appl Physiol* 1998; 85: 2146–2158.
- 33 Faisal A, Alghamdi BJ, Ciavaglia CE, *et al.* Common mechanisms of dyspnea in chronic interstitial and obstructive lung disorders. *Am J Respir Crit Care Med* 2016; 193: 299–309.
- 34 Jolley CJ, Luo YM, Steier J, *et al.* Neural respiratory drive in healthy subjects and in COPD. *Eur Respir J* 2009; 33: 289–297.
- 35 Elbehairy AF, Ciavaglia CE, Webb KA, *et al.* Pulmonary gas exchange abnormalities in mild chronic obstructive pulmonary disease. Implications for dyspnea and exercise intolerance. *Am J Respir Crit Care Med* 2015; 191: 1384–1394.
- 36 De Troyer A, Estenne M. Limitations of measurement of transdiaphragmatic pressure in detecting diaphragmatic weakness. *Thorax* 1981; 36: 169–174.
- 37 Gandevia B, Hugh-Jones P. Terminology for measurements of ventilatory capacity. A report to the Thoracic Society. *Thorax* 1957; 12: 290–293.
- 38 Leblanc P, Summers E, Inman MD, *et al.* Inspiratory muscles during exercise: a problem of supply and demand. *J Appl Physiol* 1988; 64: 2482–2489.
- 39 Parshall MB, Schwartzstein RM, Adams L, *et al.* An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 2012; 185: 435–452.
- 40 Laviolette L, Laveneziana P; ERS Research Seminar Faculty. Dyspnoea: a multidimensional and multidisciplinary approach. *Eur Respir J* 2014; 43: 1750–1762.
- 41 Seymour JM, Spruit MA, Hopkinson NS, *et al.* The prevalence of quadriceps weakness in COPD and the relationship with disease severity. *Eur Respir J* 2010; 36: 81–88.
- 42 Gandevia SC. Neural mechanisms underlying the sensation of breathlessness: kinesthetic parallels between respiratory and limb muscles. *Aust N Z J Med* 1988; 18: 83–91.