Effect of salmeterol on the ventilatory response to exercise in chronic obstructive pulmonary disease

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ABSTRACT: This study examined the effects of bronchodilator-induced reductions in lung hyperinflation on breathing pattern, ventilation and dyspnoea during exercise in chronic obstructive pulmonary disease (COPD). Quantitative tidal flow/volume loop analysis was used to evaluate abnormalities in dynamic ventilatory mechanics and their manipulation by a bronchodilator.

In a randomised double-blind crossover study, 23 patients with COPD (mean±SEM forced expiratory volume in one second 42±3% of the predicted value) inhaled salmeterol 50 µg or placebo twice daily for 2 weeks each. After each treatment period, 2 h after dose, patients performed pulmonary function tests and symptom-limited cycle exercise at 75% of their maximal work-rate.

After salmeterol *versus* placebo at rest, volume-corrected maximal expiratory flow rates increased by 175±52%, inspiratory capacity (IC) increased by 11±2% pred and functional residual capacity decreased by 11±3% pred. At a standardised time during exercise, salmeterol increased IC, tidal volume (VT), mean inspiratory and expiratory flows, ventilation, oxygen uptake (V'O$_2$) and carbon dioxide output. Salmeterol increased peak exercise endurance, V'O$_2$ and ventilation by 58±19, 8±3 and 12±3%, respectively. Improvements in peak V'O$_2$ correlated best with increases in peak VT; increases in peak VT and resting IC were interrelated. The reduction in dyspnoea ratings at a standardised time correlated with the increased VT.

Mechanical factors play an important role in shaping the ventilatory response to exercise in chronic obstructive pulmonary disease. Bronchodilator-induced lung deflation reduced mechanical restriction, increased ventilatory capacity and decreased respiratory discomfort, thereby increasing exercise endurance.
Eur Respir J 2004; 24: 86–94.

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Several recent studies have shown that improvements in exertional dyspnoea following bronchodilator therapy in chronic obstructive pulmonary disease (COPD) correlate well with reductions in lung hyperinflation, as indicated by increases in inspiratory capacity (IC) [1–5]. However, the relationship between bronchodilator-induced increases in IC and improvements in symptoms and exercise performance is complex and poorly understood. Given the multifactorial nature of dyspnoea and exercise limitation in COPD, it remains unclear why small increases in resting IC (in the order of 0.3 L) appear to be clinically important. The current study extends previous studies conducted in the present authors' laboratory using ipratropium bromide by, in addition, examining the effect of a bronchodilator (salmeterol) on plethysmographic lung volume components at rest and on breathing pattern and ventilatory capacity during exercise. Moreover, the study was designed to advance understanding of the mechanisms of bronchodilator-induced dyspnoea relief, especially the role of reduced mechanical restriction.

It has previously been shown that acute-on-chronic hyperinflation during exercise severely constrains tidal volume (VT) expansion, and that this dynamic mechanical restriction makes an important contribution to reduced ventilatory capacity, dyspnoea and exercise intolerance [6]. Thus, in hyperinflated COPD patients, close intercorrelations were found between the reduced resting IC, reduced peak VT and reduced symptom-limited peak oxygen uptake (V'O$_2$) [6]. It was reasoned that bronchodilator-induced increases in resting IC should result in greater VT expansion throughout exercise, with greater ventilatory capacity and improved exercise ability.

Similarly, it was previously hypothesised that the inability to expand VT appropriately in response to the increasing central drive of exercise can contribute to both the intensity and quality (unsatisfied inspiration) of exertional dyspnoea [7, 8]. During exercise, inspiratory effort and central drive increase progressively in the face of increasingly restricted VT expansion in COPD. This phenomenon has been termed neuromechanical dissociation. The ratio of inspiratory effort (tidal oesophageal pressure relative to maximum) to VT displacement is increased during exercise in COPD compared with health, and correlates well with intensity of inspiratory difficulty [7]. Similarly, in health, when VT is constrained by chest wall strapping during exercise, dyspnoea also intensifies [8]. When chemical drive is augmented further during exercise in volume-restricted individuals, by adding dead space, dyspnoea and the sense of unsatisfied inspiration increase dramatically [8]. The corollary of this is that an improved ability to expand VT (due to an increased IC) for a given muscular effort or drive should ameliorate respiratory

discomfort. It was desired to better understand the mechanisms of dyspnoea causation and relief by examining, for the first time, dyspnoea (Borg)/IC and dyspnoea/inspiratory reserve volume (IRV) relationships throughout exercise before and after a bronchodilator; the present authors' previous analyses considered dyspnoea/time plots only. It was also desirous to determine whether bronchodilator-induced reduction in dyspnoea intensity at a standardised time during exercise correlated with increased V_T.

In order to test these hypotheses, a randomised double-blind placebo-controlled crossover study was conducted in 23 symptomatic patients with advanced COPD using salmeterol as the bronchodilator. Quantitative tidal flow/volume loop analysis was conducted and breathing pattern (tidal flow rates, V_T and breath timing components) and operating lung volumes (IC and IRV) during symptom-limited constant-load cycle exercise compared after salmeterol and a matched placebo. Finally, using correlative analysis, the effects of reducing mechanical restriction on ventilatory capacity, exercise tolerance and dyspnoea were determined.

Methods

Subjects

Subjects included clinically stable COPD patients with a cigarette smoking history of $\geqslant 20$ pack-yrs, a forced expiratory volume in one second (FEV1) of $\leqslant 70\%$ of the predicted value and plethysmographic functional residual capacity (FRC) of $\geqslant 120\%$ pred, and significant activity-related dyspnoea (modified Baseline Dyspnea Index (BDI) focal score of $\leqslant 6$) [9]. Patients were excluded if they had a history of asthma, atopy or nasal polyps; other systemic conditions that could contribute to dyspnoea or exercise limitation; or oxygen desaturation to <80% during cycle exercise on room air.

Study design

The present randomised double-blind placebo-controlled crossover study had local university/hospital research ethics approval. After giving written informed consent, patients completed: 1) a screening visit to determine eligibility for the study (visit 1), 2) a visit 5 ± 2 days later that was designed to familiarise patients with all of the tests that would be performed during subsequent treatment visits and to avoid possible learning effects (visit 2), and 3) two 2-week treatment periods, in randomised order, with a visit at the end of each (visits 3 and 4). During treatment periods, either inhaled salmeterol (50 μg b.i.d.) or a matched placebo was added to the daily drug regimen. Long-acting β_2-agonists were discontinued $\geqslant 1$ week prior to the study. Corticosteroids, theophyllines and short-acting anticholinergics were permitted at stable doses throughout the study. Inhaled salbutamol was used as rescue medication throughout the study. Prior to each visit, short-acting β_2-agonists, anticholinergics, and short- and long-acting theophyllines were withdrawn for 4, 12, 24 and 48 h, respectively. The study medication was last taken ~12 h prior to visits. All visits were conducted at the same time of day for each subject. Subjects avoided caffeine, heavy meals, alcohol and major physical exertion prior to visits.

Visit 1 included medical history taking and clinical assessment, pulmonary function tests and a symptom-limited incremental cycle exercise test. Visit 2 included pulmonary function tests and a constant-load exercise test. At visits 3 and 4, pulmonary function tests were performed before (pre-dose) and 120±15 min after (post-dose) receiving the study treatment from the preceding treatment period. At these visits, post-dose pulmonary function tests were followed by a constant-load exercise test. Subjects recorded their daily use of study medication in a diary.

Procedures

The modified BDI incorporates multidimensional ratings of magnitude of task, magnitude of effort and functional impairment into an overall focal score of chronic activity-related breathlessness which ranges 0 (dyspnoea at rest)–12 (no exertional dyspnoea) [9]. The BDI was assessed by an unbiased observer with no specific knowledge of the subjects' pulmonary function or other measures of study outcome.

Spirometry [10], constant-volume body plethysmography using a panting frequency of 1 Hz [11], and measurement of single-breath diffusing capacity of the lung for carbon monoxide and maximum inspiratory mouth occlusion pressures (measured from FRC) were performed using automated testing equipment (Vmax229d with Autobox 6200 D_L; SensorMedics, Yorba Linda, CA, USA). Measurements were standardised as percentages of predicted normal values [12–16]; predicted normal values for IC were calculated by subtracting predicted FRC from predicted total lung capacity (TLC). Specialised flow/volume loop software (Enhanced Spirometry, Vmax229d; SensorMedics) was used to measure the maximal expiratory flows during spirometry at the resting end-expiratory lung volume (EELV) after placebo and at this same volume after salmeterol for each individual.

Cycle exercise tests were carried out as previously described [1, 6, 17], using a cardiopulmonary exercise testing system (Vmax 299d). All exercise tests consisted of a steady-state resting period and a 1-min warm-up of loadless pedalling followed by an immediate increase in work-rate; pedalling frequencies were maintained at 50–70 revolutions per minute. For incremental exercise tests, the work-rate was increased at 1-min intervals by increments of 10 W to the point of symptom limitation. Maximal work capacity was defined as the greatest work-rate that the subject was able to maintain for $\geqslant 30$ s. Constant-load exercise tests were performed similarly, except that the work-rate was increased to 75% of maximal work capacity and maintained until the point of symptom limitation. The endurance time was recorded as the duration of loaded pedalling.

Breath-by-breath measurements were collected via mouthpiece. Pre-exercise resting measurements were analysed over a 30-s interval after $\geqslant 3$ min of quiet breathing, i.e. steady state. Cardiopulmonary measurements during exercise were recorded as 30-s means, and end-exercise ("peak") values were defined as the mean over the last 30 s of exercise. Pulse oximetry, electrocardiography and blood pressure were monitored throughout exercise and for 5 min after exercise. At rest, every 2 min during exercise and at end-exercise, subjects rated the intensity of their breathing and leg discomfort using the modified Borg scale [18] and performed IC manoeuvres [6, 19]. At the end of exercise, subjects specified their reason for stopping exercise and completed a questionnaire describing the quality of their exertional dyspnoea [7, 20]. Predicted maximum values for work-rate, cardiac frequency and $V'O_2$ were taken from JONES [21].

Statistical analysis

Results are reported as mean±SEM. A p<0.05 level of significance was used for all analyses. Possible sequence

effects were assessed first [22]. Primary analyses were performed on post-dose measurements. Treatment responses were compared using paired t-tests. Exercise responses were compared at peak exercise, at a standardised level of exercise (*i.e.* the highest equivalent time achieved in all constant-load exercise tests rounded down to the nearest minute) and as slopes derived from linear regression analysis of data sets from each individual.

Selection frequencies of dyspnoea descriptor phrases and clusters were compared after placebo and salmeterol using Fisher's exact test. When one or more descriptor phrases within a cluster were chosen by a subject, the cluster was included as only one count in the frequency analysis.

Pearson's correlation was performed using the difference (salmeterol *versus* placebo) in dyspnoea intensity at a standardised level of exercise (Borg scale) as the dependent variable and concurrent differences in exercise measurements of lung hyperinflation (IC and IRV), ventilation ($V'E$), $V'O_2$, carbon dioxide output ($V'CO_2$), VT, respiratory frequency, inspiratory time (tI), expiratory time (tE), arterial oxygen saturation (Sa,O_2) and cardiac frequency, as well as changes in resting pulmonary function, as independent variables. Correlates of the difference in exercise capacity and peak $V'E$ were analysed similarly.

Results

Subjects

Twenty-three patients completed the study (table 1). Long-acting β_2-agonists were discontinued prior to the study (n=7), inhaled corticosteroids were continued as usual (n=12) and adjunct anticholinergics (n=15) were withdrawn 12 h prior to each visit. The presence of expiratory flow limitation was confirmed in all study patients by demonstrating that the expiratory flows of maximal and partial flow/volume loops were superimposed. Exercise capacity during incremental testing was significantly reduced due primarily to severe dyspnoea, *i.e.* 74% of patients stopped due to breathing discomfort or a combination of breathing and leg discomfort (table 2).

Table 1. – Subject characteristics

	Measurement	
	Value	% pred
Subjects n	23	
Males %	65	
Age yrs	64±2	
Body mass index kg·m^{-2}	26.1±0.8	
Cigarette smoking history pack-yrs	48±5	
Baseline dyspnoea index focal score	5.3±0.3	
FEV1 L	1.08±0.08	42±3
FEV1/FVC %	46±2	66±3
FVC L	2.33±0.14	62±3
TLC L	7.32±0.25	122±3
IC L	1.81±0.10	65±3
FRC L	5.51±0.22	172±6
RV L	4.63±0.20	216±10
DL,CO/VA mL·min^{-1}·mmHg^{-1}·L^{-1}	3.03±0.18	81±5

Data are presented as mean±SEM. FEV1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; IC: inspiratory capacity; FRC: functional residual capacity; RV: residual volume; DL,CO: single-breath diffusing capacity of the lung for carbon monoxide; VA: alveolar volume; % pred: per cent predicted. 1 mmHg=0.133 kPa.

Treatment compliance over the two 2-week treatment periods was excellent, ranging 93–100%. There were no significant sequence effects found when examining the main end points of the study.

Pulmonary function at rest

At the end of the treatment period, pre-dose lung function measurements had improved significantly with salmeterol (table 3). Significant post-dose drug effects were also found after treatment with salmeterol compared to placebo (table 4). The FEV1/forced vital capacity (FVC) ratio did not change in response to therapy.

Volume-adjusted mid-expiratory flow rates. By plotting the means of individual maximal expiratory flows obtained from spirometry (peak expiratory flow rate and forced expiratory flow when 75, 50 (FEF50%) and 25% of the FVC has been exhaled) along the correct volume axis (*i.e.* by anchoring to TLC), it was illustrated that maximal flow rates were greater at any given volume in the operating range after salmeterol compared to placebo (fig. 1). Mean maximal expiratory flows were 0.13±0.01 L·s^{-1} at the resting EELV after placebo, and increased after salmeterol by a mean of 0.22±0.09 L·s^{-1} (176±52%) at the same absolute lung volume (fig. 1). Maximal inspiratory flows also increased after salmeterol by 0.39±0.16 L·s^{-1} or 20±6% compared with placebo (p<0.05).

After salmeterol compared to placebo, the resting VT was

Table 2. – End-exercise[#] measurements in the incremental protocol and post-dose constant-load protocols at 75% of the peak work-rate achieved in incremental testing[¶]

	Incremental	Constant-load	
		Placebo	Salmeterol
Exercise time min	NA	4.5±0.7	6.0±0.8*
Work-rate W	60±7	46±5	46±5
Dyspnoea Borg	5.1±0.3	4.7±0.4	4.2±0.3
Leg discomfort Borg	5.3±0.3	5.2±0.4	5.4±0.5
Reason for stopping n			
Breathing discomfort	9	11	3
Leg discomfort	6	6	11
Breathing and legs	8	6	6
Other	0	0	3
$V'O_2$ mL·kg^{-1}·min^{-1}	14.8±1.1	14.6±1.0	15.6±1.0*
$V'CO_2$ L·min^{-1}	1.12±0.12	1.06±0.11	1.18±0.10*
$V'E$ L·min^{-1}	34.1±2.7	33.3±2.5	36.8±2.5*
fR breaths·min^{-1}	30.7 ± 1.4	30.6 ± 1.1	29.6 ± 1.1
VT L	1.13±0.09	1.10±0.08	1.25±0.08*
IC L	1.47±0.09	1.44±0.11	1.66±0.10*
IRV L	0.34±0.04	0.33±0.06	0.41±0.05
EILV % pred TLC	116±3	118±4	117±4
VT/tE L·s^{-1}	0.92±0.08	0.89±0.08	0.99±0.08*
VT/tI L·s^{-1}	1.50±0.11	1.47±0.10	1.61±0.09*
tI/$t$tot	0.38±0.01	0.38±0.01	0.38±0.01
fc beats·min^{-1}	114±3	113±3	116±4
Sa,O_2 %	93.3±0.6	93.1±0.7	93.9±0.5

Data are presented as mean±SEM. $V'O_2$: oxygen uptake; $V'CO_2$: carbon dioxide output; $V'E$: ventilation; fR: respiratory frequency; VT: tidal volume; IC: inspiratory capacity; IRV: inspiratory reserve volume; EILV: end-inspiratory lung volume; TLC: total lung capacity; tE: expiratory time; VT/tE: mean expiratory tidal flow rate; tI: inspiratory time; VT/tI: mean inspiratory tidal flow rate; $t$tot: duration of total breathing cycle; tI/$t$tot: inspiratory duty cycle; fc: cardiac frequency; Sa,O_2: arterial oxygen saturation; NA: not applicable; % pred: per cent predicted. [#]: mean over last 30 s of loaded exercise; [¶]: 33±3% pred maximum. *: p<0.05 *versus* placebo.

Table 3. – Pre-dose pulmonary function measurements at the end of each 2-week treatment period

	Placebo	Salmeterol
FEV1 L	1.03±0.08 (40)	1.17±0.09 (45)**
FVC L	2.25±0.12 (60)	2.48±0.12 (67)**
FEV1/FVC %	45±2 (65)	46±2 (66)
PEFR L·s⁻¹	3.35±0.23 (63)	3.75±0.20 (71)*
FEF50% L·s⁻¹	0.46±0.05 (12)	0.53±0.06 (14)*
FIF50% L·s⁻¹	2.94±0.25	3.26±0.28*
TLC L	7.31±0.26 (122)	7.25±0.27 (121)
IC L	1.74±0.11 (62)	1.96±0.11 (70)**
FRC L	5.57±0.24 (173)	5.29±0.24 (165)**
SVC L	2.66±0.14 (71)	2.83±0.14 (76)*
RV L	4.65±0.21 (216)	4.42±0.23 (206)*
DL,CO/VA mL·min⁻¹·mmHg⁻¹·L⁻¹	3.08±0.18 (82)	3.00±0.18 (79)
MIP cmH₂O	50±5 (62)	52±5 (65)

Data are presented as mean±SEM (per cent predicted). FEV1: forced expiratory volume in one second; FVC: forced vital capacity; PEFR: peak expiratory flow rate; FEF50%: forced expiratory flow when 50% of the FVC has been exhaled; FIF50%: forced inspiratory flow when 50% of the FVC has been exhaled; TLC: total lung capacity; IC: inspiratory capacity; FRC: functional residual capacity; SVC: slow expiratory vital capacity; RV: residual volume; DL,CO: single-breath diffusing capacity of the lung for carbon monoxide; VA: alveolar volume; MIP: maximal inspiratory mouth occlusion pressure. *, **: p<0.05, p<0.01: *versus* placebo. 1 mmHg=0.133 kPa.

Table 4. – Pulmonary function and resting breathing pattern measurements[#] 2 h post-dose at the end of each 2-week treatment period

	Placebo	Salmeterol
FEV1 L	1.04±0.08 (40)	1.24±0.09 (48)**
FVC L	2.24±0.12 (60)	2.67±0.13 (72)**
FEV1/FVC %	45±2 (64)	46±2 (64)
PEFR L·s⁻¹	3.35±0.21 (63)	4.16±0.23 (79)**
FEF50% L·s⁻¹	0.47±0.06 (12)	0.55±0.07 (14)*
FIF50% L·s⁻¹	2.74±0.24	3.35±0.28**
TLC L	7.29±0.26 (121)	7.22±0.27 (120)
FRC L	5.52±0.23 (172)	5.17±0.26 (160)**
SVC L	2.66±0.14 (71)	3.02±0.14 (81)**
RV L	4.63±0.21 (216)	4.20±0.23 (196)**
DL,CO/VA mL·min⁻¹·mmHg⁻¹·L⁻¹	3.06±0.17 (81)	3.01±0.18 (80)
MIP cmH₂O	47±4 (58)	56±5 (70)**
Pre-exercise breathing pattern		
IC L	1.82±0.13 (65)	2.15±0.11 (78)**
IRV L	1.19±0.12	1.49±0.11**
VT L	0.63±0.03	0.66±0.03
fR breaths·min⁻¹	19.8±0.7	19.7±0.8
VT/tI L·s⁻¹	0.59±0.03	0.59±0.03
VT/tE L·s⁻¹	0.32±0.01	0.34±0.02*
tE s	2.04±0.09	2.02±0.11

Data are presented as mean±SEM (per cent predicted). FEV1: forced expiratory volume in one second; FVC: forced vital capacity; PEFR: peak expiratory flow rate; FEF50%: forced expiratory flow when 50% of the FVC has been exhaled; FIF50%: forced inspiratory flow when 50% of the FVC has been exhaled; TLC: total lung capacity; FRC: functional residual capacity; SVC: slow expiratory vital capacity; RV: residual volume; DL,CO: single-breath diffusing capacity of the lung for carbon monoxide; VA: alveolar volume; MIP: maximal inspiratory mouth occlusion pressure; IC: inspiratory capacity; IRV: inspiratory reserve volume; VT: tidal volume; fR: respiratory frequency; tI: inspiratory time; VT/tI: mean inspiratory tidal flow rate; tE: expiratory time; VT/tE: mean expiratory tidal flow rate. [#]: reported immediately prior to exercise and after breathing on a mouthpiece at rest for ⩾3 min (steady state). *, **: p<0.05, p<0.01 *versus* placebo; (1 mmHg=0.133 kPa.).
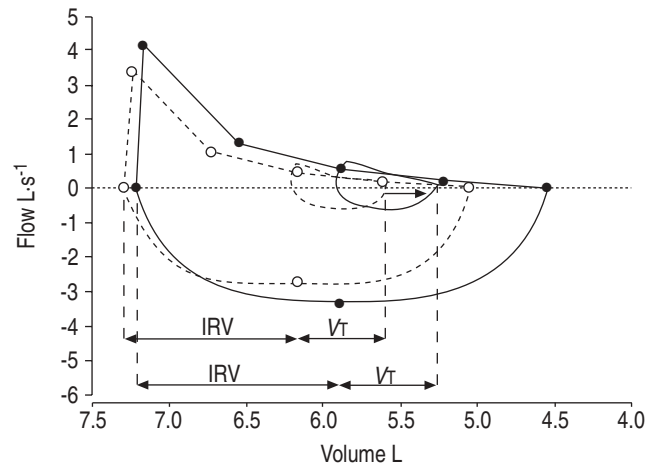

Fig. 1. – Maximal expiratory flows increased from those obtained with placebo (○, - - - -) with salmeterol (●, ——) in association with a decrease in end-expiratory lung volume, as reflected by a significant increase in inspiratory capacity (p<0.001). After salmeterol, the tidal volume (VT) was positioned at a lower operating lung volume and inspiratory reserve volume (IRV) was significantly increased (p<0.001). The post-dose expiratory curves were constructed from the means of individual measurements of peak expiratory flow rate and forced expiratory flow when 25, 50 and 75% of the forced vital capacity has been exhaled at their respective lung volumes anchored to total lung capacity; each of these flow measurements increased significantly after salmeterol compared to placebo (p<0.001).

positioned at a lower absolute lung volume, *i.e.* EELV decreased by 0.32±0.11 L (p<0.01) as IC increased by 0.33±0.07 L (p<0.0005). This increase in IC (or decrease in EELV) correlated best with the concurrent increases in FEF50% (r=0.51, p=0.014); however, the strength of this relationship between reduced lung hyperinflation and increased maximal expiratory flow rates was probably underestimated since flow rates were not measured at identical absolute lung volumes. tE did not change in response to salmeterol (table 4).

Physiological responses during rest and exercise

The ventilatory responses to exercise are shown in figure 2. The symptom-limited exercise endurance time was significantly greater after salmeterol than after placebo by 1.6±0.6 min or 58±19% (p=0.018). Patients were also able to reach greater levels of peak V'O₂, V'E, VT and tidal flow rates after salmeterol (table 2). At a standardised time during exercise (3.4±0.5 min), there were also significant increases in tidal flow rates, IC, VT and V'E after salmeterol, compared to placebo (table 5).

At rest and throughout exercise, the IC was significantly greater after salmeterol than after placebo (fig. 2). These increases in IC permitted significantly greater increases in VT throughout exercise, *i.e.* the increase in VT correlated strongly with the increase in IC at a standardised time during exercise (r=0.82, p<0.0005).

Exertional dyspnoea

Exertional dyspnoea measured in the laboratory tended to improve after salmeterol compared to placebo: slopes of Borg rating/time fell by 7±13% (p=0.07) and Borg rating at a standardised level of exercise fell by 0.9±0.5 units (p=0.07) (fig. 3). Dyspnoea intensity also decreased at a given exercise
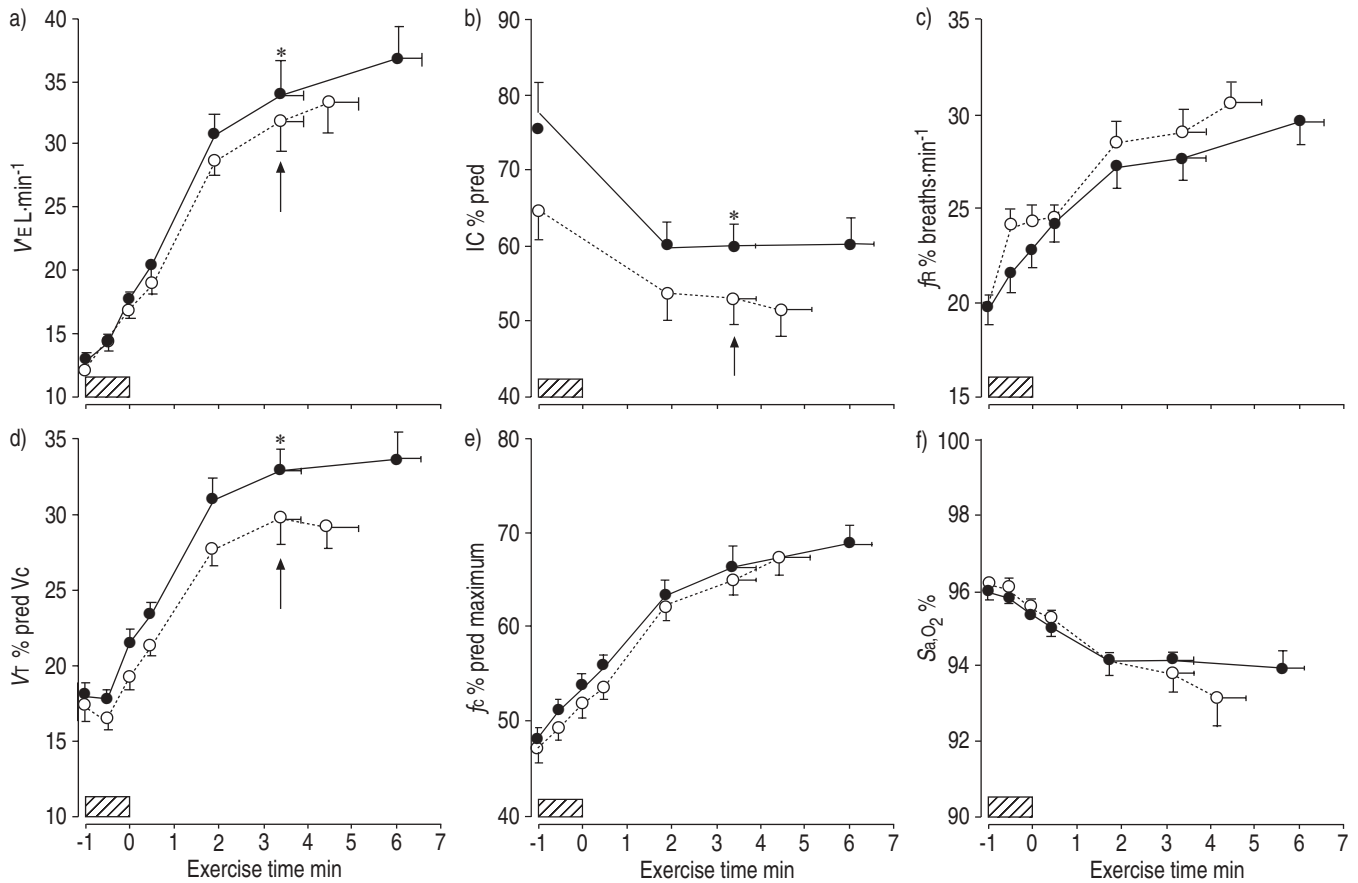
Fig. 2. – Various exercise responses as a function of exercise time during constant-load exercise at 75% of each patient′s maximum work-rate: a) ventilation ($V′E$), b) inspiratory capacity (IC), c) respiratory frequency (fR), d) tidal volume (VT), e) cardiac frequency (fc), and f) arterial oxygen saturation (Sa,O_2). The endurance time was measured from the onset of loaded exercise, which was preceded by a warm-up consisting of 1 min of loadless pedalling (▨). Data are presented as mean±SEM (measured at rest, a standardised time (3.4±0.5 min) during exercise and end-exercise). At a standardised time (vertical arrow) during exercise, measurements of $V′E$, IC and VT increased significantly after salmeterol (●) compared to placebo (○). VC: vital capacity; % pred: per cent predicted. *: p<0.05 versus placebo.

$V′E$ after salmeterol compared to placebo, i.e. Borg rating/ $V′E$ curves shifted to the right with an associated 3.1±1.5 L·min⁻¹ increase in the x-intercept or "dyspnoea threshold" (p<0.05) (fig. 3). Similarly, patients were able to tolerate a greater amount of acute dynamic hyperinflation (i.e. reduction in IC) during exercise before experiencing intolerable dyspnoea (fig. 3). Dypsnoea/IRV relationships were constant, with a common inflection point occurring at an IRV of ∼0.5 L, after which dyspnoea increased linearly (fig. 3).

Qualitative descriptors of dyspnoea. The main descriptors selected to represent the quality of exertional dyspnoea were similar after placebo and salmeterol: unsatisfied inspiration (i.e. "I cannot get enough air in", "I feel a need for more air" and "I cannot take a deep breath in"); inspiratory difficulty (i.e. "breathing in requires effort"); increased work (i.e. "my breathing requires more work"); and heaviness (i.e. "my breathing is heavy"). During exercise after salmeterol, fewer patients described unsatisfied inspiration (61 versus 83% after placebo; p=0.01) and the awareness of increased work (43 versus 52% after placebo; p<0.0005).

Locus of symptom limitation. After treatment with placebo, the primary reason for stopping exercise was "breathing discomfort" (48% of subjects), with the remaining subjects stopping due to "leg discomfort" (26% of subjects) or a combination of breathing and leg discomfort (26% of subjects). After salmeterol, 35% fewer patients reported limitation due solely to breathing discomfort, 22% more patients reported limitation due to leg discomfort and 13% more reported other reasons for stopping exercise (i.e. "dry throat", "too hot" and generally "had enough") (table 2).

Correlates of improvement

In response to salmeterol, the best correlate of improved symptom-limited cycle endurance time was the increase in resting IC as a percentage of the predicted value (r=0.57, p=0.005). The increase in peak $V′O_2$ correlated best with the increase in peak VT expressed as a percentage of the predicted vital capacity (VC) (r=0.724, p<0.0005); in turn, increases in peak VT correlated best with increases in IC as a percentage of the predicted value at rest (r=0.65, p=0.001) or at peak exercise (r=0.59, p=0.003). The increase in peak $V′E$ correlated significantly with the increase in resting IC as a percentage of the predicted value (r=0.456, p<0.05), and, as expected, correlated best with increases in peak measurements of VT expressed a percentage of the predicted VC (r=0.652, p=0.001), mean expiratory flow (r=0.944, p<0.0005) and mean inspiratory flow (r=0.877, p<0.0005).

Table 5. – Measurements at a standardised time[¶] during constant-load exercise after treatment with placebo and salmeterol

	Placebo	Salmeterol
Dyspnoea Borg	3.6±0.4	2.7±0.3[#]
Leg discomfort Borg	4.0±0.3	3.7±0.4
$V'O_2$ mL·kg^{-1}·min^{-1}	14.1±0.9	14.7±1.1
$V'CO_2$ L·min^{-1}	1.01±0.10	1.09±0.12*
$V'E$ L·min^{-1}	31.9±2.4	34.0±2.7*
$V'E/V'CO_2$	33.5±1.3	33.0±1.2
fR breaths·min^{-1}	29.0±1.2	27.7±1.2
VT L	1.12±0.09	1.23±0.08*
IC L	1.48±0.11	1.65±0.09*
Change in IC from rest L	-0.34±0.04	-0.50±0.05*
IRV L	0.36±0.05	0.43±0.03
EILV %TLC	95±1	94±1
% pred TLC	118±4	117±4
VT/tE L·s^{-1}	0.87±0.07	0.93±0.08*
VT/tI L·s^{-1}	1.42±0.09	1.50±0.10*
tE s	1.36±0.07	1.42±0.07
$tI/ttot$	0.37±0.01	0.37±0.01
fc beats·min^{-1}	109±3	111±4
Sa,O_2 %	93.7±0.5	94.1±0.3

Data are presented as mean±SEM. $V'O_2$: oxygen uptake; $V'CO_2$: carbon dioxide output; $V'E$: ventilation; fR: respiratory frequency; VT: tidal volume; IC: inspiratory capacity; IRV: inspiratory reserve volume; EILV: end-inspiratory lung volume; TLC: total lung capacity; tE: expiratory time; VT/tE: mean expiratory tidal flow rate; tI: inspiratory time; VT/tI: mean inspiratory tidal flow rate; $ttot$: duration of total breathing cycle; $tI/ttot$: inspiratory duty cycle; fc: cardiac frequency; Sa,O_2: arterial oxygen saturation; % pred: per cent predicted. [¶]: 3.4±0.5 min. *: $p<0.05$; [#]: $p=0.07$ versus placebo.

In response to salmeterol, the reduction in dyspnoea intensity at a standardised time approaching the end of exercise correlated best with the concurrent increase in VT ($r=-0.88$, $p<0.0005$) (fig. 4) or dynamic IC ($r=-0.76$, $p<0.0005$), as well as with the increase in resting IC ($r=-0.75$, $p<0.0005$).

Discussion

The major findings of the present study are as follows. First, salmeterol consistently increased volume-corrected maximal expiratory flow rates, resulting in an increased IC at rest and throughout exercise. Secondly, the reduction in lung overinflation during exercise was consistently associated with increased VT expansion with no change in breath timing components. The increased VT, in turn, resulted in increased peak $V'E$ and $V'O_2$. Thirdly, salmeterol increased exercise endurance time by a mean of 58% without increasing peak dyspnoea intensity. Finally, the decrease in dyspnoea at a standardised time (and work-rate) during exercise correlated well with the concurrent increase in VT after bronchodilator.

Effect of salmeterol on resting lung volumes

VC was consistently increased after bronchodilator treatment, reflecting improved lung emptying during the forced expiratory manoeuvre, as reflected by the reduced residual volume (RV). In keeping with numerous previous bronchodilator studies, the FEV1/FVC ratio was unchanged, indicating that increases in FEV1 were mainly the result of volume recruitment [2, 3, 23–25].

Similar to findings in two previous bronchodilator studies [2, 26], maximal expiratory flows over the critical operating volume range in which VT is positioned were consistently increased compared to placebo (fig. 1). Improvements in individual volume-corrected mid-expiratory flow rates of the magnitude seen here (a mean of 0.22 L·s^{-1} or 175%) are probably important and indicate that higher maximal (and, by extrapolation, tidal) expiratory flows could now be achieved at lower operating lung volumes. Improvement in these effort-independent flows correlated well with the reduced RV and FRC after bronchodilator. It follows that the $V'E$ required to maintain blood gas homeostasis at rest could be achieved at a lower level of lung hyperinflation after salmeterol. This probably has advantages in terms of allowing greater ventilatory capacity when the system is stressed as, for example, during exercise.

Salmeterol resulted in consistent reductions in FRC with reciprocal increases in IC, i.e. TLC remained unchanged. In flow-limited patients, EELV is a continuous variable that is dynamically rather than statically determined [27–29]. Its level depends on the extent of expiratory flow limitation and the prevailing ventilatory demand. Increased tidal expiratory flow rates, in the setting of an unchanged tE, allowed the dynamic EELV to decline to a level that was closer to the respiratory system's relaxation volume.

Effect of salmeterol on ventilation

The present COPD patients showed severe exercise intolerance: the peak symptom-limited $V'O_2$ during both the incremental and endurance tests averaged only 15 mL·kg^{-1}·min^{-1}. In the majority, intolerable respiratory discomfort was the main exercise-limiting symptom. They also demonstrated severe ventilatory constraints: peak $V'E$ represented 93% of the estimated maximal ventilatory capacity. During the baseline exercise test, IC was diminished at peak exercise by 20% of its already reduced resting value. Thus subjects reached a critically low "minimal" IRV of only 0.3 L at a low peak $V'O_2$, indicating severe mechanical restrictions on VT expansion during exercise. Clearly, the only way of increasing exercise capacity in these ventilatorily limited patients is to delay this critical mechanical limitation or, by increasing IC, to increase ventilatory capacity and reduce dyspnoea within the existing "fixed" mechanical constraints (i.e. reduced IRV).

Analysis of the exercise flow/volume loops at a standardised time during exercise showed significant increases in both inspiratory and expiratory tidal flow rates at lower operating lung volumes after salmeterol compared to placebo, indicating effective bronchodilatory action throughout exercise. The IC, and not the VC, represents the true operating limits for VT expansion during exercise. Two previous studies support the concept that lung hyperinflation gives rise to restrictive mechanics and a low peak $V'E$, which causes earlier exercise termination. [6, 30]. Salmeterol increased IC at rest and throughout exercise, allowing greater VT expansion and consequently higher submaximal and peak $V'E$ (fig. 2). Respiratory frequency and tI and tE during exercise were not different between placebo and salmeterol; the increase in $V'E$ with the latter was, therefore, due mainly to the increased VT. The increased VT following bronchodilator is probably multifactorial, with possible mechanisms including: 1) reduced mechanical constraints and elastic loading; 2) reduced airways resistance and possibly increased dynamic lung compliance; 3) increased inspiratory muscle pressure-generating capacity at the lower lung volume, and 4) reduced perceived respiratory discomfort associated with VT expansion. A reduction in lung hyperinflation means that less effort is required for a given, or increased, volume displacement.

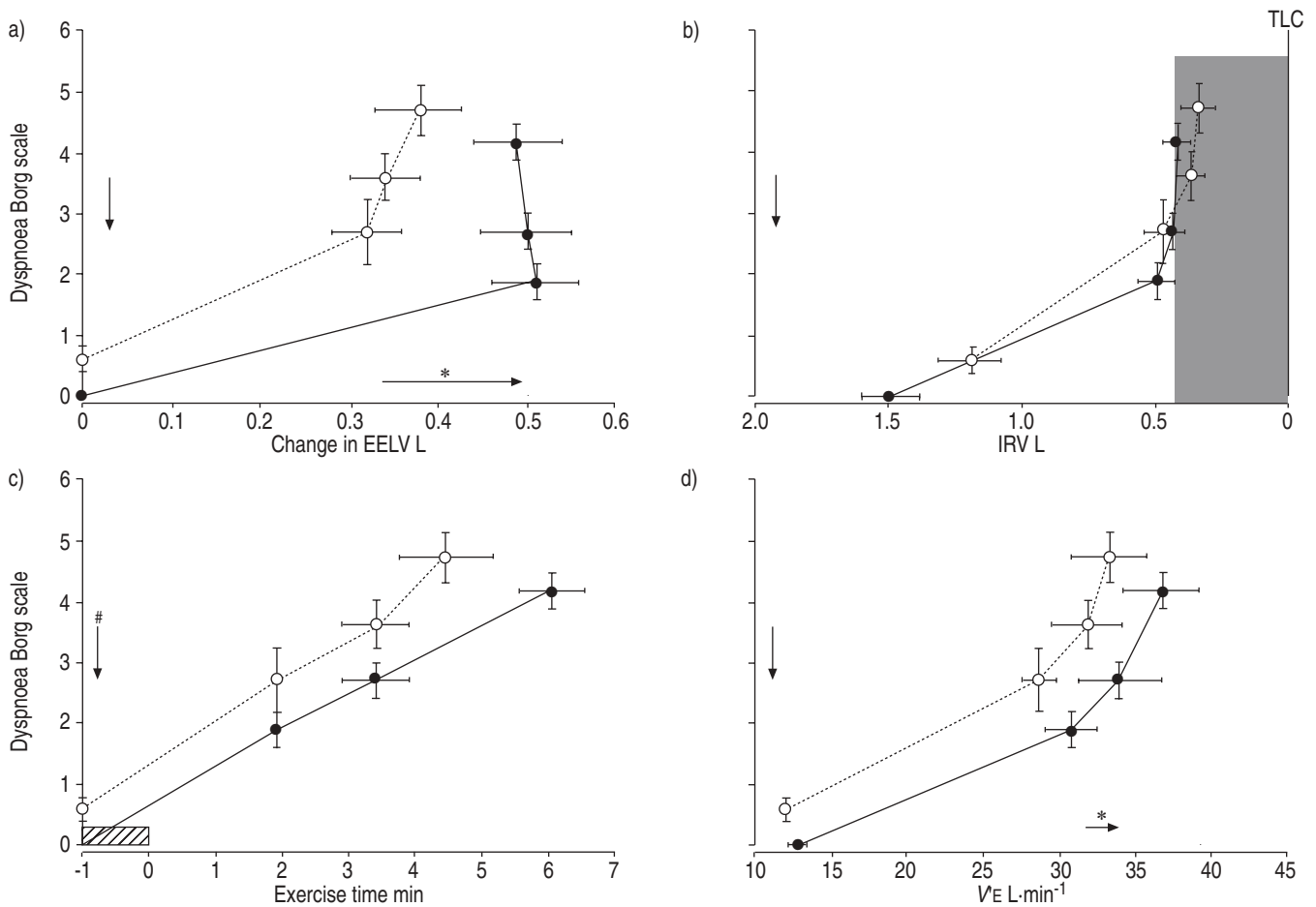The extent of exercise dynamic hyperinflation (rest-to-peak

Fig. 3. – Relationship between Borg rating of dyspnoea intensity and a) change in end-expiratory lung volume (EELV; as reflected by a decrease in inspiratory capacity (IC)), b) inspiratory reserve volume (IRV), c) exercise time and d) ventilation ($V'E$) during constant-load cycle exercise after salmeterol (●, ——) and placebo (○, - - - -). Data are presented as mean±SEM (measured at rest, a standardised time (3.4±0.5 min) during exercise and end-exercise). Arrows adjacent to the respective axes indicate the magnitude and direction of differences between salmeterol and placebo responses at a standardised time during exercise. The dyspnoea/$V'E$ and dyspnoea/IC curves shifted towards the right after salmeterol compared to placebo; therefore, subjects could tolerate greater $V'E$ and dynamic hyperinflation after salmeterol. Dyspnoea/IRV relationships were unchanged, with dyspnoea increasing rapidly once a critically reduced IRV (■) was reached. TLC: total lung capacity. *: $p<0.05$; #: $p=0.07$ versus placebo.
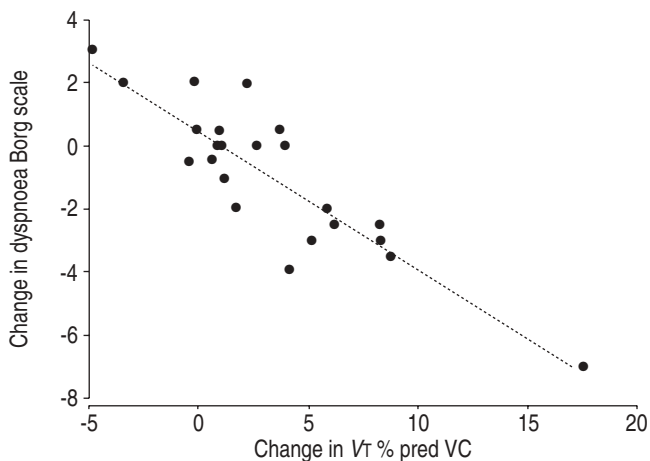

Fig. 4. – A significant correlation was found between changes in dyspnoea intensity and tidal volume (VT) at a standardised exercise time (3.4±0.5 min) after salmeterol compared to placebo (n=23, r=-0.88, $p<0.0005$). VC: vital capacity; % pred: per cent predicted.

reductions in IC) increased after salmeterol compared to placebo. However, EELV was reduced at rest and throughout exercise after salmeterol. VT expanded without further encroaching on the diminished IRV, allowing peak $V'E$ to increase by a mean of 3 L·min^{-1} and endurance time by 1.6 min (or 58%). This is the first study to show consistent increases in exercise endurance of this magnitude after salmeterol. Inconsistent effects on exercise endurance seen in previous studies probably reflect differences in study design (parallel versus crossover) and exercise test modality used [25, 31–33]. The constant-load cycle exercise endurance test has been shown to be more responsive than the 6-min walk test for the purpose of bronchodilator evaluation [33]. The contention that improved ventilatory capacity and exercise performance is explained, at least in part, by reduced lung hyperinflation is supported by the finding of close statistical inter-relationships between the increases in resting IC, peak VT, peak $V'E$ and peak symptom-limited $V'O_2$ during the constant-load exercise. It is noteworthy that changes in FEV1, FVC, RV and FRC did not correlate as well with improvement of exertional dyspnoea or exercise endurance as IC.

Comparisons of $V'O_2$ and $V'CO_2$ at a standardised time during exercise show that these were slightly, but consistently,

increased after bronchodilator. The fact that $V'E/V'O_2$ and $V'E/V'CO_2$ slopes were identical before and after salmeterol suggests that the increased $V'E$ and associated metabolic cost is a possible explanation. Alternatively, increased VT throughout exercise could improve alveolar ventilation (reduce wasted ventilation) with more efficient carbon dioxide elimination. It is of note that Sa,O_2 did not deteriorate after salmeterol despite substantial increases in exercise endurance time (fig. 2). Additional, but untested, possibilities include improved cardiac output and/or peripheral blood distribution as a result of the reduced lung hyperinflation and reduced vascular steal from the unloaded ventilatory muscles. Salmeterol may also have positive inotropic effects on the heart. All of these factors would tend to increase oxidative capacity at the peripheral muscle level.

Effect on dyspnoea

After salmeterol, patients could undertake this demanding physical task to a greater peak $V'O_2$ than achieved after placebo or during baseline incremental exercise testing. Despite the longer duration and greater peak $V'E$, they reached the same level of peak dyspnoea. Borg ratings of dyspnoea intensity were reduced (by ∼1 unit) at a standardised exercise time compared with placebo. In some patients, the primary exercise-limiting symptom changed from dyspnoea to leg discomfort (or some other new symptom) after bronchodilator therapy.

The present study extends previous work in the area by demonstrating for the first time that, in contrast to dyspnoea/time slopes, dyspnoea/IC relationships during exercise in COPD are not linear (fig. 3) [1, 34]. After salmeterol, dyspnoea/IC curves were shifted to the right. Small improvements in the resting IC or FRC of 0.35 L meant that patients could tolerate even greater dynamic hyperinflation during exercise before experiencing intolerable dyspnoea. It is noteworthy that dyspnoea/IRV relationships were also nonlinear and unaltered by the bronchodilator. It is also of note that the dyspnoea "threshold" (*i.e.* the inflection point above which dyspnoea increases sharply towards intolerable levels) occurs at the point at which a critical "minimal" IRV of <0.5 L is reached (fig. 3). The steep increase in dyspnoea once this critical mechanical constraint is reached presumably reflects the effects of the progressively increasing ventilatory drive of exercise. This increasing disparity between the central chemical drive to breathe and the mechanical response of the system (*i.e.* neuromechanical dissociation) may contribute to the quality and intensity of exertional dyspnoea in COPD. It follows that the improved dyspnoea at a similar IRV after salmeterol is related to either: 1) reduced drive, 2) greater volume expansion for a given drive (because of the increased IC), or 3) a combination of both. This latter contention is supported by the finding that reduced dyspnoea ratings at a standardised time during exercise correlated well with the simultaneous increase in VT, at a point at which IRV was not significantly different from that obtained with placebo (fig. 3).

Neuromechanical dissociation is most evident at the point in exercise at which further VT expansion is not possible because a critical reduction in IRV has been reached. Similar conclusions were reached after studying the sensory response to combined mechanical (chest wall strapping) and chemical (added dead space) loading in healthy individuals during exercise: dyspnoea increased sharply when the VT response to exercise reached an early plateau (at a minimal IRV) [8]. Similarly, imposed incremental mechanical hyperinflation, using an airway closure analogue in healthy individuals and COPD patients, resulted in similar nonlinearities of the dyspnoea/IRV and dyspnoea/IC plots to those seen in the present study [35, 36].

It has previously been reported that, in contrast to health, the most commonly selected dyspnoea descriptors during exercise in COPD are unsatisfied inspiration ("I can't get enough air in") and inspiratory difficulty [7]. At peak exercise under the two conditions, dyspnoea intensity was similar, but patients selected the descriptor "unsatisfied inspiration" less frequently (reduced by 22%) after salmeterol. These findings, and those of previous studies [6, 7], suggest that improving the ability to increase VT in response to the increasing drive of exercise has salutary effects on respiratory sensation in COPD patients.

Bronchodilators would be expected to reduce the resistive and elastic/threshold loads on the inspiratory muscles and to improve their functional weakness, thus reducing perceived inspiratory effort. An improved VT could increase alveolar ventilation and, therefore, decrease chemoreceptor activation by reducing arterial carbon dioxide tension. The relative importance of these various factors or the precise neurophysiological underpinnings of improved sensation could not be ascertained during the present study. However, it is reasonable to assume that salmeterol improved neuromechanical coupling of the ventilatory system during exercise and that dyspnoea relief is associated, at least in part, with reduced contractile inspiratory muscle effort in the setting of enhanced volume displacement.

In summary, the present results support the notion that lung hyperinflation and the consequent restrictive ventilatory mechanics make an important contribution to the abnormal ventilatory response to exercise in chronic obstructive pulmonary disease. In hyperinflated chronic obstructive pulmonary disease patients, small bronchodilator-induced increases in resting and exercise inspiratory capacity allow greater tidal volume expansion and ventilation with less respiratory discomfort while operating within the fixed mechanical constraints of a markedly diminished inspiratory reserve volume. Collectively, these factors contribute to improved exercise capabilities in patients with severe chronic obstructive pulmonary disease. A practical implication of these study results is that small changes in resting inspiratory capacity after bronchodilator can predict important clinical outcomes. This measurement may, therefore, be useful in the evaluation of bronchodilator efficacy.

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