ONLINE DATA SUPPLEMENT

Combined effects of bronchodilators and hyperoxia on dyspnoea and exercise endurance in normoxic COPD

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Methods

Exercise testing

Volume and gas calibrations were performed prior to each test. Exercise testing was conducted on a calibrated, electronically-braked cycle ergometer with a constant pedaling frequency of 50–70 rpm. At the screening visit, the seat height was adjusted so that the subject's legs were almost completely extended when the pedals were at the lowest point and the cycling rhythm practiced; the seat was adjusted to this height in all subsequent exercise challenges. The incremental exercise test consisted of a steady-state resting period of at least 3 minutes, followed by 1 minute of loadless pedaling, with subsequent systematic increases in work rate in increments of 10 watts each minute to the point of symptom limitation. Maximal work capacity (W_{max}) was defined as the greatest work rate that the subject was able to maintain for at least 30 seconds. Constant-load exercise tests consisted of a steady-state resting period, a 1-minute period of loadless pedaling, and then an immediate "step" increase in work rate to 75% W_{max} which was maintained until the point of symptom limitation. Endurance time was recorded as the time from the increase in work rate to 75%W_{max} to the point of symptom limitation.

Prior to each exercise test, a detailed explanation of the testing procedures and equipment was given to the subject, outlining the risks involved and potential complications. Indications to stop the test were clearly established in accordance with clinical exercise testing guidelines.[1, 2]

Subjects were encouraged to cycle to the point of symptom limitation by being specifically instructed to “cycle for as long as you can”. During exercise, standardized and continuous verbal encouragement to subjects was provided by a member of the study team who was blinded to the results of the lung function testing.

Subjects breathed through a mouthpiece and a low resistance flow transducer. Breath-by-breath measurements [minute ventilation (V_E), tidal volume (V_T), breathing frequency (*F*), oxygen consumption (VO_2), oxygen saturation (SaO_2)] were collected using a cardiopulmonary exercise testing system (Vmax229d; SensorMedics, Yorba Linda, CA). Due to measurement errors inherent to testing during hyperoxia, VO_2 was not analyzed for these tests. Pulse oximetry and electrocardiographic monitoring were carried out throughout exercise, while blood pressure was determined before, every 2 minutes during exercise, at the end of exercise, and 5 minutes post-exercise. Cardiopulmonary measurements were recorded as 30-second averages. At rest, every minute during exercise, and at the end of exercise, subjects rated the intensity of their breathing and leg discomfort using the modified Borg category-ratio scale.[3] Inspiratory capacity (IC) maneuvers were performed after Borg ratings pre-exercise, every second minute during exercise, and at end-exercise. At the same time points, subjects also rated the intensity of their leg discomfort. At the end of exercise, subjects were asked why the stopped exercising.

Symptom intensity during exercise

Prior to exercise testing, subjects were informed that they would be asked to rate the intensity of their “breathing discomfort” and “leg discomfort” during exercise. Subjects were given no further information about these sensations. Subjects were first familiarized with the modified Borg category-ratio scale[3] and its endpoints were anchored such that zero represented “no breathing (leg) discomfort” and 10 was “the most severe breathing (leg) discomfort that they had ever experienced or could imagine experiencing”. By pointing to the Borg Scale, subjects rated the intensity of their breathing and leg discomfort at rest, every minute during exercise, and at end-exercise. Symptom ratings preceded IC maneuvers by at least 5 breaths to avoid interference with pre-IC breathing patterns, and to avoid the possible influence that the performance of an IC maneuver might have on dyspnea intensity.

Inspiratory capacity measurements

IC measurements were collected as previously described.[4] At each visit, the correct conduct of IC maneuvers was fully explained to the patient and then practiced at rest until consistently reproducible efforts were made (i.e., within ±5% or ±100♣mL, whichever was larger). Subjects were given a few breaths warning before an IC maneuver, a prompt for the maneuver (i.e., "At the end of the next normal breath out, take a deep breath all the way IN" or "at the end of this breath out, take a big breath all the IN"), and then strong verbal encouragement to make a maximal effort (i.e., "in…, in…, in…) before returning to their regular breathing.

The resting IC was recorded as the mean of the two best reproducible efforts. Satisfactory technique and repeatability of maneuvers was ensured before proceeding with exercise testing. During the constant-load exercise tests, IC maneuvers were performed at 2-minute intervals. When subjects indicated the desire to stop exercise, an end-exercise IC maneuver was performed within 15♣seconds and the subjects were permitted to cool down; or if an acceptable IC had been performed within the preceding 30♣seconds and the breathing pattern had not restabilized, then the value for that IC was used as the end-exercise value. If an exercise IC maneuver was found to be unacceptable (i.e., submaximal effort or anticipatory changes in breathing pattern immediately preceding the IC maneuver), it was not repeated and was excluded from the analysis. End-expiratory lung volume (EELV) was calculated as total lung capacity (TLC) minus

IC, with the assumption that TLC remains constant during exercise.[5] Inspiratory reserve volume (IRV) was calculated as IC minus V_T.

Arterialized capillary blood gases

Measurements of $PaCO_2$, PaO_2, pH, bicarbonate and base excess were obtained via arterialized capillary blood samples taken from the earlobe at rest, at 2♣minutes intervals during exercise and at the end of exercise. The earlobe was warmed for at least 5♣minutes prior to testing using a warm cloth; a deep puncture was made with a lancet so that a free flow of blood appeared; a blood sample was drawn into a preheparinized capillary tube; tubes were immediately sealed, placed on ice, and analyzed (ABL; Radiometer, Copenhagen, Denmark) all together immediately at the end of the exercise test. This non-invasive method has been shown to be a reliable and sufficiently accurate for clinical exercise testing, with no significant differences between PaO_2 or $PaCO_2$ obtained by this method and simultaneous arterial blood samples.[6]

Locus of symptom limitation

To determine the locus of symptom limitation, subjects answered the following question immediately after reaching the point of symptom limitation:

Did you stop exercising because of:

- A. Breathing discomfort?
- B. Leg discomfort?
- C. A combination of breathing and leg discomfort?
- D. Some other reason?

If you answered “D”, please describe the reason.

Exercise end points for analysis

Three main time points were used for evaluation of exercise parameters, i.e., pre-exercise rest, a standardized time during exercise (isotime), and peak exercise. *Rest* was defined as the steady-state period after at least 3♣minutes of breathing on the mouthpiece while seated at rest on the cycle ergometer before exercise was started: cardiopulmonary parameters were averaged over the last 30♣seconds of this period, IC measurements for this period were collected while breathing on the same circuit immediately after completion of the quiet breathing period. *Peak* was defined as the last 30♣seconds of loaded pedaling: cardiopulmonary parameters were taken as the average over this time period, IC measurements and Borg ratings were collected immediately at the end of this period. *Isotime* was defined as the duration of the shortest exercise test on all treatment days. Values at isotime were measured within the last full minute of the shortest exercise test: cardiopulmonary measurements were averaged over the first 30♣seconds of this minute while Borg ratings and IC measurements were captured within the second 30♣seconds of this minute. If the isotime minute of exercise did not correspond with a period of IC collection (i.e., every second minute), then a value for isotime IC was derived by linear interpolation over time between the two values measured before and after the interval containing the isotime minute within that test.

Results

Randomization visits were well balanced for each intervention. No sequence effect was demonstrated for endurance time when chronological values were evaluated by ANOVA for repeated measures (p=0.34). Similarly, no sequence effect was shown for other important outcomes, i.e., isotime measurements of dyspnea intensity (p=0.92), leg discomfort (p=0.52), ventilation (p=0.85) or IC (p=0.54).

Peak exercise: incremental versus constant-load cycle testing

During symptom-limited incremental cycle exercise, peak oxygen consumption (VO_2)[1.16 (0.12) L/min or 62 (4) % predicted maximum; mean (SEM)] and work rate [55 (3) % predicted maximum] were significantly reduced as a result of ventilatory limitation. Incremental exercise was discontinued primarily due to breathing discomfort (9/16) or a combination of breathing and leg discomfort (4/16), and less often as a result of predominant leg discomfort (3/16). During constant-load exercise [control testing on room air (RA) and placebo (PL)], subjects reached a similar peak VO_2 [1.23 (0.11) L/min, 67 (4) % predicted] and V_E [38.6 (2.9) L/min] as they did during incremental exercise, suggesting that the endurance test was “maximal”. Likewise, the majority of subjects (13/16) stopped constant-load exercise due to breathing discomfort.

Breathing pattern responses

Breathing pattern responses to each intervention are summarized at isotime [4.1(0.8) min] during constant-load exercise in table 1.

Table 1 Breathing pattern measurements at isotime during constant-load cycle exercise

Variable	RA + PL	RA + BD	O_2 + PL	O_2 + BD	p value (ANOVA)
T_I (s)	0.75 (0.03)	0.84 (0.04)*	0.84 (0.04)*	0.88 (0.05)*	<0.0005
T_E (s)	1.09 (0.05)	1.21 (0.08)*	1.25 (0.07)*	1.31 (0.09)*†	<0.0005
T_I/T_{TOT}	0.41 (0.01)	0.41 (0.01)	0.40 (0.01)	0.40 (0.02)	0.595
V_T/T_I (l/s)	1.55 (0.43)	1.61 (0.46)	1.43 (0.35)*†	1.49 (0.45)†	0.005
V_T/T_E, (l/s)	1.09 (0.39)	1.16 (0.45)*	0.99 (0.36)†	1.07 (0.50)†	0.003
Tidal PEF (l/s)	1.92 (0.53)	2.03 (0.68)	1.71 (0.48)*†	1.81 (0.66)†	0.002
F (breaths/min)	34 (2)	31 (2)*	29 (2)*	29 (2)*†	<0.0005
V_T (l)	1.15 (0.09)	1.33 (0.11)*	1.19 (0.09)*†	1.30 (0.11)*‡	<0.0005

Variable	RA + PL	RA + BD	O_2 + PL	O_2 + BD	p value (ANOVA)
V_T/IC (%)	76 (2)	75 (3)	75 (3)	74 (2)	0.871

Values are means (SEM). T_I, inspiratory time; T_E, expiratory time; T_I/T_{TOT}, inspiratory duty cycle equals inspiratory time over total breath time; PEF, peak expiratory flow; *F*, breathing frequency; V_T, tidal volume; IC, inspiratory capacity.

*p<0.05 vs RA+PL; †p<0.05 vs RA+BD; ‡:p<0.05 vs O_2+PL.

Hyperoxia-induced lung volume responses

On average, operating lung volumes at rest and during exercise did not change significantly in response to O_2 in these non-hypoxic patients with COPD. However, 7 out of 16 subjects had a reduction in lung hyperinflation during exercise on O_2 compared to room air, i.e., an increase in IC at isotime. Of note, the IC response to BD did not predict the IC response to O_2 (r=0.21, p=0.43).

Compared with the 9 subjects who did not have an O_2-induced increase in exercise IC, the 7 subjects with a volume response had significantly (p<0.05): *1*) worse maximal expiratory flows [FEV_1/FVC was 48(2) versus 39(2)% and $FEF_{25–75\%}$ was 12(2) and 8(1) %predicted, respectively]; *2*) steeper dyspnea-time slopes and poorer exercise endurance on RA, with greater improvements with O_2; *3*) steeper dyspnea-V_E relationships that did not change on O_2; and *4*) more significant decreases in V_E and mean tidal expiratory flow (due to increased expiratory time) in conjunction with the increases in IC and IRV in response to O_2 (fig S1).

Correlates of improvements in exercise endurance

After each intervention compared to control (RA+PL), improvements in exercise endurance time were related to reductions in dyspnea: the percent increase in endurance time correlated with dyspnea (Borg)-time slopes after BD (r=–0.66, p=0.01), after O_2 (r=–0.58, p=0.02) and after O_2+BD combined (r=–0.45, p=0.08). The best indicator of who would increase exercise endurance in response to combined O_2 and BD was the increase in endurance time in response to O_2 alone (r=0.92, p<0.0005).

References

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