

(Manuscript version date: 06-Jan-2006)

Combined physiological effects of bronchodilators and hyperoxia on exertional dyspnea in normoxic COPD

Michelle M. Peters, Katherine A. Webb, Denis E. O'Donnell
Respiratory Investigation Unit
Department of Medicine
Queen's University
Kingston, Ontario, Canada

Address for correspondence: Dr. Denis O'Donnell
102 Stuart Street
Kingston, Ontario K7L 2V6
Canada
tel: (613) 548-2339
fax: (613) 549-1459
e-mail: odonnell@post.queensu.ca

The corresponding authors has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence on a worldwide basis to the BMJ Publishing Group Ltd to permit this article (if accepted) to be published in THORAX and any other BMJPGJL products and sublicences such as and exploit all subsidiary rights, as set out in our licence (<http://thorax.bmjournals.com/misc/ifora/licenceform.shtml>).

Running Head: Bronchodilators and oxygen in COPD.

Key words: COPD; bronchodilators; oxygen; exercise; dyspnea; lung hyperinflation.

This article has an online data supplement

ABSTRACT

Background: Studies examining the physiological interactions of oxygen (O₂) and bronchodilators (BD) during exercise in COPD should provide new insights into mechanisms of exercise intolerance. We examined the effects of O₂ and BD, alone and in combination, on dyspnea, ventilation (V_E), breathing pattern, operating lung volumes and exercise endurance.

Methods: In a randomized, double-blind, crossover study, 16 patients with COPD (FEV₁=43(3) % predicted; mean(SEM)) performed pulmonary function tests and an incremental exercise test, then completed four visits in which they received either nebulized BD (ipratropium 0.5 mg + salbutamol 2.5 mg) or placebo (PL) with either 50% O₂ or room air (RA). At 90-105 minutes post-dose, patients performed pulmonary function tests then breathed RA or O₂ during symptom-limited constant-load exercise at 75% peak work rate.

Results: With BD, inspiratory capacity (IC) increased 0.3(0.1) L (p<0.05) at rest and during exercise permitting greater tidal volume (V_T) expansion during exercise and a greater peak V_E. With O₂, V_E decreased during exercise as a result of decreased breathing frequency (*F*), with no significant change in IC. During exercise with BD+O₂, IC and V_T increased, *F* decreased, and V_E did not change. Dyspnea decreased with all interventions at a standardized time during exercise compared with PL+RA (p<0.05). Endurance time was significantly (p<0.05) greater with BD+O₂ (10.4(1.6) min) than with O₂ (8.5(1.4) min), BD (7.1(1.3) min) and PL+RA (5.4(0.9) min).

Conclusion: By combining the benefits of BD (i.e., reduced hyperinflation) and O₂ (i.e., reduced ventilatory drive), additive effects on exercise endurance were observed in normoxic COPD.

INTRODUCTION

In more advanced COPD, ventilatory constraints and the associated respiratory discomfort (dyspnea) contribute importantly to poor exercise performance. Recent consensus guidelines have correctly highlighted the importance of reducing dyspnea and activity limitation as an effective means of improving perceived health status in these patients.[1][2] An individualized, integrated management plan that combines pharmacologic and non-pharmacologic interventions is most likely to be successful in achieving these goals.

Our understanding of the mechanisms of dyspnea relief following bronchodilator therapy continues to grow. All classes of bronchodilators have been shown to improve airway conductance and to facilitate lung emptying. In patients with moderate to severe disease, the consequent reduction in end-expiratory (EELV) and end-inspiratory (EILV) lung volumes, allow greater tidal volume expansion and ventilation during exercise with less exertional dyspnea.[3][4][5][6] However, the impact of different bronchodilators on these operating volume components during exercise appear to vary and this inter-patient variability has not been studied. Moreover, the relative importance of increases in inspiratory capacity (IC) and inspiratory reserve volume (IRV) (reflecting decreases in EELV and EILV, respectively) in contributing to improvement in dyspnea and activity limitation remains unknown and is, therefore, explored further in this study.

Several controlled studies have shown positive effects of hyperoxia on dyspnea and exercise performance, even in patients with insignificant arterial oxygen desaturation.[7][8][9][10][11][12] Exertional dyspnea relief during hyperoxia is multifactorial but appears to be linked to the attendant reduction in ventilation during exercise.[7][13] However, it remains uncertain whether hyperoxia-induced reduction in ventilation is associated with a reduced rate of dynamic hyperinflation during exercise in normoxic patients with COPD. In this regard, different studies have yielded conflicting results, suggesting that there is considerable inter-patient variability in this response.[7][8][13] Therefore, we wished to further examine the relative contribution of reduced ventilation and reduced lung volumes to dyspnea relief during hyperoxia.

In the past, dyspnea-relieving interventions, such as bronchodilator therapy and supplemental oxygen (O₂), have been studied only in isolation and no information is available on their combined physiological interactions and resultant clinical consequences. In this study we therefore compared the acute effects of bronchodilators and hyperoxia (50% O₂), both singly and in combination, in order to gain new insights into the mechanisms of improved dyspnea and exercise performance. We reasoned the combination of therapies, that both improve dynamic ventilatory mechanics and reduce ventilatory demand, would have additive or possibly even synergistic effects on dyspnea and exercise endurance in patients with moderate to severe COPD who were not significantly hypoxemic during activity.

METHODS

Subjects

We studied 16 clinically stable patients with COPD ($FEV_1 \leq 60\%$ predicted, $FEV_1/FVC < 70\%$) who were not hypoxic (resting $PaO_2 > 65$ mmHg, exercise $SaO_2 \geq 88\%$) and had significant activity-related breathlessness (modified Baseline Dyspnea Index score ≤ 6)[14]. Patients with significant cardiovascular disease, other pulmonary disease, or other disorders that could contribute to dyspnea or exercise limitation were excluded.

Study Design

This was a randomized, double-blind, placebo-controlled crossover study with local university/hospital research ethics approval. Subjects were recruited from a list of patients who had participated in previous exercise studies. After giving informed consent and screening of medical history, patients were familiarized with all procedures and completed pulmonary function tests and a symptom-limited incremental cycle exercise test. During four subsequent visits conducted 2-7 days apart, subjects received one of four treatment combinations, in random order: bronchodilator (BD)+room air (RA), placebo (PL)+RA, BD+O₂, or PL+O₂. At these visits, subjects were given either PL or BD, they waited 105 ± 15 minutes prior to performing pulmonary function tests, then completed a constant-load cycle endurance test at 75% of their maximal incremental work rate while breathing either RA or 50% O₂. Subjects adhered to the standard withdrawal of bronchodilators prior to testing: short-acting β_2 -agonists (4 hours), short-acting anticholinergics (6 hours), long-acting β_2 -agonists (12 hours), long-acting anticholinergics (48 hours), theophyllines (48 hours) and antileukotrienes (48 hours). Subjects avoided caffeine, alcohol, and heavy meals for 4 hours prior to testing and avoided major physical exertion entirely on visit days.

Interventions

PL and BD were administered by nebulizer (Parimaster compressor with Pari LC Jet+ nebulizer; PARI Respiratory Equipment, Inc., Richmond, VA) in a double-blind fashion. BD was Combivent® (0.5 mg ipratropium bromide, 2.5 mg salbutamol) and PL was sterile 0.9% saline solution. Subjects breathed either RA (21% O₂) or 50% O₂ on demand from a 200 L Douglas bag reservoir for at least 10 minutes at rest before starting exercise and throughout exercise; subjects were blinded to the gas mixture being breathed at each test.

Procedures

Pulmonary function measurements were collected using automated equipment (Vmax 229d with Autobox 6200 DL; SensorMedics, Yorba Linda, CA) and expressed as percentages of predicted normal values;[15][16][17][18][19][20] predicted IC was calculated as predicted total lung capacity (TLC) minus predicted functional residual capacity (FRC). Symptom-limited exercise tests were conducted on an electrically braked cycle ergometer (Ergometrics 800S; SensorMedics) using a cardiopulmonary exercise testing system (Vmax229d; SensorMedics). Incremental testing was performed at the first visit. Subsequent constant-load tests were conducted at 75% of the maximal incremental work rate. Exercise test measurements included: intensity of dyspnea (breathing discomfort) and leg discomfort using the 10-point modified Borg scale;[21] operating lung volumes derived from IC maneuvers;[22][23] arterialized capillary blood samples taken from the earlobe; and reason for stopping exercise. Endurance time was

defined as the duration of loaded pedaling. *See the online supplement for a more detailed description of procedures.*

Statistical Analysis

The sample size of 16 provides the power (80%) to detect a difference in IC measured at a standardized exercise time based on a relevant difference of 0.3 L, a SD of 0.3 L for IC changes found at our laboratory, $\alpha=0.05$, and a two-tailed test of significance. Results are reported as means (SEM). A $p<0.05$ significance level was used for all analysis. Comparisons were made using ANOVA for repeated measures for linear exercise response slopes and for measurements at *rest* (pre-exercise steady-state), at *isotime* during exercise (the highest common exercise time achieved during all tests performed by a given subject), and at *peak* exercise (average of last 30-seconds of loaded pedaling). Paired t-tests were used for post hoc analyses. Reasons for stopping exercise were analyzed using Fisher's exact test. Pearson correlations were used to establish associations between standardized dyspnea ratings (and exercise endurance time) and relevant independent variables; forward stepwise multiple regression analysis was carried out with significant variables and relevant covariates.

RESULTS

Sixteen subjects with moderate to severe airflow obstruction and lung hyperinflation, and significantly reduced exercise capacity completed the study (table 1). One additional subject was enrolled in the study but was withdrawn after the first treatment visit due to an adverse reaction (dizziness, nausea) to acute administration of the bronchodilator.

Table 1. Subject characteristics

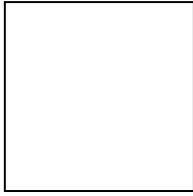
	Measured value	% Predicted
Male : female, n	9 : 7	
Age, years	62 (2)	
Height, cm	168 (2)	
Weight, kg	75.8 (3.8)	
Body mass index, kg/m ²	26.8 (1.1)	
Smoking history, pack-years	50 (7)	
Duration of COPD, years	9 (2)	
Pulmonary function:		
FEV ₁ , L	1.16 (0.10)	43 (3)
FVC, L	2.66 (0.19)	71 (4)
FEV ₁ /FVC, %	43.9 (1.9)	62 (3)
PEFR, L/s	4.02 (0.26)	56 (4)
TLC, L	6.74 (0.28)	114 (4)
RV, L	3.66 (0.21)	174 (10)
FRC _{pl} , L	4.73 (0.21)	150 (6)
IC, L	2.01 (0.15)	72 (4)
P _I max, cmH ₂ O	56 (5)	72 (7)
DL _{CO} /V _A , ml/min/mmHg × L ⁻¹	3.31 (0.17)	87 (5)
Peak incremental exercise *:		
Work rate, watts	78 (8)	55 (3)
Heart rate, beats/min	120 (4)	71 (2)
$\dot{V}O_2$, L/min	1.16 (0.12)	62 (4)
$\dot{V}E$, L/min	38.5 (2.9)	98 (5)†
EILV/TLC, %	94 (1)	
IRV, L	0.37 (0.07)	
SaO ₂ , %	93 (1)	
Dyspnea, Borg Scale	5.4 (0.5) “severe”	
Leg discomfort, Borg Scale	5.1 (0.5) “severe”	

Values are means (SEM).

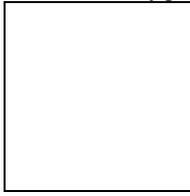
* Predicted maximum exercise values from Jones.[24]

† $\dot{V}E$ expressed as % of estimated maximal ventilatory capacity ($35 \times FEV_1$).

DL_{CO}/V_A , diffusing capacity of the lung for carbon monoxide corrected for alveolar volume; FRC_{pl} , plethysmographic functional residual capacity; FEV_1 , forced expired volume in one second; FVC , forced vital capacity; $P_{I\max}$, maximal inspiratory pressure; $PEFR$, peak expiratory flow rate; RV , residual volume; SaO_2 , oxygen saturation; TLC , total lung capacity;



V_E , minute ventilation;



$\dot{V}O_2$, oxygen consumption.

Resting Pulmonary Function

Pulmonary function parameters are shown in [table 2](#). These parameters were measured before exercising with either RA or O₂ and reflect responses to nebulized BD or PL only. Measurements on the two PL days were similar (and similar to those at visit 1), demonstrating good repeatability of measurements. Improvements in pulmonary function on the two BD days were also comparable.

Table 2. Resting pulmonary function measured after PL or BD but before breathing O₂ or RA

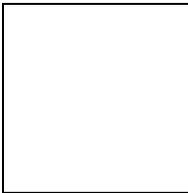
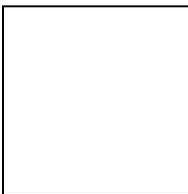
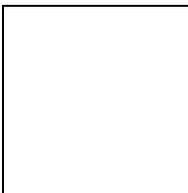
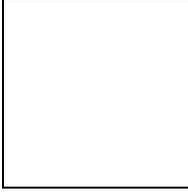
	RA + PL visit	RA + BD visit	O ₂ + PL visit	O ₂ + BD visit	p value (ANOVA)
FEV ₁ , L	1.17 (0.09)	1.50 (0.13) *	1.17 (0.09) †	1.47 (0.13) *‡	< 0.0005
FVC, L	2.68 (0.17)	3.09 (0.20) *	2.67 (0.17) †	3.09 (0.20) *‡	< 0.0005
FEV ₁ /FVC, %	44 (2)	48 (2) *	44 (2) †	48 (2) *‡	< 0.0005
PEFR, L/s	3.92 (0.23)	4.84 (0.35) *	3.86 (0.27) †	4.88 (0.34) *‡	< 0.0005
IC, L	1.96 (0.13)	2.28 (0.16) *	1.98 (0.15) †	2.23 (0.14) *‡	< 0.0005
SVC, L	3.06 (0.20)	3.45 (0.21) *	3.11 (0.21) †	3.41 (0.20) *‡	< 0.0005
FRC _{pl} , L	4.72 (0.18)	4.31 (0.21) *	4.80 (0.19) †	4.34 (0.19) *‡	< 0.0005
RV, L	3.62 (0.15)	3.14 (0.16) *	3.67 (0.16) †	3.17 (0.14) *‡	< 0.0005
TLC, L	6.68 (0.24)	6.58 (0.27)	6.78 (0.27)	6.58 (0.23)	0.055
sRaw, cmH ₂ O·s	22.9 (1.6)	14.5 (1.7) *	22.8 (1.5) †	15.3 (1.4) *‡	< 0.0005
D _L CO, ml/min/mmHg	16.0 (1.3)	15.9 (1.2)	15.9 (1.3)	16.7 (1.2) *†‡	0.025
P _I max, cmH ₂ O	62 (4)	61 (5)	58 (5)	64 (5)	0.282

Values are means (SEM).

* p<0.05 vs RA+PL; † p<0.05 vs RA+BD; ‡ p<0.05 vs O₂+PL.

sRaw, specific airway resistance.

Table 3. Symptom-limited peak of constant-load cycle exercise at 75% W_{max} [57 (6) watts, 39 (2) % of predicted maximum]

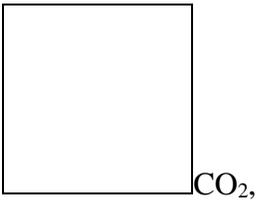
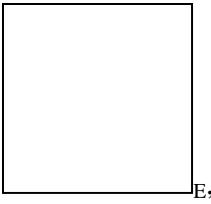
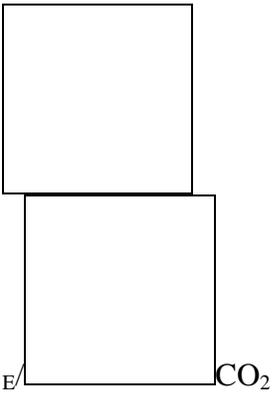
Variable	RA + PL	RA + BD	O ₂ + PL	O ₂ + BD	p value (ANOVA)
Endurance time, min	5.4 (0.9)	7.1 (1.3)	8.5 (1.4)*	10.4 (1.6)*†‡	0.002
Dyspnea, Borg	6.4 (0.5)	5.8 (0.6)	5.4 (0.6)	5.3 (0.5)	0.095
Leg discomfort, Borg	4.9 (0.5)	5.4 (0.5)	5.2 (0.5)	5.9 (0.5)	0.069
Heart rate, beats/min	122 (5)	124 (4)	121 (5)	124 (5)	0.239
SaO ₂ , %	92 (1)	93 (1)	97 (0)*†	97 (1)*†	<0.0005
 CO ₂ , L/min	1.15 (0.11)	1.26 (0.12)*	1.21 (0.12)	1.30 (0.14)*	0.071
 E, L/min	38.6 (2.9)	44.3 (3.5)*	37.2 (2.7)†	41.5 (3.5)*†‡	<0.0005
 E/  CO ₂	35.5 (1.6)	36.9 (1.6)*	32.4 (1.3)*†	33.5 (1.5)†	<0.0005
<i>F</i> , breaths/min	34 (2)	36 (2)	33 (2)	34 (2)	0.063
T _E , sec	1.08 (0.05)	1.06 (0.06)	1.12 (0.06)	1.10 (0.06)	0.202
T _I , sec	0.73 (0.04)	0.71 (0.04)	0.75 (0.04)	0.74 (0.05)	0.526

V _T , L	1.16 (0.09)	1.28 (0.10)*	1.14 (0.08)†	1.26 (0.10)*‡	<0.0005
IC, L	1.50 (0.12)	1.67 (0.13)*	1.48 (0.10)†	1.68 (0.13)*‡	<0.0005
IRV, L	0.34 (0.05)	0.37 (0.06)	0.34 (0.04)	0.42 (0.05)	0.335
EELV, L	5.17 (0.22)	4.91 (0.24)*	5.30 (0.23)†	4.90 (0.21)*‡	<0.0005
EILV/TLC, %	95 (1)	94 (1)	95 (1)	94 (1)	0.227
PaCO ₂ , mmHg	41.4 (1.2)	40.2 (1.7)	45.7 (1.4)*†	43.5 (2.0)*‡	0.012
HCO ₃ ⁻	22.5 (0.5)	22.0 (0.5)	23.5 (0.7)*†	22.6 (0.5)	0.028
Base excess, mmol/L	-2.4 (0.5)	-2.7 (0.5)	-2.3 (0.8)	-2.8 (0.5)	0.342
pH	7.36 (0.01)	7.36 (0.01)	7.33 (0.01)	7.34 (0.01)	0.713

Values are means (SEM).

* p<0.05 vs RA+PL; † p<0.05 vs RA+BD; ‡ p<0.05 vs O₂+PL.

Table 4. Measurements at isotime [4.1(0.8) min] during constant-load cycle exercise

Variable	RA + PL	RA + BD	O ₂ + PL	O ₂ + BD	ANOVA (p value)
Dyspnea, Borg	3.9 (0.4)	2.5 (0.4)*	2.4 (0.4)*	2.1 (0.5)*	<0.0005
Leg discomfort, Borg	3.4 (0.4)	2.9 (0.4)	2.5 (0.4)*	2.6 (0.4)*	0.054
Heart rate, beats/min	118 (4)	118 (4)	111 (4)*†	114 (4)*†	<0.0005
SaO ₂ , %	93 (1)	93 (1)	97 (1)*†	98 (0)*†	<0.0005
 CO ₂ , L/min	1.10 (0.11)	1.16 (0.12)	1.13 (0.12)	1.16 (0.14)	0.463
 E, L/min	37.8 (3.0)	40.0 (3.3) p=0.06 vs RA+PL	34.5 (2.6)*†	36.7 (3.5)†	<0.0005
 E/ CO ₂ L/min	36.5 (1.8)	36.5 (1.8)	32.6 (1.6)*†	33.7 (1.7)*†	<0.0005
F, breaths/min	34 (2)	31 (2)*	29 (2)*	29 (2)*†	<0.0005
T _I , sec	0.75 (0.03)	0.84 (0.04)*	0.84 (0.04)*	0.88 (0.05)*	<0.0005
T _E , sec	1.09 (0.05)	1.21 (0.08)*	1.25 (0.07)*	1.31 (0.09)*†	<0.0005
V _T , L	1.15 (0.09)	1.33 (0.11)*	1.19 (0.09)*†	1.30 (0.11)*‡	<0.0005
IC, L	1.53 (0.11)	1.78 (0.13)*	1.57 (0.10)†	1.74 (0.12)*‡	<0.0005

IRV, L	0.37 (0.04)	0.45 (0.07)	0.38 (0.04)	0.45 (0.04)	0.310
EELV, L	5.15 (0.21)	4.80 (0.22)*	5.20 (0.22)†	4.84 (0.20)*‡	<0.0005
EILV, % TLC	94 (1)	93 (1)	94 (1)	93 (1)	0.242
P _{ET} CO ₂ , mmHg	46.3 (1.4)	44.9 (1.2)	51.0 (1.4)*†	48.2 (1.7)†‡	<0.0005
PaCO ₂ , mm Hg	41.9 (1.1)	40.8 (1.8)	44.7 (1.1)†	45.0 (1.9)*†	0.109
HCO ₃ ⁻ , mmol/L	23.0 (0.5)	22.1 (0.5)*	24.2 (0.5)*†	23.3 (0.5)†	0.002
pH	7.36 (0.01)	7.36 (0.02)	7.36 (0.01)	7.34 (0.02)	0.636
Base excess, mmol/L	-1.94 (0.44)	-2.71 (0.63)*	-1.05 (0.46)† p=0.09 vs RA+PL	-2.25 (0.54)	0.038

Values are means (SEM).

* p<0.05 vs RA+PL; † p<0.05 vs RA+BD; ‡ p<0.05 vs O₂+PL.

Exercise Response to Bronchodilators

Endurance time increased by 1.7(0.9) min (41(16)%) after BD(+RA) compared with PL(+RA)($p=0.067$)(table 3). The main reasons for stopping exercise did not change significantly in response to BD (fig 2). After BD compared with PL, dyspnea intensity decreased at isotime during exercise ($p=0.008$) (table 4) and the slope of Borg dyspnea ratings over time also fell significantly ($p=0.039$) (fig 1). Dyspnea- V_E slopes shifted rightwards after BD compared with PL, such that dyspnea fell by 1.2(0.3) Borg units ($p=0.001$) at a standardized V_E of 33.4(2.5) L/min (fig 3).

BD-induced increases in peak V_{CO_2} , V_E , V_T , IC are shown in table 3. Compared with PL at isotime (4.1(0.8) min) during exercise, BD increased IC and V_T ($p<0.005$), decreased F as a result of increased T_I and T_E ($p<0.05$), with a resultant increase in V_E ($p=0.06$)(table 4, fig 4). At a standardized V_E , the only difference between BD and PL was a reduction in lung hyperinflation (all $p\leq 0.01$): decreases in EELV (-0.35(0.09) L) and EILV (-0.31(0.10) L), with reciprocal increases in IC (0.25(0.07) L) and IRV (0.21(0.07) L).

All but three subjects reduced lung hyperinflation at rest with BD compared to PL. In 10 subjects, the reduction in resting lung hyperinflation continued during exercise, i.e., IC at isotime increased. These 10 subjects reduced dyspnea at isotime by -1.7(0.7) Borg units ($p=0.031$) and improved exercise endurance by 2.7(1.3) min or 64(23)% ($p=0.023$), whereas the 6 subjects with no volume response during exercise did not change dyspnea at isotime (-0.9(0.6) Borg units) or endurance time (0.1(0.5) min).

Correlates of improvement: Reductions in dyspnea-time slopes were greatest in subjects with the steepest non-intervention (RA+PL) dyspnea-time slopes ($r=-0.59$, $p=0.016$). Dyspnea-time slopes decreased most in those who experienced the greatest expansion of V_T standardized as % of predicted VC measured at isotime ($r=-0.54$, $p=0.027$) or at peak exercise ($r=-0.69$, $p=0.003$), and in those with the largest increases in T_E at isotime ($r=-0.60$, $p=0.014$) or at peak exercise ($r=-0.56$, $p=0.024$). Reductions in dyspnea at isotime correlated best with reductions in concurrent measurements of F ($r=0.64$, $p=0.007$), and with increases in isotime T_I ($r=-0.62$, $p=0.010$) and T_E ($r=-0.57$, $p=0.020$); the combination of change in F and change in $EELV\%prTLC$ explained 50% of the variance in change in dyspnea at isotime. Reductions in dyspnea at iso- V_E correlated best with the concurrent increase in IC ($r=-0.46$, $p=0.074$). Reductions in dyspnea did not correlate with improvements in FEV_1 ($p>0.5$).

Exercise Response to Oxygen

Endurance time increased by 3.1(1.1) min (76(28) %) with O_2 (+PL) compared with RA(+PL) ($p=0.011$). The main reasons for stopping exercise did not change significantly in response to O_2 (fig 2). Slopes of Borg ratings of both dyspnea and leg discomfort over time fell significantly ($p<0.05$) in response to O_2 (fig 1). Dyspnea- V_E slopes were similar on O_2 and RA (fig 3).

Figure 4 shows exercise responses to O_2 . Isotime V_E fell as a result of a concurrent decrease in F ($r=0.65$, $p<0.01$) which, in turn, correlated with increases in T_I ($r=-0.87$, $p<0.0005$) and T_E ($r=-0.64$, $p<0.01$). Changes in V_E also correlated with concurrent changes in V_{CO_2} ($r=0.80$, $p<0.0005$), pH ($r=-0.65$, $p<0.05$) and base excess ($r=-0.58$, $p<0.05$). $PaCO_2$ and HCO_3^- increased during exercise with O_2 compared with RA, but not at rest.

On average, operating lung volumes at rest and during exercise did not change significantly with hyperoxia. On O_2 compared to RA, 7 out of the 16 subjects reduced lung hyperinflation during exercise, i.e., increased IC at isotime. These subjects had worse maximal expiratory flows compared to the 9 subjects with no volume response to O_2 : FEV_1/FVC ratios

were 39(2) versus 48(2)% ($p=0.009$), respectively. Volume-responders had significantly steeper dyspnea-time slopes ($p=0.012$) and poorer exercise endurance ($p=0.045$) on RA, with greater improvements with O_2 . Dyspnea- V_E relationships were also steeper in volume-responders than non-responders on RA and did not change on O_2 (fig 3). O_2 -induced changes in the ventilatory responses to exercise were generally similar across subgroups, but volume-responders had more significant associated decreases in V_E and V_T/T_E (due to increased T_E).

Correlates of improvement: Decreases in dyspnea-time slopes were largest in subjects with the steepest slopes on RA+PL ($r=-0.70$, $p=0.002$). Since dyspnea- V_E relationships did not change in response to O_2 , decreases in dyspnea were directly related to decreases in V_E . After accounting for differences in isotime V_E , increases in isotime IC% predicted explained an additional 45% ($p<0.005$) of the variance in improvement of dyspnea-time slopes.

Exercise Response to Combined Oxygen and Bronchodilators (O_2 +BD)

With O_2 +BD combined, endurance time increased by 5.0(1.5) min (127(40) %) compared with RA+PL ($p=0.004$). This increase was greater ($p=0.01$) than with either intervention alone and equaled the sum of increases with BD and O_2 singly ($p=0.86$; agreement measured by $r=0.86$, $p<0.0005$). By combining interventions, dyspnea was displaced as the predominant exercise-limiting symptom such that more subjects now stopped due to combined breathing and leg discomfort and due to other reasons such as being too hot, too tired, or too uncomfortable sitting on the bicycle seat (fig 2). Dyspnea-time slopes fell significantly in response to O_2 +BD compared with RA+PL ($p=0.001$), and were also different from those with BD ($p=0.010$) and O_2 ($p=0.045$) alone (fig 1). Slopes of Borg ratings of perceived leg discomfort over time fell significantly in response to O_2 +BD compared to RA+PL ($p=0.002$) and compared to BD alone ($p=0.021$) (fig 1).

For all interventions, dyspnea-IRV relationships remained constant (fig 5). Once IRV reached its “minimal” level of 0.4 L, on average, dyspnea increased steeply until it reached its peak level. The plateau in IRV at this point (fig 5) corresponded with the plateau in the V_T response to exercise (fig 4).

By combining O_2 and BD, the opposing changes in exercise V_E resulting from each intervention alone were negated, i.e., an increase in V_T (similar to with BD alone) and a decrease in F (similar to with O_2 alone) resulted in no change in V_E (fig 4). Adding BD to O_2 also reduced ($p<0.05$) the magnitude of increase in $PaCO_2$ and HCO_3^- shown with O_2 alone (table 3).

Correlates of improvement: Baseline diffusing capacity (D_{LCO} ; %predicted) correlated with improvements in the dyspnea-time slope with O_2 +BD ($r=0.62$, $p=0.010$) as well as with this slope prior to intervention (i.e., on RA+PL; $r=-0.64$, $p=0.007$). Decreases in dyspnea at isotime correlated best with reductions in isotime F ($r=0.81$, $p<0.0005$), but also with decreases in V_E ($r=0.58$, $p=0.019$) and increases in T_E ($r=-0.52$, $p=0.041$); stepwise regression selected the combination of changes in F and EILV/TLC to best predict the relief of dyspnea at isotime ($r^2=0.74$, $p<0.0005$). Reductions in dyspnea did not correlate with improvements in FEV_1 ($p>0.2$).

Additional results are presented in the online supplement.

DISCUSSION

This is the first study to demonstrate additive effects of BD and O₂ therapy on dyspnea and exercise endurance in normoxic COPD, reflecting the combined salutary influences of improved dynamic mechanics and reduced ventilatory drive. The other novel aspect of this study is that it helps us to understand how these treatments interact.

The effects of hyperoxia on breathing pattern and operating lung volumes were distinctly different from those of bronchodilators in the same patients. Consistent with the results of previous studies,[4][5][6][25] BD therapy was associated with a 17% increase in resting IC, thus allowing greater V_T expansion “from below” throughout exercise, within the constraints of the existing diminished IRV. In contrast to previous studies,[4-6] mean IRV at a standardized time during exercise was not increased after BD compared with placebo and dyspnea-IRV relationships remained superimposed. It follows that IRV recruitment during exercise is not a prerequisite for dyspnea alleviation during BD therapy, provided greater V_T expansion is achieved as a result of an increased IC. Reductions in breathing frequency (increased T_I and T_E) in conjunction with increased V_T during exercise likely reflect BD-induced improvements in the operating limits for volume expansion. While bronchodilators increased IC, V_T and V_E, hyperoxia was associated with reduced V_E as a result of reduced breathing frequency, with minimal change in V_T or IC. Reduced frequency reflected prolongation of both T_I and T_E, but correlated more closely with the increase in T_I (r=-0.87, p<0.0005); there was no change in the inspiratory duty cycle (T_I/T_{TOT}). This consistent effect on respiratory timing must ultimately reflect altered peripheral chemoreceptor input.

The mechanisms of reduced ventilation are debated. Most short-term studies in health show either no change,[9][26][27][28][29] or a reduction in V_E during exercise due to a drop in breathing frequency, especially at higher submaximal exercise levels.[30][31][32] In studies in non-hypoxic patients with COPD, the range of reduction in exercise V_E varied between 6 and 15% (i.e., approximately 2-6 L/min), again due to a decrease in breathing frequency.[30][31][32]

Previous studies on the effect of hyperoxia on oxygen uptake and ventilatory kinetics and blood lactate levels in normoxic COPD show conflicting results, with the majority of studies showing an improvement in oxidative capacity. [7][9][33] We previously reported a reduction in lactate in conjunction with a reduced V_E during hyperoxia in both hypoxic and non-hypoxic COPD patients.[7][13] In the current study, the relationship between V_E and base excess (which is inversely related to blood lactate) was superimposable on O₂ and room air, suggesting that the reduction in V_E during hyperoxia was linked to reduced metabolic acidosis. However, in the present study there was a significant decrease in the V_E/VCO₂ ratio at a standardized exercise time during O₂ with no change during BD. This suggests that the decrease in V_E and the increase in arterial CO₂ during hyperoxia are independent of metabolic factors and that direct effects of hyperoxia (independent of reduced acidosis) on carotid receptor input cannot be ruled out.

In accordance with the results of our previous study on the effects of hyperoxia in normoxic COPD patients,[7] only 7 of the 16 patients in the current study reduced operating lung volumes in response to 50% O₂ compared with room air. This small subset of patients had significantly greater baseline airway obstruction, greater ventilatory constraints during exercise, and poorer exercise performance with steeper dyspnea-V_E slopes. Moreover, these volume-responders had greater depression of V_E and prolongation of T_E, and experienced greater dyspnea relief with supplemental O₂ than the remaining patients.

Combined Bronchodilators and Hyperoxia

The physiological interactions of the combined interventions resulted in additive effects on exertional dyspnea and exercise endurance time. The magnitude of this effect (a 1.75 unit decrease in standardized dyspnea ratings and nearly a two-fold increase in endurance time) was impressive and likely clinically important. The dominant physiological effects that were evident when interventions were considered in isolation were still discernable when given in combination. However, the net effect of the combination on exercise V_E was neutral: the decrease in V_E as a result of decreased breathing frequency during hyperoxia was counterbalanced by the increased V_E as a result of increased V_T secondary to BD. Timing component changes during the combination mimicked those seen during hyperoxia alone. The increase in IC at rest and exercise in the bronchodilator arm of the study was also preserved during combined therapy. Finally, in spite of an increased cumulative V_E over an extended exercise duration with the combined therapies, dyspnea intensity was significantly diminished.

Mechanisms of Symptom Relief

As previously reported during exercise in COPD,[5] this study showed a discernible inflection point in the dyspnea-IRV relationship such that dyspnea rose steeply after reaching a “minimal” IRV where further V_T expansion was not possible (fig 5). After this inflection, dyspnea at this minimal IRV likely rises with the increasing disparity between neural drive (and inspired effort) and the V_T response which is essentially fixed, i.e., neuromechanical dissociation.[34] It is noteworthy that BD, O_2 or their combination had no significant effect on the time course of change of the IRV with exercise or on the dyspnea-IRV relationship, suggesting that factors other than change in IRV are instrumental in both dyspnea causation and its relief. Thus, when a minimal IRV is reached during exercise, dyspnea relief is possible if the intervention releases V_T constriction by increasing IC (e.g., in response to BD), reduces neural drive (e.g., in response to O_2) or accomplishes both of these together. Of note, patients (10 out of 16) who increased exercise IC with BD showed important improvements in dyspnea and endurance, whereas those with no change in IC did not. It is also of interest that despite impressive increases in FEV₁ (by an average of 28%) following high-dose BD therapy, there was no correlation between this variable and improvements in either dyspnea or exercise endurance. The finding that dyspnea relief correlated with increased V_T , reduced breathing frequency and reduced EELV supports the idea that reduced elastic loading is importantly linked to dyspnea relief with BD.

A comparison of the effects of BD and O_2 , singly and in combination, on dyspnea- V_E slopes allowed us to identify different underlying mechanisms of dyspnea relief. Dyspnea intensity fell for a given V_E after BD compared with placebo, likely reflecting the improvement in ventilatory mechanics outlined above. By contrast, mean dyspnea- V_E slopes during hyperoxia and room air were exactly superimposed suggesting that reduction of dyspnea at a standardized time during O_2 mainly reflected the concomitant reduction of V_E . Interestingly, dyspnea- V_E slopes remained superimposed on O_2 and room air even in the subgroup (7/16) of patients who reduced operating lung volumes. However, after accounting for the reduction in V_E , reductions in lung hyperinflation further contributed to dyspnea relief during O_2 . Although improved ventilatory mechanics and reduced neural drive have been identified as possible contributory factors in dyspnea relief in this study, we recognize that other oxygen-induced factors (not evaluated in this study) such as reduced pulmonary hypertension, improved left ventricular function, central effects of hyperoxia on the perception of dyspneogenic stimuli and reduced anxiety may all affect the intensity and quality of exertional dyspnea on an individual basis.

Combined O₂ and BD had additive effects on dyspnea-time slopes; dyspnea also fell at a given ventilation during exercise. Seventy-four percent of the variance in change of dyspnea ratings at a standardized exercise time was explained by the combination of reduced breathing frequency and EILV. Patients with the lowest D_LCO, the most severe exertional dyspnea and worst impairment of exercise endurance derived the greatest subjective benefit from the combined interventions. O₂ with BD resulted in a dramatic shift in the locus of sensory limitation to exercise such that dyspnea was now rarely selected by patients as the primary exercise-limiting symptom.

During the O₂ applications (alone and in combination with BD), perceived leg discomfort fell significantly whereas no such effect was seen with BD alone. The mechanism of benefit is unknown but may indicate an improved metabolic milieu in the active peripheral skeletal muscles with increased intracellular O₂ tension. Recent studies by Hogan *et al* have shown that an oxygen-rich environment in the exercising muscles of healthy individuals attenuated muscle fatigue.[35] A similar effect has been suggested during 30% O₂ in mildly hypoxemic patients with COPD.[36] Improved oxygenation may alter sensory afferent inputs from muscle mechanoreceptors and metaboreceptors or enhance neuromuscular coupling. Reduced fatigue would result in reduced central motor command output and, possibly, attendant reductions in ventilation.[37] This may translate into a concomitant reduction of perceived effort required for a given force generation by these muscles. It is intriguing to speculate that similar salutary effects may occur in the ventilatory and peripheral muscles in response to O₂, with favorable consequences for the perception of both leg discomfort and exertional dyspnea.

Summary

This study extended the results of previous mechanistic studies on pharmacotherapy in COPD by demonstrating that effective dyspnea relief is possible with BD in the absence of increase in IRV during exercise provided there is also an increase in V_T expansion. This study also showed that alleviation of exertional dyspnea during O₂ breathing is possible in normoxic COPD patients in the absence of any consistent reductions in the rate of dynamic hyperinflation. As our analysis of dyspnea-V_E slopes suggests, dyspnea relief during O₂ is mainly linked to reduced ventilatory demand. The benefits following O₂ and combined O₂ and BD were most pronounced in those with the most severe disease and these individuals showed greater reduction in operating lung volumes during exercise than patients with less severe COPD. The physiological interactions of combining BD and O₂ culminated in impressive improvements in exertional symptoms and exercise endurance, thus underscoring the incremental benefits of reducing neural drive and improving dynamic ventilatory mechanics. Finally, this study provides a physiological rationale for the recommendation of O₂ therapy as an adjunct to exercise reconditioning for patients with more advanced, normoxic COPD who remain incapacitated by dyspnea despite optimization of bronchodilators.

.....

Presented, in part, at the ALA/ATS International Conference, San Diego, May 2005 (Peters MM, Webb KA, O'Donnell DE. The effects of supplemental oxygen and bronchodilators on exertional dyspnea and exercise performance in patients with COPD. *Am J Respir Crit Care Med* 2005; 171:A495).

Supported by: Ontario Ministry of Health; Ontario Thoracic Society; William M. Spear Endowment Fund, Queen's University.

Competing interests: None of the authors have any competing interests to declare.

REFERENCES

1. Celli BR, MacNee W, and committee members. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23:932-46.
2. O'Donnell DE, Aaron S, Bourbeau J, *et al.* Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease – 2003. *Can Respir J* 2003;10:11A-65A.
3. O'Donnell DE, Lam M, Webb KA. Measurement of symptoms, lung hyperinflation and endurance during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;158:1557-65.
4. O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;160:542-9.
5. O'Donnell D, Flüge T, Gerken F, *et al.* Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* 2004;23:832-40.
6. O'Donnell DE, Voduc N, Fitzpatrick M, Webb KA. Effect of salmeterol on the ventilatory response to exercise in COPD. *Eur Respir J* 2004;24:86-94.
7. O'Donnell DE, Bain DJ, Webb KA. Factors contributing to relief of exertional breathlessness during hyperoxia in chronic airflow limitation. *Am J Respir Crit Care Med* 1997;155:530-5.
8. Somfay A, Porszasz J, Lee SM, *et al.* Dose-response effect of oxygen on hyperinflation and exercise endurance in non-hypoxemic COPD patients. *Eur Respir J* 2001;18:77-84.
9. Somfay A, Porszasz J, Lee SM, *et al.* Effect of hyperoxia on gas exchange and lactate kinetics following exercise onset in nonhypoxemic COPD patients. *Chest* 2002;121:393-400.
10. Dean NC, Brown JK, Himelman RB, *et al.* Oxygen may improve dyspnea and endurance in patients with chronic obstructive pulmonary disease and only mild hypoxemia. *Am Rev Respir Dis* 1992;146:941-5.
11. Vyas MN, Banister EW, Morton JW, *et al.* Response to exercise in patients with chronic airway obstruction. II. Effects of breathing 40 per cent oxygen. *Am Rev Respir Dis* 1971;103:401-12.
12. Emtner M, Porszasz J, Burns M, *et al.* Benefits of supplemental oxygen in exercise training in nonhypoxemic chronic obstructive pulmonary disease patients. *Am J Respir Crit Care Med* 2003;168:1034-42.
13. O'Donnell DE, D'Arsigny C, Webb KA. Effects of hyperoxia on ventilatory limitation during exercise in advanced chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;163:892-8.
14. Stoller JK, Ferranti R, Feinstein AR. Further specification and evaluation of a new clinical index for dyspnea. *Am Rev Respir Dis* 1986;135:1129-34.
15. Morris JF, Koski A, Temple WP, *et al.* Fifteen-year interval spirometric evaluation of the Oregon predictive equations. *Chest* 1988;92:123-7.
16. Knudson RJ, Lebowitz MD, Holberg CJ, *et al.* Changes in normal maximal expiratory flow-volume curves with growth and aging. *Am Rev Respir Dis* 1983;127:725-34.
17. Crapo RO, Morris AH, Clayton PD, *et al.* Lung volumes in healthy nonsmoking adults. *Bull Europ Physiopath Resp* 1982;18:419-25.
18. Burrows B, Kasik JE, Niden AH, *et al.* Clinical usefulness of the single-breath pulmonary diffusing capacity test. *Am Rev Respir Dis* 1961;84:789-806.

19. Briscoe WA, Dubois AG. The relationship between airway resistance, airway conductance, and lung volumes in subjects of different age and body size. *J Clin Invest* 1959;37:1279-85.
20. Hamilton AL, Killian KJ, Summers E, *et al.* Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. *Am J Respir Crit Care Med* 1995;152:2021-31.
21. Borg GAV. Psychophysical basis of perceived exertion. *Med Sci Sports Exerc* 1982;14:377-81.
22. O'Donnell DE, Lam M, Webb KA. Measurement of symptoms, lung hyperinflation and endurance during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;158:1557-65.
23. 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: 770-7.
24. Jones NL. Clinical exercise testing, 3rd ed. Philadelphia: WB Saunders Company 1988:306.
25. Belman MJ, Botnick WC, Shin JW. Inhaled bronchodilators reduce dynamic hyperinflation during exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;153:967-75.
26. Griffiths TL, Henson LC, Whipp BJ. Influence of inspired oxygen concentration on the dynamics of the exercise hyperpnoea in man. *J Physiol* 1986;380:387-403.
27. Hughes RL, Clode M, Edwards RHT, *et al.* Effect of inspired O₂ on cardiopulmonary and metabolic responses to exercise in man. *J Appl Physiol* 1968;24(3):336-47.
28. Davies CTM, Sargeant AJ. Physiological responses to one- and two-leg exercise breathing air and 45% oxygen. *J Appl Physiol* 1974;36(2):142-8.
29. Casaburi R, Stremel RW, Whipp BJ, *et al.* Alteration by hyperoxia of ventilatory dynamics during sinusoidal work. *J Appl Physiol* 1980;48(6):1083-91.
30. Ekblom B, Huot R, Stein EM, *et al.* Effect of changes in arterial oxygen content on circulation and physical performance. *J Appl Physiol* 1975;39(1):71-5.
31. Bye PTP, Esau SA, Walley KR, *et al.* Ventilatory muscles during exercise in air and oxygen in normal men. *J Appl Physiol* 1984;56(2):464-71.
32. Welch HG, Bonde-Petersen F, Graham T, *et al.* Effects of hyperoxia on leg blood flow and metabolism during exercise. *J Appl Physiol* 1977;42(3):385-90.
33. Palange P, Galassetti P, Mannix ET, *et al.* Oxygen effect on O₂ deficit and VO₂ kinetics during exercise in obstructive pulmonary disease. *J Appl Physiol* 1995;78(6):2228-34.
34. O'Donnell DE, Chau LKL, Bertley JC, *et al.* Qualitative aspects of exertional breathlessness in chronic airflow limitation: pathophysiologic mechanisms. *Am J Respir Crit Care Med* 1997;155:109-15.
35. Hogan MC, Richardson RS, Haseler LJ. Human muscle performance and PCr hydrolysis with varied inspired oxygen fractions: a ³¹P-MRS study. *J Appl Physiol* 1999;99:1367-73.
36. Gosselin N, Durand F, Poulain M, *et al.* Effect of acute hyperoxia during exercise on quadriceps electrical activity in active COPD patients. *Acta Physiol Scand* 2004;181:333-43.
37. Gandevia SC. Neural mechanisms underlying the sensation of breathlessness: kinesthetic parallels between respiratory and limb muscles. *Aus N Z J Med* 1988;18(1):83-91.

FIGURES

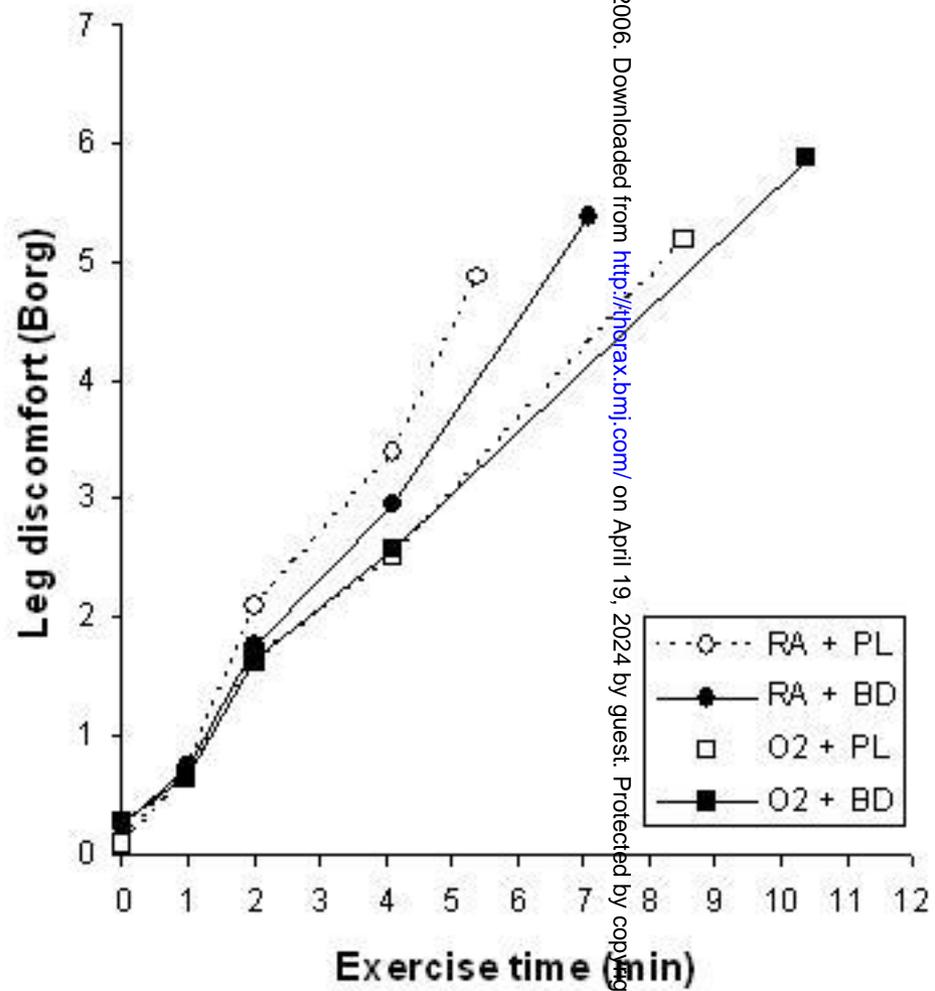
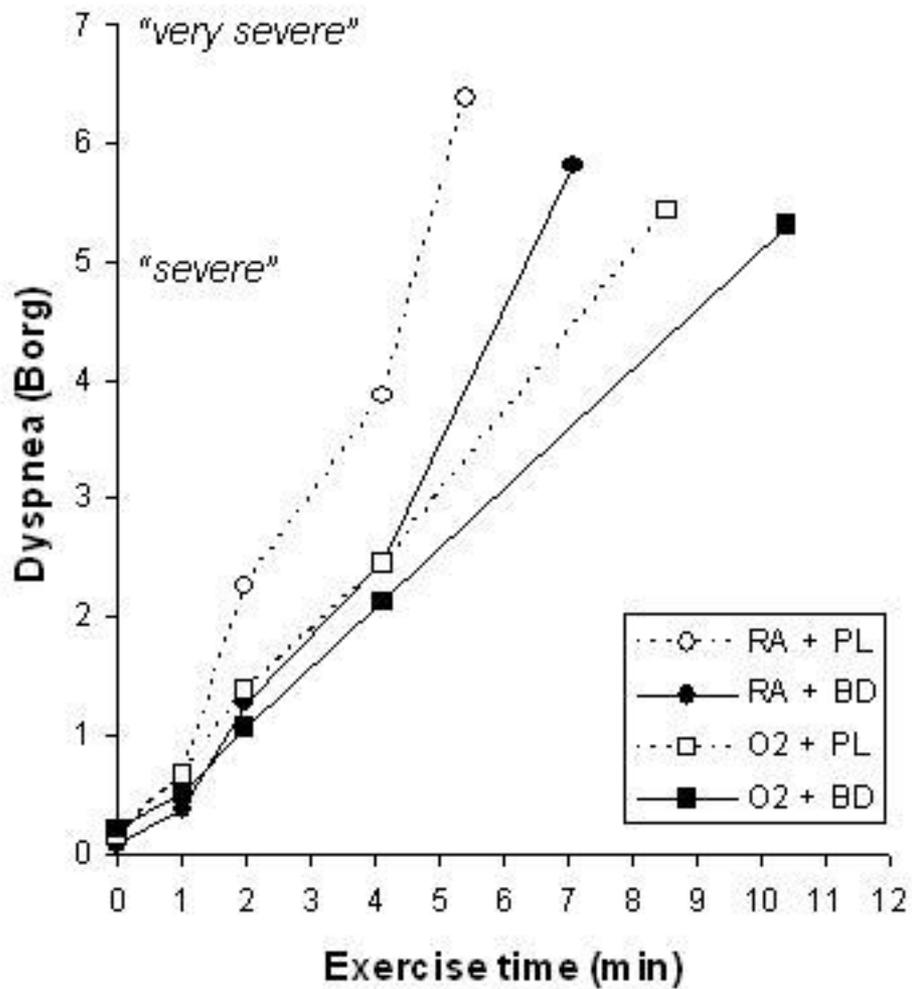
Figure 1. Average Borg ratings of dyspnea and leg discomfort are shown over time during constant-load cycle exercise at 75% of peak work rate. Dyspnea-time slopes decreased significantly ($p<0.05$) with bronchodilators (BD) and 50% oxygen (O_2), alone and in combination; the combination of O_2 +BD resulted in greater ($p<0.05$) dyspnea relief than either BD or O_2 alone. Slopes of leg discomfort over time fell significantly ($p<0.05$) with O_2 , either alone or in combination with BD. Abbreviations: PL = placebo; RA = room air.

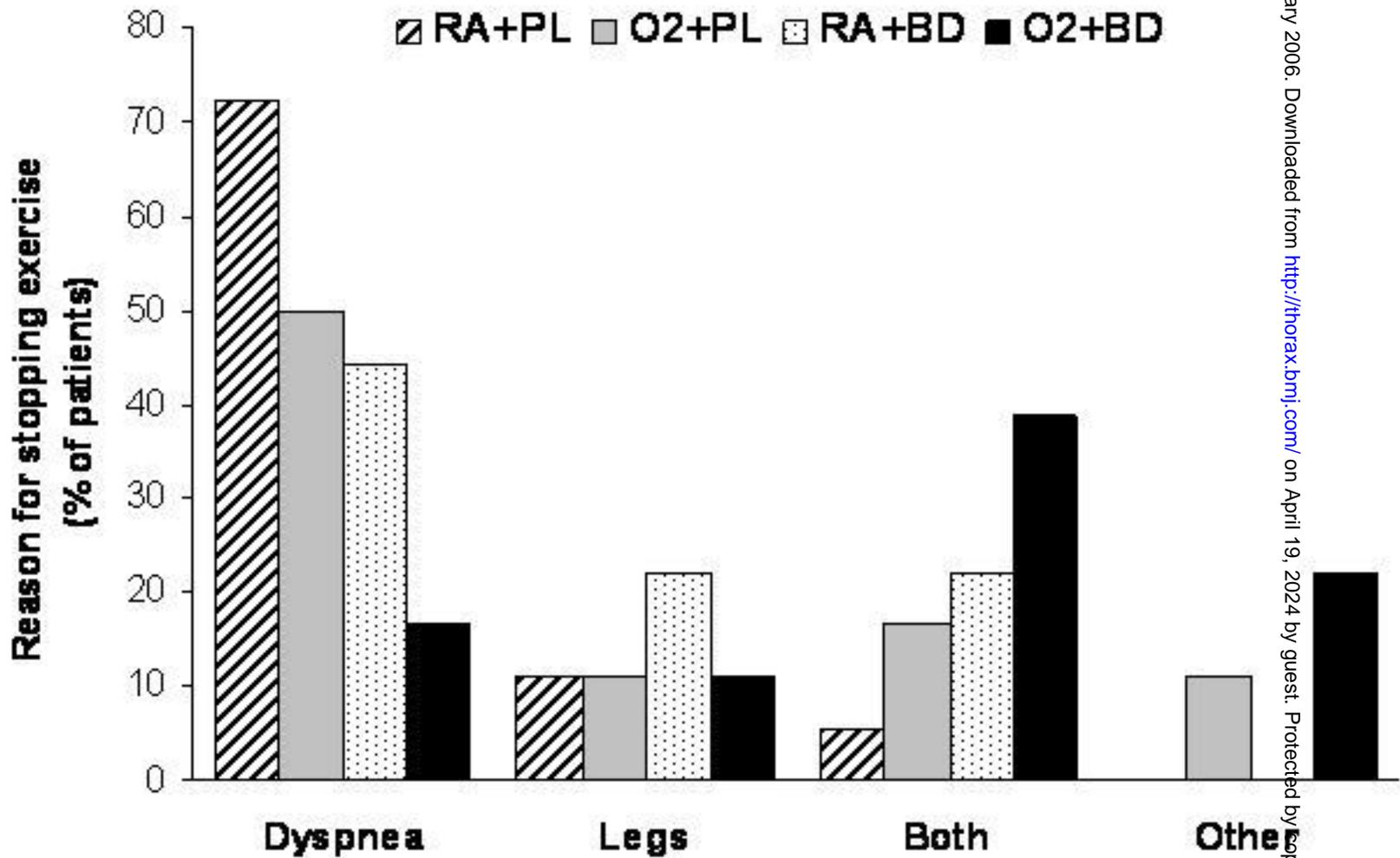
Figure 2. The selection frequency of reasons for stopping symptom-limited cycle endurance tests. The percent of patients stopping exercise mainly because of dyspnea decreased with O_2 and BD, alone or in combination, while other reasons or leg discomfort (combined with dyspnea) became more predominant. The distribution of reasons for stopping was significantly ($p<0.01$) different with the treatment combination (O_2 +BD) compared with during room air and placebo (RA+PL).

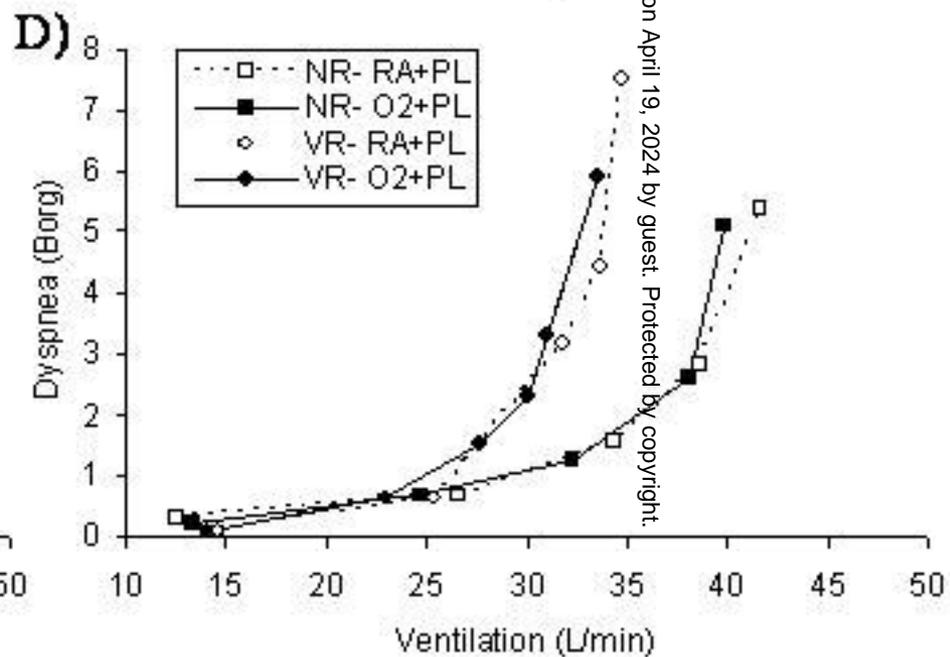
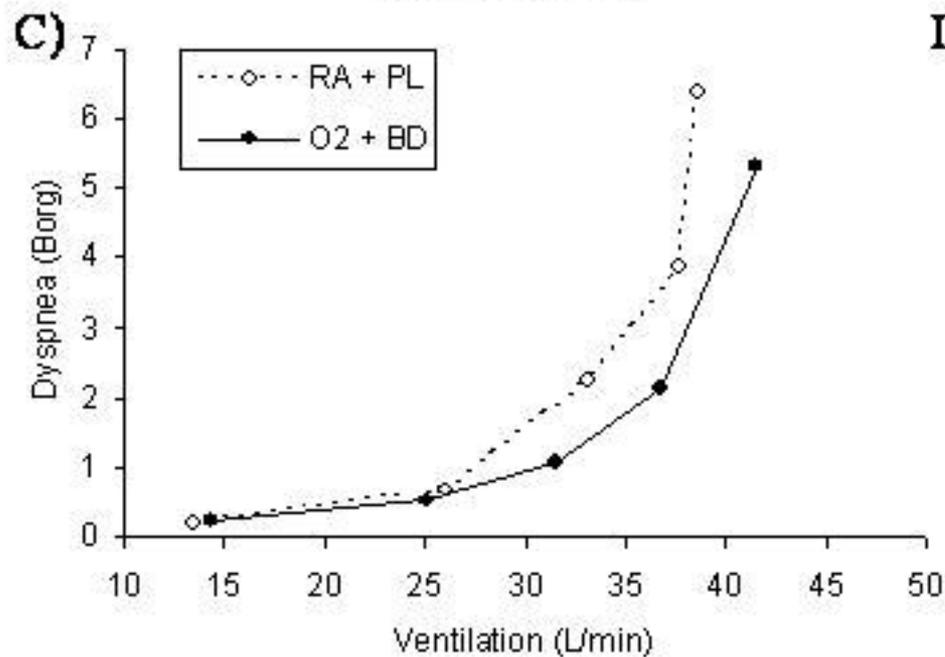
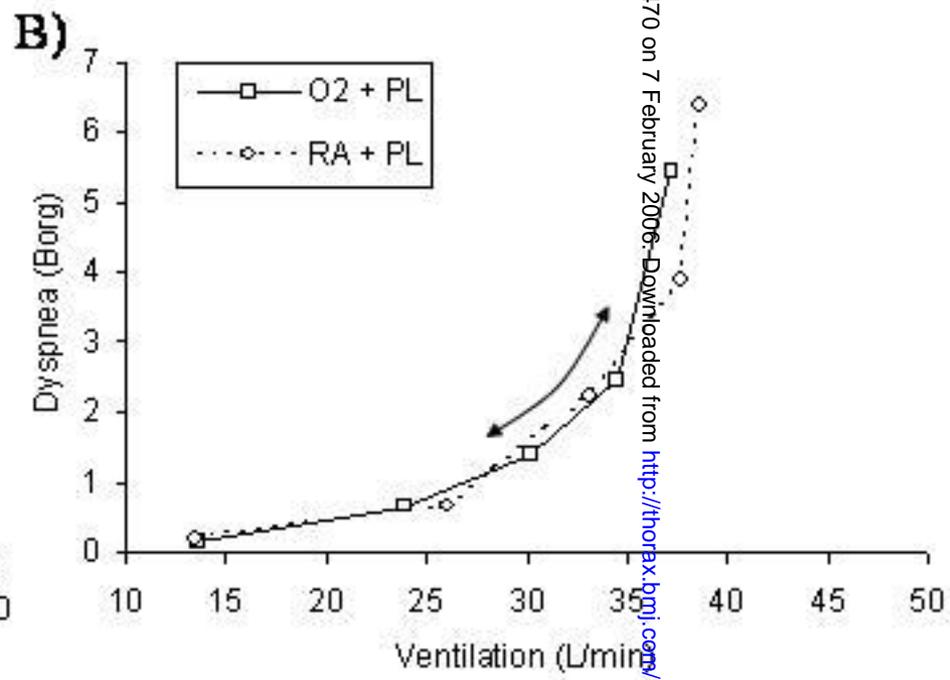
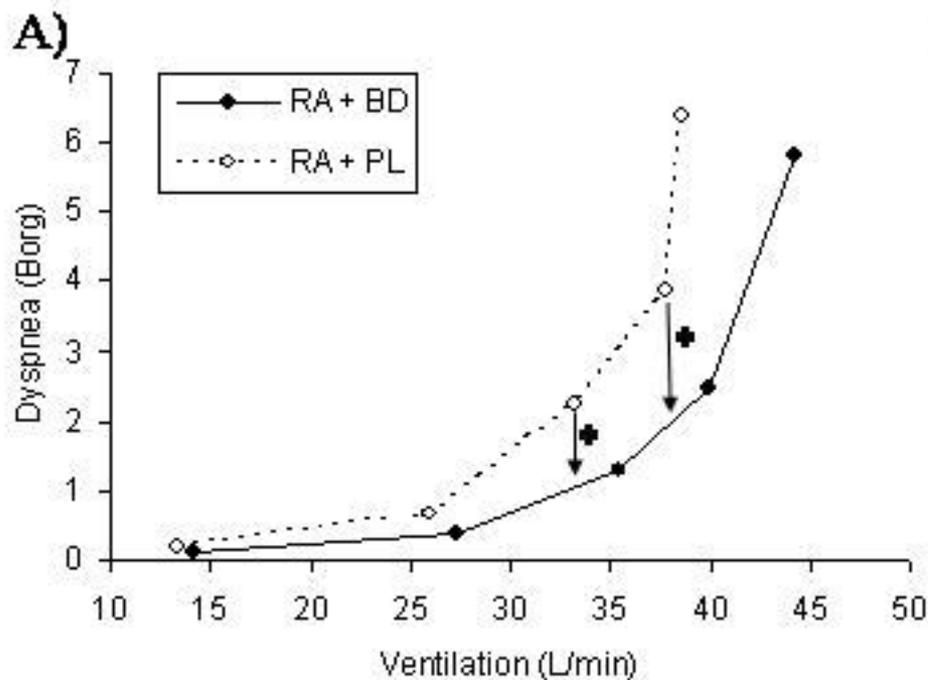
Figure 3. Dyspnea-ventilation (V_E) plots are shown for bronchodilators (BD) and 50% oxygen (O_2), alone and in combination, compared with placebo (PL) and room air (RA). **(A)** Dyspnea- V_E slopes shift downwards and to the right with BD such that dyspnea is significantly ($*p<0.05$) reduced for a given V_E during exercise. **(B)** With O_2 , dyspnea- V_E relationships remain unchanged so that dyspnea falls in conjunction with a fall in V_E . **(C)** With O_2 +BD combined, the dyspnea- V_E response falls between those of BD and O_2 alone. **(D)** Responses to O_2 are shown for O_2 -induced “volume-responders” (VR: i.e., those who increased exercise IC) and “non-responders” (NR: i.e., those with no change in exercise IC). Despite differences in slopes on room air and placebo (RA+PL) across subgroups, dyspnea- V_E relationships did not change with O_2 in either group.

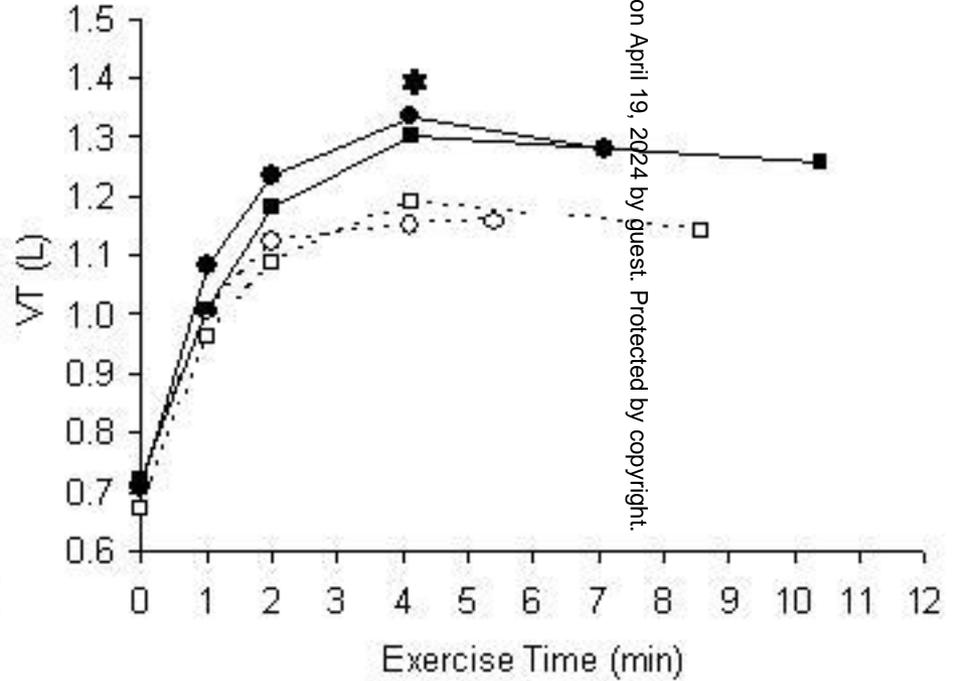
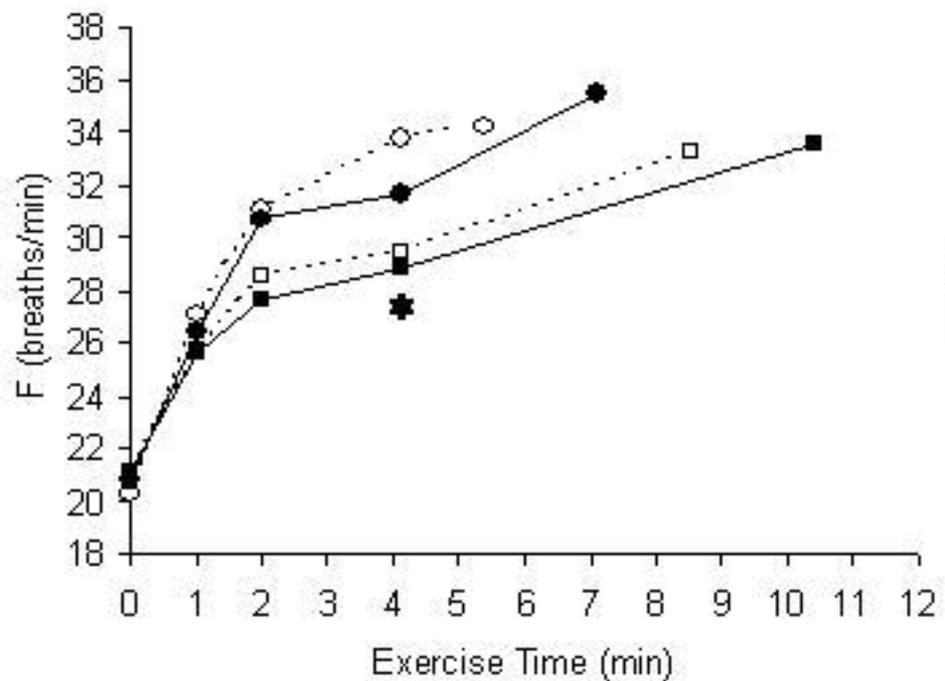
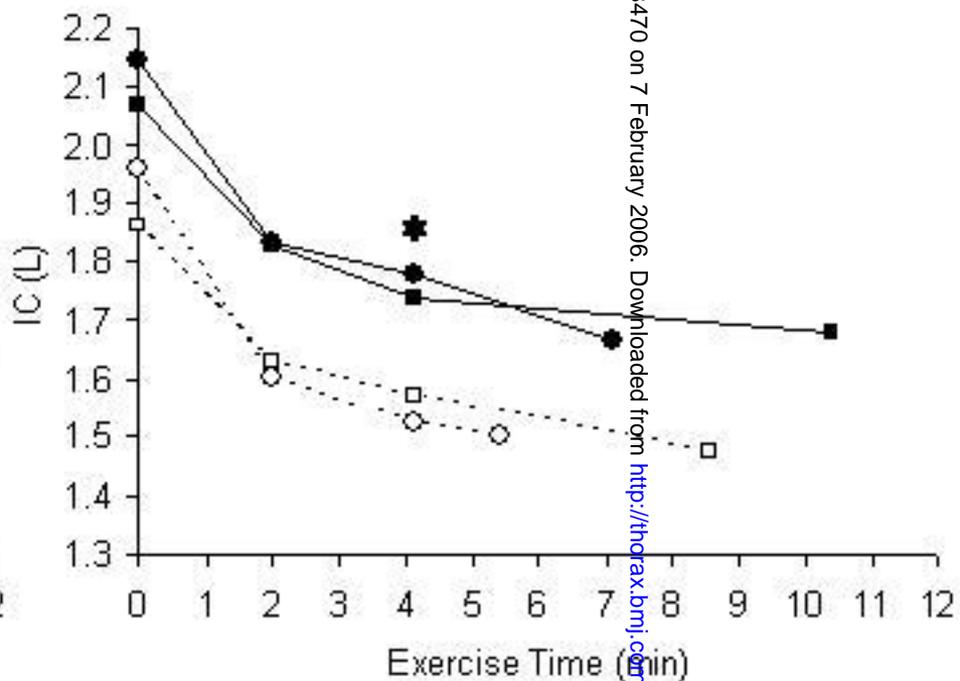
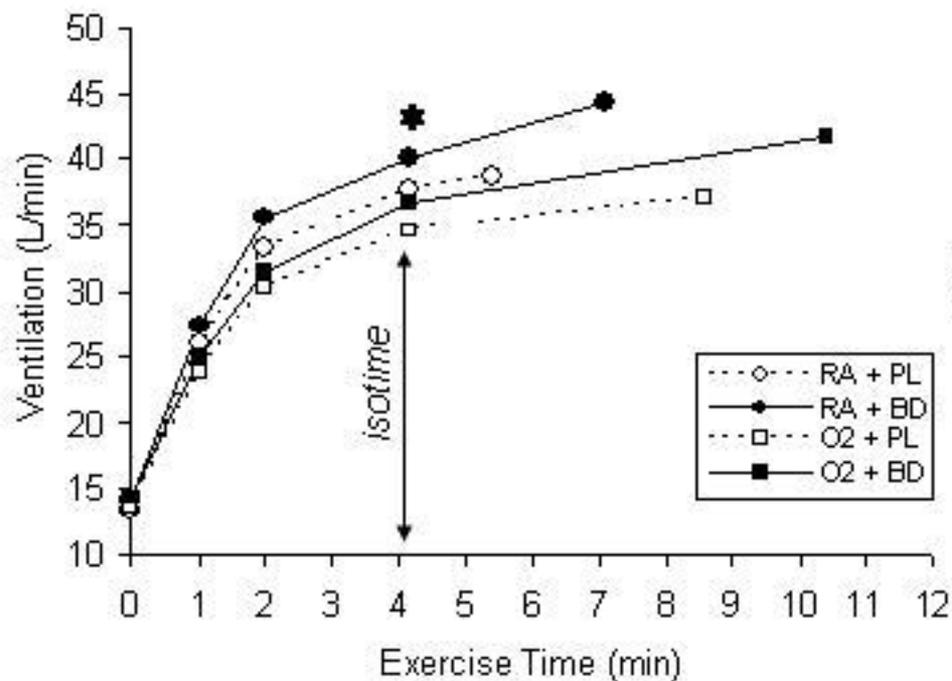
Figure 4. Ventilatory responses to constant-load cycle exercise are shown for 50% oxygen (O_2) and bronchodilators (BD), alone and in combination, compared with room air (RA) and placebo (PL). * See Table 4 for significant differences between tests at a standardized time (*isotime*) during exercise.

Figure 5. Relationships between dyspnea and inspiratory reserve volume (IRV) during exercise were superimposable for each test. Once a *minimal* IRV was reached, dyspnea intensity increased steeply to reach its peak level while no further change in IRV occurred.









33470 on 7 February 2006. Downloaded from <http://thorax.bmj.com/> on April 19, 2024 by guest. Protected by copyright.

