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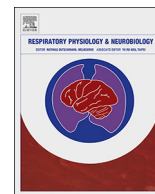
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Acute bronchodilator therapy does not reduce wasted ventilation during exercise in COPD



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ABSTRACT

This randomized, double-blind, crossover study aimed to determine if acute treatment with inhaled bronchodilators, by improving regional lung hyperinflation and ventilation distribution, would reduce dead space-tidal volume ratio (V_D/V_T); thus contributing to improved exertional dyspnea in COPD.

Twenty COPD patients ($FEV_1 = 50 \pm 15\%$ predicted; mean \pm SD) performed pulmonary function tests and symptom-limited constant-work rate exercise at 75% peak-work rate (with arterialized capillary blood gases) after nebulized bronchodilator (BD; ipratropium 0.5mg + salbutamol 2.5 mg) or placebo (PL; normal saline).

After BD versus PL: Functional residual capacity decreased by 0.4L ($p = .0001$). Isotime during exercise after BD versus PL ($p < .05$): dyspnea decreased: 1.2 ± 1.9 Borg-units; minute ventilation increased: 3.8 ± 5.5 L/min; IC increased: 0.24 ± 0.28 L and V_T increased 0.19 ± 0.16 L. There was no significant difference in arterial CO_2 tension or V_D/V_T , but alveolar ventilation increased by 3.8 ± 5.5 L/min ($p = .02$). Post-BD improvements in respiratory mechanics explained 51% of dyspnea reduction at a standardized exercise time.

Bronchodilator-induced improvements in respiratory mechanics were not associated with reduced wasted ventilation – a residual contributory factor to exertional dyspnea during exercise in COPD.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition that affects small and large airways, alveoli and the pulmonary vasculature in variable combination. The resultant respiratory mechanical and vascular functional abnormalities contribute to patients' symptoms of exertional dyspnea and exercise intolerance (O'Donnell et al., 2007).

The increase in dyspnea during exercise in COPD is multifactorial, but appears to be directly related to increased inspiratory neural drive to breathe from cortical and bulbopontine-medullary centers in the brain to the respiratory muscles (O'Donnell et al., 2007).

Bronchodilator treatment is the first step in the management of dyspnea in these patients (O'Donnell et al., 2016). Exertional dyspnea relief following bronchodilator treatment is linked to improvement in the load-capacity ratio of the respiratory muscles and enhanced coupling of respiratory effort to tidal volume (V_T) displacement during exercise due to reduced lung hyperinflation (O'Donnell et al., 2016; Boni et al., 2002; Taube et al., 2000; O'Donnell et al., 2004a). In this way, bronchodilators should reduce inspiratory neural drive from the motor cortex for a given ventilation (\dot{V}_E) and ameliorate accompanying dyspnea (Qin et al., 2015). In the current study, our overarching objective was to determine other potentially positive effects of bronchodilator therapy on pulmonary gas exchange that can contribute (directly or

Abbreviations: \dot{V}_A , alveolar ventilation; \dot{V}_A/Q , ventilation/perfusion; $\dot{V}CO_2$, carbon dioxide production; \dot{V}_D , dead space ventilation; \dot{V}_E , minute ventilation; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; $\dot{V}O_2$, oxygen uptake; COPD, chronic obstructive pulmonary disease; CWR, constant work rate; D_LCO , diffusing capacity of the lungs for carbon monoxide; EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; FEV_1 , forced expired volume in one second; FVC, forced vital capacity; HR, heart rate; IC, inspiratory capacity; IRV, inspiratory reserve volume; MVC, maximal ventilatory capacity; PCO_2 , partial pressure of carbon dioxide; PEEP, positive end-expiratory pressure; PO_2 , partial pressure of oxygen; RV, residual volume; TLC, total lung capacity; V_A , alveolar volume; V_D , dead space volume; V_T , tidal volume

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indirectly) to improved respiratory sensation during exercise in COPD (Lammi et al., 2012; Sunderrajan et al., 1983; Krachman et al., 1997).

Pulmonary gas exchange abnormalities during exercise are present across the continuum of COPD compared with healthy controls (Elbehairy et al., 2015; Neder et al., 2015). A common abnormality is the presence of lung regions with increased alveolar ventilation to perfusion ratio (\dot{V}_A/Q) (i.e., wasted ventilation) within the lungs (Elbehairy et al., 2015; Weatherald et al., 2018). The higher the physiological dead space to tidal volume ratio (V_D/V_T) within the lungs, the greater the chemo-stimulation (pulmonary CO_2 output ($\dot{V}\text{CO}_2$) component) of medullary centers and in all likelihood, the greater the accompanying respiratory discomfort. Indeed, previous studies have shown that reduced ventilatory efficiency (during incremental cycle ergometry), a surrogate for physiological dead space, has been associated with increased exertional dyspnea in COPD (Elbehairy et al., 2017; Jones et al., 2017).

The effect of bronchodilator treatment on arterial blood gases and arterial oxygen saturation (SaO_2) in COPD during exercise have been shown to be modest or non-existent (Khoukaz and Gross, 1999). To the best of our knowledge, there is only one previous study that examined the effect of bronchodilators on pulmonary gas exchange during exercise in patients with severe COPD (Marvin et al., 1983). They showed that the use of oral bronchodilators (theophylline and terbutaline) had small effects on airflow and insignificant effects on pulmonary gas exchange during rest and semi-recumbent exercise (Marvin et al., 1983). However, regardless of effects on SaO_2 , bronchodilators might increase \dot{V}_A and reduce V_D/V_T by increasing V_T (due to increased inspiratory capacity (IC)) or by regional lung deflation which could improve pulmonary blood flow and \dot{V}_A/Q relationships by mechanical decompression of intra-alveolar blood vessels. Moreover, reduced positive end-expiratory pressure (PEEP) and intra-thoracic pressure excursions as a result of reduced airways resistance and lung hyperinflation after bronchodilators may improve central cardiac hemodynamics and increase cardiac output, pulmonary and peripheral blood flow (Lammi et al., 2012; Laveneziana et al., 2009; Chiappa et al., 2008; Chiappa et al., 2009). Improved cardio-pulmonary interactions as a result of reduced lung hyperinflation could directly influence respiratory sensation by improving pulmonary blood flow or act indirectly by delaying the ventilatory (anaerobic) threshold and attendant increase in chemoreflexic inspiratory neural drive (Lammi et al., 2012; Laveneziana et al., 2009; Chiappa et al., 2008; Chiappa et al., 2009).

The objective of the current study was to determine if: acute inhalation of combined short-acting β_2 agonists and antimuscarinic bronchodilators, which improve respiratory mechanics, have additional associated beneficial effects on pulmonary gas exchange and respiratory sensation. We tested the hypothesis that acute administration of inhaled bronchodilator treatment – in addition to improving respiratory mechanics – would reduce V_D/V_T during exercise in COPD. To test this hypothesis, we compared pulmonary gas exchange, perceptual, mechanical and indirect cardiovascular responses to exercise after single administration of inhaled combined bronchodilators versus placebo and evaluated their interactions.

2. Methods

2.1. Subjects and study design

This retrospective analysis included 20 subjects from two studies approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (DMED-730-03 and DMED-929-06) (Laveneziana et al., 2009; Peters et al., 2006). These similar randomized, double-blind, placebo-controlled, crossover studies included an inhaled bronchodilator (BD) and a placebo (PL) arm and focused on lung mechanics and ventilatory kinetics during exercise (Laveneziana et al., 2009; Peters et al., 2006); the current analysis does not overlap with previous analyses. Inclusion criteria: stable patients

with Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade 2–3 (i.e., moderate-to-severe) COPD, i.e., post-bronchodilator forced expiratory volume in 1 s (FEV_{1s})/forced vital capacity ratio < 0.7 and FEV_{1s} 30–80% predicted (GOLD, 2017); age > 40 years; smoking history ≥ 20 pack-years; body mass index ≤ 35 kg/m². Exclusions included: bronchial asthma, significant medical conditions that could contribute to dyspnea or exercise limitation, contraindications to exercise testing, and use of daytime oxygen.

After signing written informed consent, participants completed 3 visits conducted at the same time of the day (all in the morning): *Visit 1*: screening for eligibility with characterization of the study population and included: medical history, clinical assessment, symptom questionnaires, pulmonary function tests (PFTs), and a symptom-limited incremental cycle exercise test. *Visit 2 and 3* included PFTs and a constant work rate (CWR) exercise test at 75% of the maximal incremental work rate 90–105 min after nebulized BD (ipratropium 0.5 mg + salbutamol 2.5 mg) or PL (sterile 0.9% saline solution). As previously validated (Zavorsky et al., 2007; Murphy et al., 2006), arterialized capillary blood gas samples were taken from the earlobe during rest and exercise. Participants avoided caffeine, heavy meals, alcohol four hours before testing and avoided major physical exertion prior to visits days. According to usual recommendations, participants withdrew regular bronchodilators before testing: short-acting β_2 -agonists (4 h), short-acting anticholinergics (6 h), long-acting β_2 -agonists (12 h), and long-acting anticholinergics (48 h).

2.2. Procedures

Spirometry, body plethysmography, diffusing capacity of the lung for carbon monoxide ($D_L\text{CO}$) were performed using automated equipment Vmax229d and Autobox V62J; and MasterScreen IOS; SensorMedics, Yorba Linda, CA; measurements were expressed relative to predicted normal values (Miller et al., 2005; Wanger et al., 2005; Macintyre et al., 2005; Crapo et al., 1982; Burrows et al., 1961; Briscoe and Dubois, 1958). Symptom-limited exercise tests were conducted on an electrically braked cycle ergometer (Ergometrics 800S; SensorMedics) using a cardiopulmonary exercise testing system (Vmax229d; SensorMedics) as previously described (Ofir et al., 2008). PL and BD were administered in 5 mL of solution by nebulizer (Parimaster compressor with Pari LC Jet + nebulizer; PARI Respiratory Equipment Inc, Richmond, VA, USA).

Incremental exercise tests used stepwise increments of 10W/min. CWR tests were performed at 75% of the peak incremental work rate. Endurance time was defined as the duration of loaded pedalling. Exercise measurements included: breath-by-breath cardiorespiratory and breathing pattern parameters; O_2 saturation by pulse oximetry; heart rate (HR) by 12-lead ECG; dynamic lung volumes calculated from IC, with the rest-to-exercise decrease in IC reflecting the magnitude of dynamic hyperinflation (O'Donnell et al., 2001). Dyspnea and leg discomfort intensity were measured with the modified 10-point Borg scale (Borg, 1982). Arterialized capillary blood samples were drawn from the earlobes at rest, at 2 min intervals during exercise and at end-exercise as previously described (Peters et al., 2006). V_D/V_T was calculated using the modified Bohr equation: $V_D/V_T = [(\text{PaCO}_2 - \text{P}_E\text{CO}_2)/\text{PaCO}_2] - (V_{DM}/V_T)$, where P_ECO_2 is the partial pressure of mixed expired CO_2 , PaCO_2 is the partial pressure of arterialized (capillary) CO_2 , V_{DM} is the volume of the breathing valve and mouthpiece, and V_T is the tidal volume (Elbehairy et al., 2015).

2.3. Statistical analysis

This was an observational physiological study with main outcomes consisting of measurement of pulmonary gas exchange parameters during exercise in COPD. In previous studies performed at our laboratory, small sample sizes between 12 and 22 were large enough to detect between-group and/or between-treatment differences in these variables

Table 1
Subject characteristics.

Variable	Measured value	%predicted
Male: female, n	12:8	
Age, years	63 ± 8	–
Height, cm	170 ± 9	–
Body mass index, kg/m ²	26.8 ± 4.5	–
Baseline Dyspnoea Index (0–12)	6.6 ± 2.1	–
Smoking history, pack-years	52 ± 29	–
Inhaled medications, n		
• SABA	19	–
• SAMA	3	–
• LABA	9	–
• LAMA	9	–
• ICS	9	–
Pulmonary function:		
FEV ₁ , L	1.36 ± 0.54	50 ± 15
FVC, L	2.97 ± 0.99	78 ± 18
FEV ₁ /FVC, %	45 ± 8	64 ± 11
PEF, L/min	4.49 ± 1.42	62 ± 15
FEF _{25–75%} , L/s	0.38 ± 0.24	14 ± 8
SVC, L	3.35 ± 0.96	88 ± 16
IC, L	2.22 ± 0.70	79 ± 19
FRC, L	4.74 ± 0.85	147 ± 26
TLC, L	6.96 ± 1.17	115 ± 14
RV, L	3.61 ± 0.77	169 ± 36
RV/TLC, %	52 ± 9	146 ± 36
D _L CO, ml/min/mmHg	17.1 ± 5.6	78 ± 20
D _L /V _A , ml/min/mmHg/L	3.39 ± 0.62	89 ± 17
sRaw, cmH ₂ O s	21.4 ± 7.3	512 ± 194
Peak incremental exercise:		
Work rate, watts	88 ± 38	59 ± 15
Heart rate, beats/min	123 ± 19	73 ± 11
Ventilation, L/min	46 ± 19	88 ± 27 ^a
ṠO ₂ , L/min	1.36 ± 0.65	69 ± 20
IRV, L	0.41 ± 0.24	–
SpO ₂ , %	94 ± 3	–
Dyspnoea, Borg scale	5.9 ± 2.0	–
Leg discomfort, Borg scale	5.7 ± 2.3	–

Values are means ± SD.

Abbreviations: D_LCO = diffusing capacity of the lung for carbon monoxide; D_L/V_A = D_LCO relative to alveolar volume; FEF_{25–75%} = forced expiratory flow between 25 and 75% of forced vital capacity; FEV₁ = forced expired volume in 1 s; FVC = forced vital capacity; FEV₁/FVC = ratio between FEV₁ and FVC; FRC = functional residual capacity; IC = inspiratory capacity; ICS = inhaled corticosteroid; LABA = long-acting β₂-agonist; LAMA = long-acting anti-muscarinic; SABA = short-acting β₂-agonist; SAMA = short-acting anti-muscarinic; RV = residual volume; sRaw = specific airway resistance; SVC = slow vital capacity; TLC = total lung capacity; ṠO₂ = oxygen uptake.

^a Ventilation expressed as% of estimated maximal ventilatory capacity (35 × FEV₁).

(Elbehairy et al., 2015; Laveneziana et al., 2009; Peters et al., 2006).

Results are reported as means ± SD unless otherwise specified. A *p* < .05 significance level was used for all analysis. Paired *t*-tests were used to compare differences in PFTs as well as dyspnea intensity, cardiorespiratory, metabolic, gas exchange and operating lung volume measurements at rest, isotime (the highest common exercise time achieved during all tests performed by a given subject) and end exercise. Reasons for stopping exercise were analysed using Fisher's exact test. Inter-relationships between iso-time ventilatory equivalent for carbon dioxide (Ṡ_E/Ṡ_{CO₂}) and the slope of dyspnea/exercise-time during exercise were tested using a multivariable linear regression model incorporating condition (BD, PL) as a categorical effect and an interaction term to determine whether the relationship being tested was similar across conditions (variable × condition).

3. Results

Study included 20 patients with moderate-to-severe COPD

Table 2

Effect of bronchodilator (BD) and placebo (PL) on resting lung function.

Variable	BD	PL
FEV ₁ , L	1.68 ± 0.62* (61 ± 16 [†])	1.34 ± 0.50 (49 ± 14)
FVC, L	3.34 ± 0.91* (88 ± 15 [†])	2.99 ± 0.95 (78 ± 17)
FEV ₁ /FVC, %	50 ± 9* (70 ± 13 [†])	45 ± 7 (63 ± 10)
PEF, L/min	5.28 ± 1.63* (73 ± 16 [†])	4.33 ± 1.23 (60 ± 13)
FEF _{25–75%} , L/s	0.57 ± 0.39* (20 ± 11 [†])	0.39 ± 0.23 (14 ± 7)
SVC, L	3.68 ± 0.92* (96 ± 13 [†])	3.36 ± 0.98 (88 ± 18)
IC, L	2.50 ± 0.74* (89 ± 18 [†])	2.23 ± 0.77 (79 ± 21)
FRC, L	4.35 ± 0.82* (135 ± 26 [†])	4.75 ± 0.75 (147 ± 22)
TLC, L	6.85 ± 1.18* (114 ± 14 [†])	6.98 ± 1.13 (116 ± 13)
RV, L	3.18 ± 0.61* (149 ± 30 [†])	3.62 ± 0.61 (169 ± 28)
RV/TLC, %	47 ± 8*	53 ± 9
sRaw, cmH ₂ O s	13.6 ± 6.2* (328 ± 165 [†])	21.9 ± 6.9 (522 ± 170)
D _L CO, ml/min/mmHg	16.9 ± 5.1 (77 ± 18)	17.3 ± 5.7 (79 ± 21)
D _L /V _A , ml/min/mmHg/L	3.29 ± 0.59* (86 ± 16 [†])	3.46 ± 0.70 (91 ± 19)
V _A , L	5.12 ± 1.18	4.96 ± 1.20
TLC-V _A , L	1.73 ± 0.59*	2.02 ± 0.66

Values are means ± SD, with values in parentheses representing% of predicted normal values.

Abbreviations: D_LCO = diffusing capacity of the lung for carbon monoxide; D_L/V_A = D_LCO relative to alveolar volume; FEF_{25–75%} = forced expiratory flow between 25 and 75% of forced vital capacity; FEV₁ = forced expired volume in 1 s; FVC = forced vital capacity; FEV₁/FVC = ratio between FEV₁ and FVC; FRC = functional residual capacity; IC = inspiratory capacity; RV = residual volume; sRaw = specific airway resistance; SVC = slow vital capacity; TLC = total lung capacity; V_A = alveolar volume.

* *p* < .05 BD versus PL.

(FEV₁:50 ± 15%predicted), significant smoking history (52 ± 29 pack-years) and severe activity-related dyspnea (Baseline Dyspnea Index: 6.6 ± 2.1 on the 0–12 scale). Table 1 summarizes participants' characteristics, inhaled medications, PFTs and peak incremental exercise test responses. Incremental exercise was terminated due to a combination of severe dyspnea and leg discomfort at a low peak work rate and oxygen uptake (ṠO₂).

3.1. Resting lung function

Table 2 shows PFTs responses to treatment with BD versus PL. After BD versus PL, FEV₁ increased by 0.33 ± 0.25L and IC increased by 0.27 ± 0.33L (both *p* < .01). BD showed improvements in peak expiratory flow, pulmonary gas trapping [reduction in RV/TLC (residual volume/total lung capacity) and functional residual capacity] and the TLC-alveolar volume difference (TLC-V_A: an index of ventilation distribution); all *p* < .001 (Fig. 1). There was no difference in D_LCO.

3.2. Constant-work rate exercise

Exercise endurance time was numerically greater after BD versus PL by 1.22 ± 3.36 min, but was not statistically significant (*p* = .12). At end-exercise after BD versus PL, participants reached a higher Ṡ_E (52 ± 21 versus 45 ± 18 L/min; *p* < .0005) by increasing V_T by 0.13 ± 0.13 L (*p* < .0005) rather than breathing frequency; however, the ratio between Ṡ_E and the estimated maximum ventilatory capacity was lower after BD versus PL by 8 ± 12% (*p* = .010) (Table 3). Exertional dyspnea was selected as the main reason for stopping exercise in 9/20 with BD versus 14/20 with PL, but there was no significant difference in dyspnea intensity at end-exercise despite significant increases in peak Ṡ_E (Table 3).

Isotime changes after BD versus PL (Table 3): There was no significant difference in V_D, V_D/V_T, PaCO₂ or SaO₂ (Fig. 2). Isotime comparisons of Ṡ_E/Ṡ_{CO₂} showed no difference between BD versus PL (37 ± 7 versus 36 ± 7) (online Supplementary), and values were not statistically different from Ṡ_E/Ṡ_{CO₂}-nadir point during the initial incremental cycle exercise test. Additionally, Ṡ_E-to-Ṡ_{CO₂} slopes during the

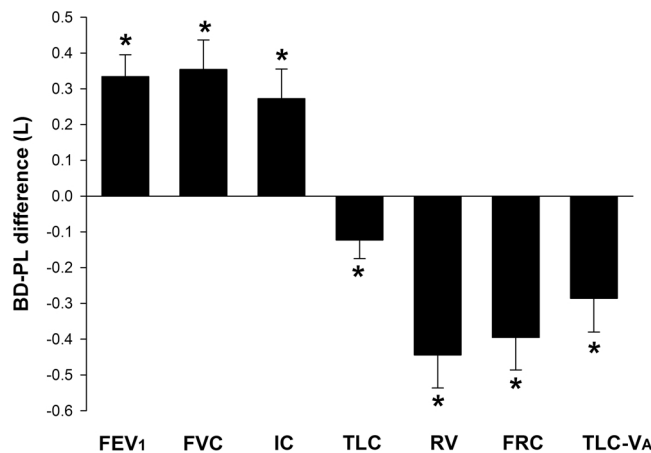


Fig. 1. Differences in resting lung volume measurements after treatment with bronchodilator (BD) versus placebo (PL). * $p < .05$ bronchodilator versus placebo. *Abbreviations:* FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity; FRC = functional residual capacity; IC = inspiratory capacity; TLC = total lung capacity; RV = residual volume; V_A = alveolar volume.

incremental exercise tests and placebo-CWR were not statistically different (28.8 ± 6.3 versus 28.3 ± 4.5 , respectively, $p = .5$) (online Supplementary). \dot{V}_E and \dot{V}_A increased by 3.8 ± 5.5 L/min ($p = .006$) and 4.7 ± 6.5 L/min ($p = .017$), respectively, with no change in dead space ventilation (\dot{V}_D) (Figs. 3 and 4). Following BD, isotime end-tidal CO₂ (P_{ET}CO₂) decreased ($p = .01$) with marginal insignificant decrease in PaCO₂; thus, Pa-ETCO₂ remained unaltered, Table 3. There was no significant difference in O₂ pulse or HR (online Supplementary).

Table 3
Measurements at isotime and end-exercise during CWR exercise in response to BD and PL.

Variable	BD		PL	
	Isotime	End-exercise	Isotime	End-exercise
Endurance time, min	–	7.2 ± 4.7	–	5.9 ± 3.7
\dot{V}_{O_2} , L/min (%predicted)	1.39 ± 0.59 (71 ± 16)	1.47 ± 0.59* (75 ± 16*)	1.35 ± 0.55 (69 ± 16)	1.41 ± 0.57 (72 ± 17)
\dot{V}_{CO_2} , L/min	1.36 ± 0.64*	1.45 ± 0.62*	1.26 ± 0.54	1.33 ± 0.57
\dot{V}_E , L/min (% predicted MVC)	47.5 ± 20.1* (80 ± 10*)	52.1 ± 20.9* (89 ± 12*)	43.7 ± 17.1 (93 ± 15)	45.4 ± 17.9 (97 ± 14)
V _T , L	1.50 ± 0.54*	1.44 ± 0.52*	1.32 ± 0.50	1.32 ± 0.49
Fb, breaths/min	32 ± 8	36 ± 8	34 ± 6	35 ± 6
T _I /T _{TOT}	0.42 ± 0.05	0.41 ± 0.05	0.41 ± 0.05	0.41 ± 0.05
IC, L (%predicted)	1.92 ± 0.58* (68 ± 14*)	1.84 ± 0.60* (64 ± 14*)	1.68 ± 0.53 (60 ± 13)	1.65 ± 0.55 (58 ± 13)
Δ IC from rest, L	–0.48 ± 0.34	–0.55 ± 0.36	–0.50 ± 0.37	–0.54 ± 0.44
IRV, L	0.42 ± 0.26	0.39 ± 0.22	0.37 ± 0.19	0.33 ± 0.17
EILV, %TLC	94 ± 4	94 ± 3	95 ± 3	95 ± 3
P _{ET} CO ₂ , mmHg	43.1 ± 5.5*	42.8 ± 6.4*	44.8 ± 6.1	45.1 ± 6.6
\dot{V}_E/\dot{V}_{CO_2}	37 ± 7	37 ± 6*	36 ± 7	36 ± 6
SpO ₂ , %	94 ± 4	93 ± 4	93 ± 3	93 ± 3
R	0.96 ± 0.10*	0.98 ± 0.10*	0.93 ± 0.08	0.94 ± 0.07
HR, beats/min (% predicted)	125 ± 20 (74 ± 12)	131 ± 21 (78 ± 13)	125 ± 21 (74 ± 20)	127 ± 21 (76 ± 12)
O ₂ pulse, mL/beat	11.2 ± 4.3	11.3 ± 4.3	10.8 ± 4.1	11.1 ± 4.3
Dyspnoea, Borg scale	3.0 ± 1.9*	6.2 ± 2.5	4.2 ± 1.7	6.6 ± 2.1
Leg discomfort, Borg scale	3.7 ± 2.5	6.0 ± 2.3	4.0 ± 2.0	5.6 ± 2.4
pH	7.35 ± 0.06	7.35 ± 0.05	7.36 ± 0.03	7.35 ± 0.03
PaCO ₂ , mmHg	38.5 ± 7.4	37.8 ± 7.6	40.4 ± 5.2	39.7 ± 5.9
Pa-ETCO ₂ , mmHg	–3.99 ± 5.9	–4.54 ± 5.3	–4.61 ± 4.4	–5.56 ± 4.4
PaO ₂ , mmHg	81.8 ± 15.9	84.0 ± 16.4	81.3 ± 18.0	83.9 ± 20.9
HCO ₃ ⁻ , mmol/L	21.5 ± 2.9	20.4 ± 3.7	22.9 ± 1.8	21.4 ± 3.2
Calculated V _D /V _T	0.23 ± 0.12	0.22 ± 0.10	0.25 ± 0.89	0.23 ± 0.09

Values are means ± SD.

Abbreviations: CWR = constant work rate; EILV = end-inspiratory lung volume; Fb = breathing frequency; HCO₃⁻ = bicarbonate; HR = heart rate; IC = inspiratory capacity; IRV = inspiratory reserve volume; MVC = maximal ventilatory capacity; O₂ pulse = oxygen pulse; PaCO₂ = partial pressure of arterial carbon dioxide; PaO₂ = partial pressure of arterial oxygen; P_{ET}CO₂ = partial pressure of end-tidal carbon dioxide; R = respiratory exchange ratio; SpO₂ = arterial oxygen saturation measured by pulse oximetry; T_I/T_{TOT} = inspiratory duty cycle; TLC = total lung capacity; \dot{V}_E = min ventilation; \dot{V}_E/\dot{V}_{CO_2} = ventilatory equivalent for carbon dioxide; \dot{V}_{O_2} = oxygen uptake; V_D = dead space volume; V_T = tidal volume; isotime is the highest common exercise time achieved during all tests performed by a given subject.

* $p < .05$ BD (bronchodilator) versus PL (placebo).

Dyspnea intensity decreased by 1.2 ± 1.9 Borg units ($p = .013$); mean expiratory flow increased ($p < .005$); end-expiratory lung volume (EELV) was lower by 0.36 ± 0.30 L ($p < .0005$), allowing IC and V_T to increase by 0.24 ± 0.28 and 0.19 ± 0.16 L, respectively (both $p < .005$) (Fig. 4); the decrease in IC from rest was unchanged. Isotime differences in \dot{V}_E , IC and EELV explained 51% of the BD-induced reduction in dyspnea intensity (online Supplementary). In addition, isotime differences in \dot{V}_E/\dot{V}_{CO_2} correlated with the slope of dyspnea/exercise-time (partial $r = 0.25$, $p < .001$); this relationship was similar in both test conditions. After accounting for the small change in \dot{V}_E between BD and placebo, there were no significant differences in V_A, and V_D when expressed as a function of increasing \dot{V}_E (online Supplementary).

4. Discussion

The main findings of the study are as follows: 1) bronchodilator therapy was associated with improved respiratory mechanics at rest and during exercise with attendant increases in \dot{V}_E and \dot{V}_A and reduced exertional dyspnea ratings; 2) there was no improvement in V_D, V_D/V_T, PaO₂, PaCO₂, or indirect indices of cardiovascular function following bronchodilator treatment. The results do not support the hypothesis that the beneficial effects of acute bronchodilator therapy extend to improvements in pulmonary gas exchange – an important residual source of dyspnea during exercise in COPD.

Study participants had moderate-to-severe airway obstruction and lung hyperinflation and reported persistent activity-related dyspnea despite regular inhaled bronchodilator and inhaled corticosteroid therapy. Incremental cardiopulmonary exercise testing confirmed poor exercise tolerance with severe mechanical ventilatory constraints: inspiratory reserve volume (IRV) had declined to 0.41 L at a peak \dot{V}_E of

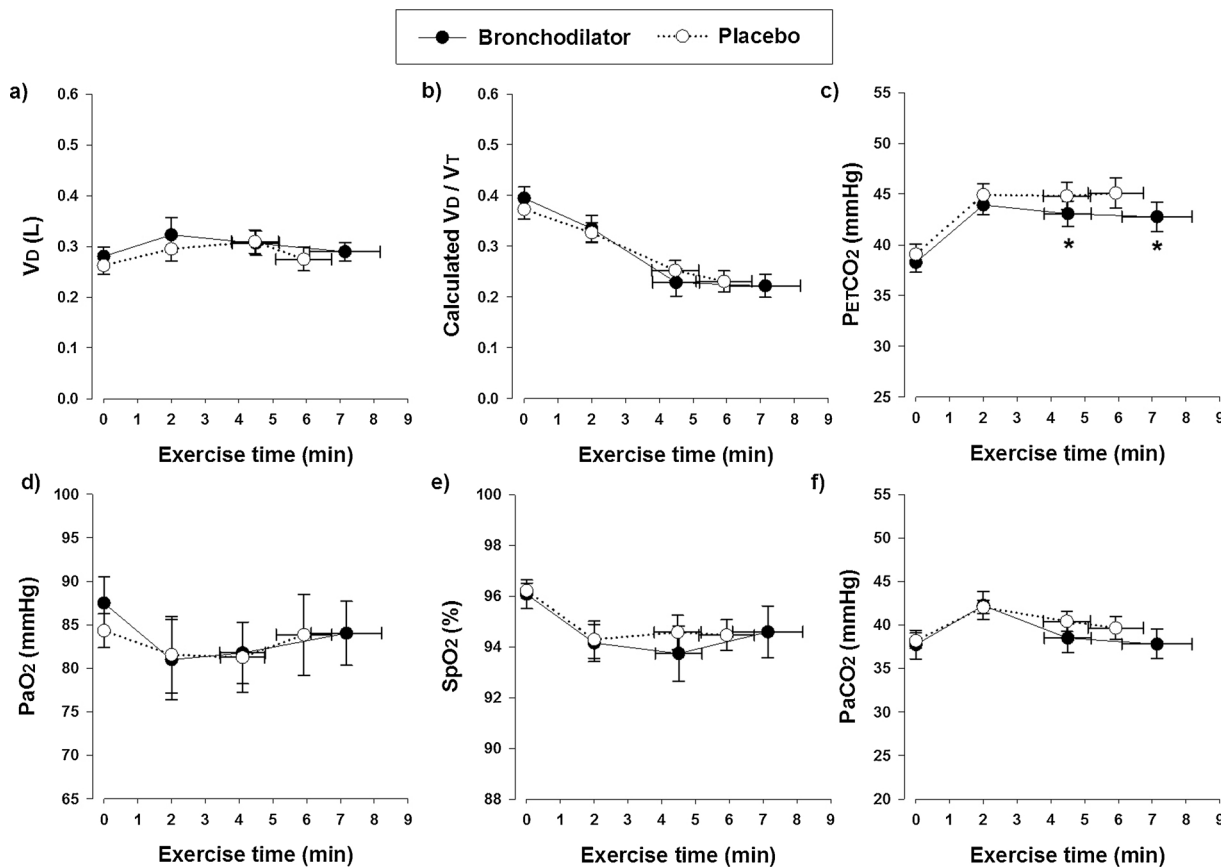


Fig. 2. Measures of pulmonary gas exchange during constant work rate exercise after treatment with either bronchodilator or placebo. Values are means \pm SEM. * $p < .05$ bronchodilator versus placebo at the same time point during exercise and at peak. *Abbreviations:* PaO₂ = partial pressure of arterialized (capillary) oxygen; PaCO₂ = partial pressure of arterialized (capillary) carbon dioxide; P_{ET}CO₂ = partial pressure of end-tidal carbon dioxide; SpO₂ = oxygen saturation measured by pulse oximetry; \dot{V}_E = min ventilation; $\dot{V}CO_2$ = CO₂ production; $\dot{V}_E/\dot{V}CO_2$ = ventilatory equivalent for CO₂; V_D = dead space volume; V_D/V_T = dead space to tidal volume fraction.

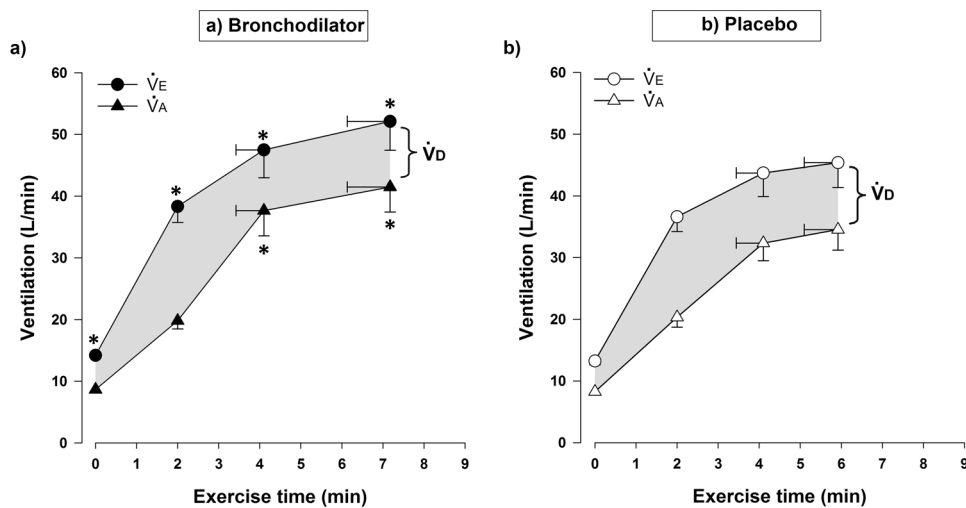


Fig. 3. Minute ventilation (\dot{V}_E) and alveolar ventilation (\dot{V}_A) during constant work rate exercise after treatment with either bronchodilator (BD, panel a) or placebo (PL, panel b). Values are means \pm SEM. Shaded areas represent dead space ventilation (\dot{V}_D). * $p < .05$ difference in \dot{V}_E and \dot{V}_A after BD vs. PL at the same time point during exercise and at peak. There was no difference in \dot{V}_D .

only 46L/min (Table 1). Dyspnea was the main exercise-limiting symptom at a peak power output of 59% predicted.

In keeping with several previous studies (Casaburi et al., 2014; Maltais et al., 2011; O'Donnell et al., 2009), acute bronchodilator therapy significantly reduced dyspnea ratings (> 1 Borg unit) at a standardized time compared with placebo during the CWR endurance test. Moreover, there was no further increase in dyspnea despite participants being able to generate and sustain higher V_T and \dot{V}_E over a longer exercise duration (Fig. 4). Based on previous studies (Casaburi

et al., 2014; Maltais et al., 2011; O'Donnell et al., 2009), such improvements in dyspnea have been shown to be related, in part, to reduced lung hyperinflation with increased IC at rest and during exercise and a resultant delay of the onset of critical ventilatory constraints. Accordingly, in the current study, changes in IC, EELV and \dot{V}_E together explained 50% of dyspnea relief post-BD (online Supplementary). The observation that dyspnea reduction was linked to increased ventilatory capacity following bronchodilator therapy points to the importance of reduced mechanical loading even in the absence of improved

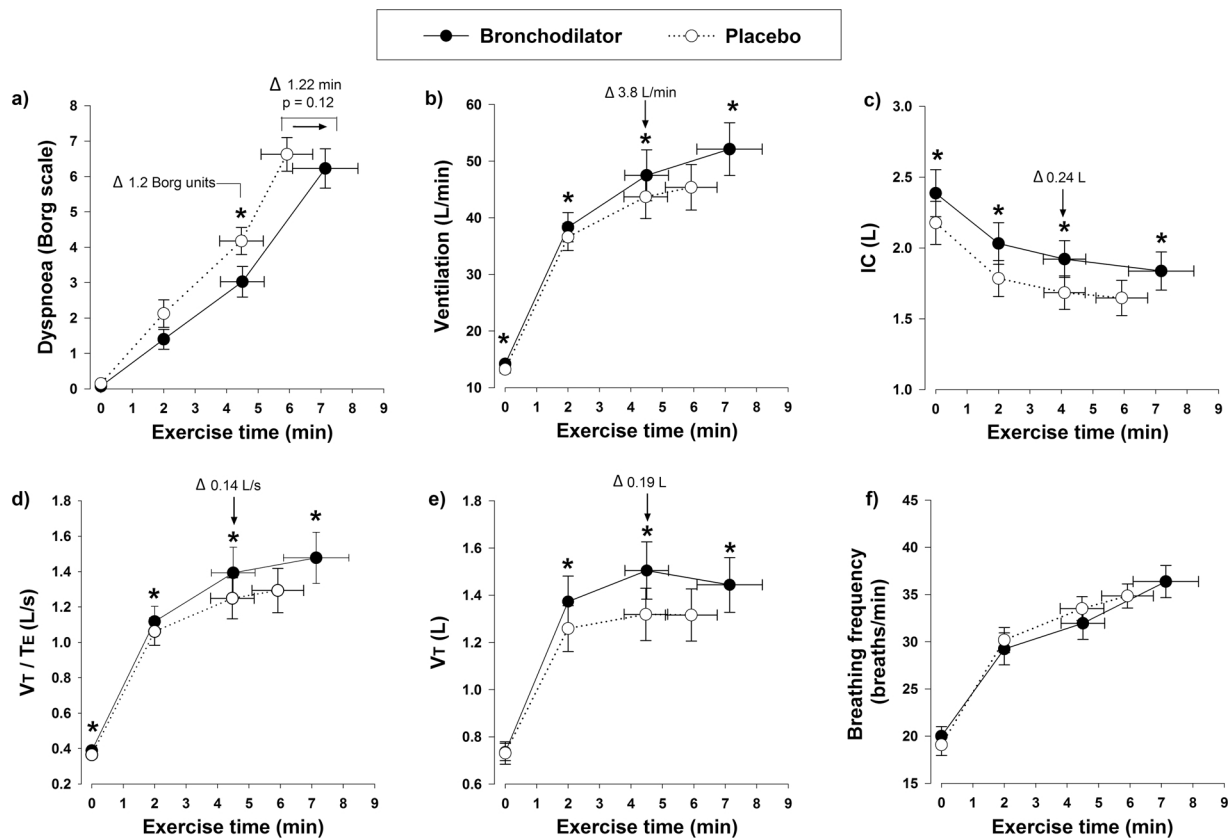


Fig. 4. Dyspnea intensity and breathing pattern during constant work rate exercise after treatment with either bronchodilator or placebo. Values are means \pm SEM. * $p < .05$ bronchodilator versus placebo at the same time point during exercise and at peak. *Abbreviations:* IC = inspiratory capacity; V_T = tidal volume; T_E = expiratory time; Δ = difference.

pulmonary gas exchange.

This is the first study to examine the effects of inhaled short-acting bronchodilator therapy on \dot{V}_A , V_D , V_D/V_T and PaCO_2 , during exercise in COPD. In milder COPD, high V_D/V_T or increased wasted ventilation can contribute to increased inspiratory neural drive to the diaphragm (relative to maximum), which has been shown to be associated with increased exertional dyspnea (Elbehairy et al., 2015; Neder et al., 2015). Theoretically, bronchodilator inhalation could reduce physiological dead space and improve ventilatory efficiency by: 1) improving alveolar gas distribution; 2) increasing V_T by increasing IC or; 3) increasing pulmonary perfusion distribution and cardiac output by reducing regional lung hyperinflation and attendant intrinsic PEEP. Indeed, compared with placebo, there were small improvements in ventilation distribution at rest ($\text{TLC}-V_A$ decreased by 0.3L, Fig. 1) and in V_T and \dot{V}_A during exercise (Figs. 3 and 4). Interestingly, recruitment of V_T , \dot{V}_E and \dot{V}_A following pharmacological lung deflation was not associated with any significant decreases in V_D/V_T or V_D at isotime during exercise (Fig. 2). These measures of wasted ventilation were not significantly different after accounting for small changes in \dot{V}_E and $\dot{V}\text{CO}_2$ close to exercise termination following BD compared with PL (online Supplementary). The results suggest that increased V_T and \dot{V}_A predominantly affected lung units with better preserved \dot{V}_A/Q matching at baseline. The decreases in $P_{\text{ET}}\text{CO}_2$ in the setting of increased \dot{V}_A with bronchodilation compared with placebo likely reflects improved regional airway conductance.

Isotime comparisons of $\dot{V}_E/\dot{V}\text{CO}_2$ during CWR were similar to $\dot{V}_E/\dot{V}\text{CO}_2$ nadir during the incremental cycle test and not different between BD and placebo applications (online Supplementary). These results are consistent with the notion that a fixed high dead space exists in COPD during exercise and is not significantly reduced by acute combined BD therapy. The lack of improvement in pulmonary gas exchange

efficiency may also possibly reflect small increases in anatomical dead space following bronchodilator therapy, which have been previously described (Pecchiari et al., 2017).

Interestingly, $\dot{V}\text{CO}_2$ increased slightly at isotime with inhaled BD. The source of this “extra- CO_2 ” remains unclear: it is unlikely that this derives from greater lactic acid buffering or acute changes in muscle fiber recruitment (type II) after an intervention that can actually improve peripheral O_2 delivery (Berton et al., 2010; Travers et al., 2007). Higher $\dot{V}\text{CO}_2$ may reflect the greater metabolic cost of increasing \dot{V}_E at higher exercise intensities even in the presence of mechanical unloading with bronchodilation. Finally, no consistent changes in crude indices of cardio-circulatory function (i.e., HR or O_2 pulse) occurred following bronchodilation and lung deflation (online Supplementary).

The mechanisms of dyspnea alleviation during exercise in COPD following bronchodilator therapy are not fully understood and are multifactorial. In particular, the factors contributing to the variability in sensory responses to bronchodilator treatment across the continuum of COPD have not been adequately studied. Our results confirm that improved dynamic respiratory mechanics are important and based on previous studies likely improve dyspnea by reducing the respiratory effort or inspiratory neural drive required to generate a greater ventilation during exercise (O'Donnell et al., 2006, 2004b). This would correspond to reduced central corollary discharge from cortical motor command centers in the brain to the somatosensory-cortex with a corresponding sense of reduced inspiratory muscle effort. We have also argued that greater harmonization of the relation between respiratory effort and the muscular/mechanical response of the respiratory system attenuates dyspnea intensity or its major qualitative dimension “unsatisfied inspiration” at a given or increased \dot{V}_E during exercise (O'Donnell et al., 2006). However, while these are desirable mechanical effects and can facilitate increased exercise performance, they by no

means abolish exertional or chronic dyspnea. Thus, our patients still reported significant persistent activity-related dyspnea (Baseline Dyspnea Index < 7) despite optimized long-acting bronchodilator treatment. Moreover, after study medication (compared with placebo) participants still reported severe dyspnea at a relatively low work rate compared with historic healthy age-matched controls. Clearly, severe mechanical abnormalities and neuromechanical dissociation of the respiratory system still persist after acute combined bronchodilation (O'Donnell et al., 2006).

The results further suggest the existence of non-modifiable contributing factors to increased inspiratory neural drive during exercise such as increased dead space ventilation. Thus, in the current study isotime \dot{V}_E/\dot{V}_{CO_2} (a surrogate for physiological dead space) was associated with dyspnea intensity during exercise regardless of bronchodilator effect. In this context, bronchodilators are unlikely to modify the magnitude of stimulation of medullary and bulbopontine centers in the brain due to persisting increased “pulmonary \dot{V}_{CO_2} component” (compromised elimination of alveolar CO_2) (Poon et al., 2015). To the extent that both chemical and mechanical factors (and their variable combination) ultimately determine the magnitude of respiratory neural drive during exercise, bronchodilators which primarily improve mechanics, will only be partially effective in relieving this troublesome symptom.

5. Limitations

We used capillary rather than arterial CO_2 to calculate dead space fraction on the basis that previous studies have shown that arterialized capillary blood gas samples from the earlobe provide an accurate assessment of $PaCO_2$ and can be reliably used during exercise in healthy individuals and patients with COPD (Murphy et al., 2006; Zavorsky et al., 2007). We used isotime CWR comparisons of \dot{V}_E/\dot{V}_{CO_2} following active drug and placebo. Such comparisons are generally conducted during incremental rather than CWR tests. However, \dot{V}_E/\dot{V}_{CO_2} over work rate slopes were similar regardless of the mode of exercise testing (online Supplementary) and iso-CWR \dot{V}_E/\dot{V}_{CO_2} on placebo was similar to \dot{V}_E/\dot{V}_{CO_2} nadir calculated from the incremental test. This strongly suggests that, as is the case in patients with cardiac disease (Hoshimoto-Iwamoto et al., 2008), that sub-maximal CWR \dot{V}_E/\dot{V}_{CO_2} can be used as a surrogate for physiological dead space particularly when the arterial CO_2 set point is unchanged. We have used indirect indices of cardiovascular responses to lung deflation (e.g. O_2 pulse and HR): invasive central hemodynamic measurements would be required during exercise to make definitive conclusions on possible cardio-circulatory effects.

6. Conclusions

Bronchodilator-related improvements in expiratory flow rates, operating lung volumes, breathing pattern and \dot{V}_A did not significantly influence $PaCO_2$, V_D , V_D/V_T or isotime \dot{V}_E/\dot{V}_{CO_2} during exercise in patients with COPD. While the use of inhaled bronchodilators is associated with improvements in ventilatory capacity, high ventilatory demand persists during exercise because of persistent high physiological dead space and wasted ventilation. We postulate that this is a residual source of increased inspiratory neural drive and severe exertional dyspnea. In order to achieve further improvements in exertional dyspnea in patients with COPD, we will need to develop a new treatment that can effectively reduce wasted ventilation within the lungs.

Authors' contributions

All authors played a role in the content and writing of the manuscript. In addition: DEO was the principal investigator and contributed the original idea for the study; KAW took part in the data collection; AFE and KAW performed data analysis and prepared it for presentation.

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Competing interests

Amany F. Elbehairy received financial support from the British Academy of Medical Sciences through the Daniel Turnberg UK/Middle East Travel Fellowship scheme. Nicolle J Domnik received financial support from Banting Postdoctoral Fellowships program. The funders had no role in the study design, data collection and analysis, or preparation of the manuscript. The authors have no conflicts of interest that are directly relevant to the content of this article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.resp.2018.03.012>.

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