RESPIRATORY MEDICINE (1998) **92**, 1116–1121

Comparison of the effects of salmeterol and ipratropium bromide on exercise performance and breathlessness in patients with stable chronic obstructive pulmonary disease

D. PATAKAS, D. ANDREADIS, E. MAVROFRIDIS, AND P. ARGYROPOULOU

Respiratory Failure Unit, Department of Medicine, Aristotle University of Thessaloniki, Greece

To compare the effects of salmeterol, an adrenergic drug, and ipratropium bromide, an anticholinergic drug, on breathlessness and gas exchange during exercise in patients with chronic obstructive lung disease (COPD), we performed a progressive treadmill exercise test on 15 patients on 3 days (24 h apart), after inhalation placebo, ipratropium bromide (120 μg) or salmeterol (50 μg) in a randomized fashion. Dyspnoea during exercise was evaluated from the regression slope between Borg scale (BS) scores and distance walked each minute on the treadmill. The regression was expressed as the distance walked at BS score 5, the threshold load of dyspnoea (TLD) and breakpoint load of dyspnoea. During and after the exercise, oxygen saturation was monitored by pulse oxymeter and we measured the lower SaO_2 during exercise and the recovery time of SaO_2 after exercise.

In comparison to placebo inhalation we found the same small but significant improvement in airflow limitation after salmeterol or ipratropium inhalation, also the distance walked on treadmill increased after bronchodilators. After bronchodilators the magnitude of oxyhaemoglobin desaturation with exercise was similar to that observed after placebo but the duration of the recovery from sustained SaO_2 desaturation after exercise was shorter to the same extent as after ipratropium or salmeterol. Dyspnoeic sensation, when assessed by the TLD and by the distance walked at BS score 5, was decreased after salmeterol and after ipratropium bromide to a similar extent.

We conclude that the salmeterol, when given in conventional doses, produces significant improvement in the airway obstruction in the recovery of postexercise HbO_2 desaturation and in dyspnoeic sensation in patients with COPD, effects which were similar to those observed after inhalation of the anticholinergic agent ipratropium bromide.

RESPIR. MED. (1998) **92**, 1116–1121

Introduction

A large number of trials have compared anticholinergic drugs to other bronchodilators in patients with stable chronic obstructive pulmonary disease (COPD) (1–5). Some trials that have employed conventional doses of each agent show that an anticholinergic agent results in more bronchodilation than an adrenergic agent in this patient population. The finding is surprising and contrasts with studies in asthma patients which show that adrenergic agents are more effective bronchodilators. The different order of efficacy of the two classes of bronchodilators is confirmed by a number of studies in which asthmatic and bronchitic group have been studied with both drugs (5). Anticholinergic agents also have a rather small effect on gas exchange. Neither atropine nor its quaternary ammonium congeners lower the PaO_2 even in hypoxaemic patients with COPD (6).

Several studies have shown that there is a relatively poor correlation between the exercise tolerance of patients with COPD and their level of pulmonary function. In general, the correlation coefficient between any measure of pulmonary function and the exercise tolerance is about 0·60, which indicates that only about 36% of the variance in the exercise tolerance can be explained by the level of pulmonary dysfunction (7). Thus it is possible that the administration of bronchodilators drugs could not improve the exercise tolerance of patients with COPD in spite of their bronchodilating effect. To our knowledge, however, little information is available as to the effects of bronchodilator agents on dyspnoea during exercise in COPD. Teramoto *et al.* (8) found that inhaled oxipropium bromide produces improvement both in dyspnoea during exercise and in exercise performance in stable COPD. On the other hand, Leitch *et al.* (9) reported that 12-min walk distance in COPD could not be influenced by ipratropium bromide

Received 24 October 1997 and accepted in revised form 18 May 1998.
Correspondence should be addressed to: D. Patakas, Respiratory Failure Unit, George Papanikolaou Hospital, Exohi, Thessaloniki, Greece.

0954-6111/98/091116+06 $12.00/0

TABLE 1. Anthropometric and physiologic data (on selection day)

No.	Age year	Ht m	Treatment	FVC (% predicted) l	FEV_1 (% predicted) l	$\dot{V}_{Emax50}$ (% predicted) l s^{-1}	$\dot{V}_{Imax50}$ l s^{-1}	DCO (% predicted) ml min^{-1} $mmHg^{-1}$	FEV_1* (postbroncho-dilation) l
1	64	1·69	B, C	1·61 (43)	0·77 (27)	0·19 (4)	4·00	9·1 (47·2)	0·83
2	63	1·67	B, T	1·71 (47)	0·70 (24)	0·35 (9)	2·30	7·2 (57·1)	0·71
3	66	1·68	B, T, C	1·98 (54)	0·75 (26)	0·35 (9)	2·06	7·4 (55·1)	0·81
4	47	1·73	B	2·68 (61)	1·45 (40)	0·85 (21)	3·75	11·7 (61·0)	1·57
5	62	1·60	B, C	1·66 (51)	0·80 (30)	0·29 (7)	2·37	8·6 (58·0)	0·85
6	65	1·78	B, C	2·11 (50)	1·37 (42)	0·94 (24)	4·31	11·5 (62·3)	1·51
7	62	1·64	B, C, T	1·70 (61)	1·01 (46)	0·66 (19)	3·36	6·3 (52·1)	1·15
8	70	1·70	B, C	1·57 (43)	0·92 (33)	0·55 (14)	2·78	8·6 (54·1)	1·01
9	60	1·65	B, T	1·34 (43)	0·77 (33)	0·46 (13)	2·10	4·2 (41·2)	0·85
10	74	1·62	B, C	1·56 (51)	0·57 (24)	0·27 (7)	2·92	5·8 (44·2)	0·65
11	64	1·68	B, C, T	2·25 (64)	1·12 (56)	0·51 (14)	3·82	6·3 (45·2)	1·25
12	66	1·65	B	1·69 (49)	1·05 (35)	0·74 (19)	2·23	7·0 (60·1)	1·20
13	72	1·50	B	2·03 (78)	1·12 (19)	0·61 (19)	2·80	7·0 (50·0)	1·27
14	77	1·68	B, C	1·61 (56)	0·92 (43)	0·73 (22)	3·09	5·7 (44·3)	1·01
15	57	1·76	B, T	2·09 (49)	0·75 (27)	0·39 (9)	3·58	12 (61·0)	0·70

*FEV_1 after inhalation of 4 puffs (200 μg) salbutamol.
Ht, heights; B, inhaled bronchodilators; C, corticosteroids; T, theophylline.

administration. Tobin *et al.* (10) reported that the cycle ergometer exercise capacity was increased in COPD after ipratropium, but not after fenoterol administration. Salmeterol is a rather new long-acting, effective, selective β_2-agonist, the safety and potency profile of which compares very favourably with those of other β_2-agonists (11–14). The effects of salmeterol on exercise performance, and dyspnoea sensation of patients with COPD were studied.

The aim of this study was to examine and compare the effects of an anticholinergic drug, ipratropium bromide, on exercise performance and breathlessness of patients with chronic obstructive lung disease, to those of salmeterol, an adrenergic long-acting agent.

Materials and Methods

SUBJECTS

Fifteen patients (age 64·6 ± 7·2 years) with stable COPD participated in the study. To be included in this study patients were required to have a forced expiratory volume in 1 s (FEV_1) less than 65% of predicted, less than 20% reversibility on β-adrenergic inhalation and diffusing capacity of the lung for CO (Dco) no more than 65% of predicted normal value. All patients were in a stable condition for at least 1 month; no patient was taking sedative drugs and all continued taking their usual treatment.

Patients were excluded if they had coronary heart disease, left ventricular dysfunction, severe hypertension, disease of major organ system such as diabetes, renal failure, or neuromuscular disease that affected exercise performance. Informed consent was obtained from all subjects prior to entry into the study. The protocol was approved by our institutional review board.

Demographic and pulmonary function data of our patients are presented in Table 1.

STUDY DESIGN

On a screening day the patients had spirometry before and after inhalation of 4 puffs (200 μg) salbutamol to ascertain if they met our study criteria (Table 1). The patient was then familiarized with the Borg scale (BS) (15) and the perceived dyspnoea treadmill exercise test (16). Patients were also informed to not take theophylline and anticholinergic compounds for 48 h before the study and no inhaled bronchodilators in the morning of the study days.

The study was conducted on three separate days 24 h apart. Early in the morning subjects underwent a control pulmonary function test. As spirometric indices we chose the best of three maximal flow volume curves obtained using a Jaeger Transfersreen II spirometer. Measurements were made on forced vital capacity (FVC), FEV_1 and forced maximal expiratory ($\dot{V}_{E50}$) and inspiratory ($\dot{V}_{I50}$) flows at 50% of FVC. After completing the control studies the subjects inhaled from a spacer (Volumatic, Glaxo) six puffs placebo or six puffs ipratropium bromide (120 μg) or two puffs salmeterol (50 μg). The order of the treatment was randomly distributed. Pulmonary function tests were repeated 30 min after drug inhalation and then a progressive incremental exercise test was performed on a treadmill.

During the exercise test patients walked on a horizontal treadmill with a logarithmic increase in speed each minute

TABLE 2. Spirograms before and after inhalation placebo, ipratropium or salmeterol (mean ± SD)

	Placebo	Ipratropium	Salmeterol
FVC (l)			
before	1·83 ± 0·34	1·69 ± 0·40	1·69 ± 0·36
after	1·83 ± 0·33	2·08 ± 0·32**	2·06 ± 0·31**
FEV_1 (l)			
before	0·94 ± 0·25	0·91 ± 0·25	0·89 ± 0·26
after	0·95 ± 0·24	1·12 ± 0·35*	1·13 ± 0·24*
$\dot{V}_{E50}$ (l s^{-1})			
before	0·52 ± 0·22	0·53 ± 0·26	0·51 ± 0·23
after	0·55 ± 0·23	0·64 ± 0·37	0·64 ± 0·25
$\dot{V}_{I50}$ (l s^{-1})			
before	3·03 ± 0·74	2·84 ± 0·59	2·76 ± 0·67
after	3·14 ± 0·77	3·41 ± 0·73*	3·42 ± 0·92*

P values refer to comparisons between drugs and placebo (*$P<0·05$; **$P<0·01$).
$\dot{V}_{E50}$, middle maximal expiratory flow.
$\dot{V}_{I50}$, middle maximal inspiratory flow.

to exhaustion (1·2, 1·8, 2·5, 4·4, 5·9, 8·0 km h^{-1}). At the end of each minute, patients scored breathlessness on a 10-cm visual BS (dyspnoea: nothing at all to intolerable). The breathlessness score was then plotted against the distance walked (17). There were significant positive linear correlation between the dyspnoea expressed in BS and the distance walked in metres (m) in all patients ($P<0·05$). From these correlations we introduced three parameters for the quantitative assessment of dyspnoea: (1) the BS slope, which expressed as the distance walked at breathlessness score 5; (2) the break load of dyspnoea (BLD), which was expressed as the total distance walked in m and (3) the threshold load of dyspnoea-TLD (the distance walked on the treadmill with breathlessness score zero), which was expressed by the intercept of the regression line. The three parameters and the maximum score on Borg's scale with peak exercise (BS_{max}) were compared on the 3 study days.

Arterial oxygen saturation (SaO_2) was continuously monitored before, during and after the exercise test with a pulse oxymeter (Criticon, Johnson-Johnson). Rest SaO_2 was determined before exercise and nadir SaO_2 was determined as the minimum value that was observed during exercise. We also measured the recovery time, which was the time in seconds needed for SaO_2 recovery from its nadir at the end of exercise to the pre-exercise value. Rest SaO_2, nadir SaO_2 and SaO_2 recovery time were compared after placebo, salmeterol and ipratropium.

Statistical analysis was performed using Student's paired *t*-test for paired data; $P<0·05$ was accepted as statistically significant. Data were presented as mean ± standard deviation (SD).

Results

Lung function measurements during the 3 days of the study, before and after placebo or drugs administration, are summarized in Table 2. We found no statistically significant differences between the initial FVC, FEV_1, $\dot{V}_{E50}$, $\dot{V}_{I50}$ values, before placebo or salmeterol or ipratropium inhalation. We found no changes in these parameters after placebo. After inhalation of ipratropium bromide and salmeterol there was a small but statistically significant improvement in FVC, FEV_1 and $\dot{V}_{I50}$ values. When we compared the posttreatment values of FVC, FEV_1, $\dot{V}_{I50}$ and $\dot{V}_{E50}$ we found no difference; the bronchodilating effect of salmeterol was similar to that of ipratropium bromide.

The resting SaO_2 after ipratropium or salmeterol was not different from that after placebo. Furthermore, nadir SaO_2 during exercise, following inhalation of bronchodilators was not different from the nadir SaO_2 recorded during exercise after placebo inhalation (Table 3). In contrast, the SaO_2 recovery time after ipratropium or after salmeterol was significantly shorter than after placebo administration. The SaO_2 recovery time was shorter after ipratropium that after salmeterol, but this difference was not significant.

In all patients there was a close linear relationship between distance walked on treadmill and dyspnoea sensation expressed in BS, after inhalation of placebo, salmeterol or ipratropium. From these correlations we have calculated four parameters (BLD, distance walked at BS score 5, TLD, BS_{max}), for the quantitative assessment of dyspnoea. The changes in the dyspnoea indices during exercise after inhalation of placebo, ipratropium and salmeterol are shown in Table 4. The distance walked (BLD, m) increased statistically significantly after ipratropium and after salmeterol. The TLD did not show drastic change after inhalation of ipratropium but was significantly increased after salmeterol ($P<0·05$). Both drugs improved the distance walked at BS score 5. The BS_{max} score during exercise, did not improve significantly after ipratropium or salmeterol treatment.

The mean heart rate (HR) after placebo at rest was 83 ± 15·5 and after exercise 134·8 ± 12·2 beats min^{-1}, the

TABLE 3. Arterial oxygen saturation (SaO_2) with rest and exercise, before and after inhalation of placebo, ipratropium or salmeterol and their recovery time of SaO_2 (mean ± SD)

	Placebo	Ipratropium	Salmeterol
Rest SaO_2 (%)	93·5 ± 2·5	94·1 ± 2·6	94·1 ± 2·7
Nadir exercise SaO_2 (%)	85·5 ± 8·6	86·7 ± 8·1	86·4 ± 7·7
Δ Sat (%)	8·13 ± 7·3	7·46 ± 6·3	7·7 ± 6·1
Recovery time of SaO_2 (s)	114·4 ± 53·1	66·6 ± 33·4**	72·6 ± 31·9*

P values refer to comparisons between drugs and placebo (*$P<0.05$; **$P<0.01$).

TABLE 4. Dyspnoea indices during exercise after inhalation placebo, ipratropium, or salmeterol (mean ± SD)

	Placebo	Ipratropium	Salmeterol
BLD (m)	270·4 ± 73·1	350 ± 67·3**	366·5 ± 78·6**
Distance walked at BS score (5 (m)	176·2 ± 59·9	237 ± 74·2*	248·2 ± 92·3*
TLD (m)	42·9 ± 60·8	70·8 ± 61·8	80·8 ± 68·1*
BS_{max}	8·26 ± 1·09	7·8 ± 1·59	7·8 ± 1·61

BLD, Breakpoint load of dyspnoea: BS, Borg scale; TLD, threshold load of dyspnoea; BS_{max}, the maximum score on Borg scale during exercise. *P* values refer to comparisons between drugs and placebo (*$P<0.05$; ** $P<0.01$).

respective values after ipratropium were 78·9 ± 14·8 and 132·6 ± 15·4 and after salmeterol 80·4 ± 14·4 and 133·4 ± 18·4 beats min^{-1}. The blood pressure (BP) after placebo at rest was 132 ± 13 over 82 ± 5 mmHg and the maximum during exercise 175 ± 17 over 89 ± 9·6 mmHg. After ipratropium the BP was at rest 125 ± 14 over 81 ± 7 and during exercise 174 ± 9 over 92 ± 7. The concomitant values after salmeterol were 128 ± 126 over 76 ± 7 and 175 ± 11 mmHg over 91·3 ± 7 mmHg. The values of BP and HR after salmeterol or ipratropium were not statistically significantly different from those after placebo.

It is important to notice the absence of significant correlations between the changes in pulmonary function parameters (FVC, FEV_1, $\dot{V}_{E50}$, $\dot{V}_{I50}$ nadir exercise SaO_2, recovery time of SaO_2) observed after salmeterol or ipratropium and the improvements of dyspnoae indices. Also we found no statistically significant differences in pulmonary function parameters, in dyspnoea indices and in haemodynamic parameters recorded after the ipratropium and salmeterol treatment.

In addition, no adverse effects after the administration of salmeterol or placebo were observed in patients in the present study.

Discussion

Although patients with COPD do not respond to bronchodilators as dramatically as do asthmatic patients, some increase in the FEV_1 and a reduction in dyspnoea are nearly always achieved on the administration of bronchodilator agents. A large number of trials have compared anticholinergic drugs to other bronchodilators in stable COPD (5). Trials that have employed conventional doses of each agent almost universally show that anticholinergic agents result in more bronchodilation than adrenergic agents. In this patient population this finding is surprising and in contrast with studies in asthmatic patients, which show that adrenergic are more effective bronchodilators. However, this efficacy of anticohlinergic agents in COPD is probably due to the difference in the optimal dose of bronchodilator, since in studies which have employed large or sequential doses of each class of agent the bronchodilating effects were similar (18). In the present study we found that after a single treatment of ipratropium bromide (120 μg) or salmeterol (50 μg) the bronchodilatory effect was similar.

The decrease in SaO_2 during exercise in COPD is considered to result from ventilation perfusion mismatching, the lowering of central venous SaO_2 or from diffusion limitations (19,20). After salmeterol or ipratropium bromide administration the magnitude of oxyhaemoglobin desaturation with exercise followed a pattern similar to that which was observed after placebo inhalation. Therefore, it suggests that inhaled salmeterol or ipratropium bromide, has little effect on gas exchange both at rest and during exercise in COPD patients. It is interesting that the duration of the recovery from sustained oxyhaemoglobin desaturation after exercise following ipratropium was similar to that after salmeterol, but both were significantly shorter when compared to the recovery time of SaO_2 after exercise following

placebo. The cause of improvement of postexercise oxyhaemoglobin desaturation after bronchodilators inhalation could not be explained from our data. Teramoto *et al.* (8) suggested that the improvement of postexercise oxyhaemoglobin desaturation after oxiproprium bromide (a new anticholinergic agent) inhalation is due to a lower ventilatory equivalent for oxygen uptake after exercise. They also postulated that increased cardiac output following exercise tests after oxiproprium administration and the increase in blood flow improve the $\dot{V}/\dot{Q}$ inequality. Furthermore, the improvement of airflow limitation after bronchodilators may contribute to early recovery from exercise induced oxyhaemoglobin desaturation.

Exertional dyspnoea is a common and often incapacitating symptom in patients with advanced COPD. In the present study we examined and compared the change in the dyspnoeic sensation during exercise after inhalation placebo, ipratropium bromide or salmeterol. Despite exercising for longer periods after inhalation of ipratropium or salmeterol, our patients had, at maximal exercise, BS_{max} identical to those recorded at maximal exercise after placebo. There was a significant increase in the distance walked on the treadmill after bronchodilators, but at these higher levels of exercise COPD patients terminated their task when they felt dyspnoea of the same maximal intensity as when taking the placebo. For the above reason the improvement in exertional dyspnoea after bronchodilators was not ascertained in COPD patients using score of BS_{max} alone. On the contrary, consistent results were obtained as to dyspnoeic sensation during exercise in the COPD patients, when we assessed the dyspnoea using the TLD and the distance walked at BS score 5. In comparison with placebo, both parameters improved after salmeterol and the second after ipratropium inhalation. Also we found that the effect of salmeterol was similar to that of ipratropium when dyspnoeic sensation during exercise was assessed using these parameters.

The mechanism of the decrease in dyspnoea during exercise following salmeterol or ipratropium bromide administration is not clear. Relief of breathlessness can be achieved with various bronchodilators in the presence of only a small improvement in FEV_1, i.e. <15% (23–25). The small improvement in airflow obstruction can produce an increase in maximal breathing capacity (MBC) and may reduce the sense of effort in breathing during exercise by decreasing the ventilatory index (minute ventilation expressed as fraction of maximal breathing capacity, $\dot{V}_E$/MBC).

The patients with COPD have an increased cholinergic tone, which may be responsible for the impaired pulmonary function at rest (25). Since ipratropium bromide may induce smooth muscle relaxation by modulating the afferent pathway of the vagal reflex, this may contribute to the reduction in the airway resistance during exercise. Stimulation of vagal afferent nerve ending in the airways and the lung have, in animals, effects on ventilation (26), but their role in mediating respiratory sensation in our patients is not clearly proven. Salmeterol, an adrenergic bronchodilating agent, not acting on airways by stimulation of vagal afferent nerve endings, had a similar effect on breathlessness sensation during exercise to ipratropium in our COPD patients and it is logical to assume that this mechanism, if it exists, is not unique.

We conclude that the inhaled adrenergic agent salmeterol, when given in conventional doses, produces significant improvements in the airflow obstruction, in the recovery from postexercise oxyhaemoglobin desaturation and the dyspnoeic sensation in patients with COPD; effects which were similar to those produced after the inhalation of the anticholinergic agent ipratropium bromide. The equivalent action of two drugs, exerting their bronchodilating effects acting in different neurohumoral mechanisms, indicates that the change in respiratory mechanics is the important factor which is responsible for the improvement in exertional dyspnoea and in the recovery from the postexercise oxyhaemoglobin desaturation. Exercise and postexercise-induced hypoxaemia in patients with COPD may occur with modest exercise and probably contribute to exercise limitation, and to pulmonary hypertension (27). Both drugs decrease the sustained postexercise oxyhaemoglobin desaturation and this effect is thought to be of some clinical benefit for the patients with COPD.

References

1. Taskin DP, Ashutosh K, Bleeker ER, Britt EJ, Cugell OW, Cummiskey JM. Comparison of the anticholinergic bronchodilator ipratropium bromide with metaproterenol in chronic obstructive pulmonary disease: a 90-day multi-center study. *Am J Med* 1986; **81** (Suppl. 5A): 81–90.
2. Thiessen B, Pederson OF. Maximal expiratory flows and forced vital capacity in normal, asthmatic and bronchitic subjects after salbutamol and ipratropium bromide. *Respiration* 1982; **43:** 304–316.
3. Passamonte PM, Martinez AS. Effects of inhaled atropine or metoproterenol in patients with chronic airway obstruction and therapeutic serum theophylline levels. *Chest* 1984; **85:** 610–615.
4. Karpel JP, Pesin J, Greenberg D, Centry E. A comparison of the effects of ipratropium bromide and metaproterenol sulfate in acute exacerbation of COPD. *Chest* 1990; **98:** 835–839.
5. Gross NJ, Scorodin MS. Anticholinergic, antimuscarinic bronchodilators. *Am Rev Respir Dis* 1984; **129:** 856–870.
6. Gross NJ, Bankawala Z. Effects of an anticholinergic bronchodilator on arterial blood gases off hypoxemic patients with COPD: comparison with a beta-adrenergic agent. *Am Rev Respir Dis* 1987; **136:** 1091–1094.
7. Light RW. Exercise testing and disability evaluation. In George RB, Light RW, Matthan RA, eds. *Chest Medicine*. New York: Churchill Livingston, 1983: 158–201.
8. Teramoto S, Fu Kuchi Y, Orimo H *et al.* Effects of inhaled anticholinergic drug on dyspnoea and gas exchange during exercise in patients with COPD. *Chest* 1993; **103:** 1774–1782.

9. Leitch AG, Hopkin JM, Ellis DA, Merchants Me, Hardy GJR. The effect of aerosol ipratropium bromide and salbutamol on exercise tolerance in chronic bronchitis. *Thorax* 1978; **33:** 711–713.
10. Tobin MJ, Hughes JA, Hutchinson DCS. Effect of ipratropium bromide and fenoterol aerosols on exercise tolerance. *Eur J Resp Dis* 1984; **65:** 1441–446.
11. Palmer JBD, Stuart AM, Shephard KJ. Inhaled salmeterol in the treatment of patients with moderate to severe reversible obstructive airways disease-a 3 month comparison of the efficacy and safety of twice-daily salmeterol (100 mg) with salmeterol 50 μg. *Respir Med* 1992; **86:** 409–417.
12. Gongora HC, Wisniewski AFZ, Tattersfield E. A single dose comparison of inhaled albuterol and two formulations of salmeterol on airway reactivity in asthmatic subjects. *Am Rev Respir Dis* 1991; **144:** 626–629.
13. Pearlmon DS, Chervinsky P, La Force C. A comparison of salmeterol with albuterol in the treatment of mild to moderate asthma. *N Engl J Med* 1992; **327:** 1420–1425.
14. Cheung D, Timmers MC, Zwinderman AH, Bel EH, Dijkman JH, Sterk PJ. Long-term effects of a long acting b_2-adrenoceptor agonist salmeterol, on airway hyper-responsiveness in patients with mild asthma. *N Engl J Med* 1992; **327**: 1198–1203.
15. Borg CAV. Psychophysical bases of preceived exertion. *Med Sci Sports Exerc* 1982; **14:** 377–381.
16. Johnson MA, Woodcock AA, Dehahu M, Geddes DM. Are pink puffers more breathless than blue bloaters? *Br Med J* 1983; **286:** 17–183.
17. Argyropoulou P, Patakas D, Koukou A *et al.* Buspirone effect on breathlessness and exercise performance in patients with COPD. *Respiration* 1993; **60:** 216–220.
18. Easton PA, Jadue C, Dhingra S, Anthonisen NR. A comparison of the bronchodilating effect of a beta-2 adrenergic agent (albuterol) and an anticholinergic agent (ipratropium bromide), given by aerosol alone or in sequence. *N Engl J Med* 1986; **315:** 735–739.
19. Dantrker DR, D'Alonso GE. The effect of exercise on pulmonary gas exchange in patients with severe COPD. *Am Rev Dis* 1986; **134:** 1135–1139.
20. Wagner PD. Ventilation–Perfusion matching during exercise. *Chest* 1992; **101** (Suppl.): 1925–1985.
21. Wolkove N, Dajczman E, Colacone A, Kreismman H. The relationship between pulmonary function and dyspnea in obstructive lung disease. *Chest* 1989; **96:** 1247–1251.
22. Dullinger D, Kroneberg R, Niewohner DE. Efficacy of inhaled metaproterenol and orally administered theophylline in patients with chronic air flow obstruction. *Chest* 1986; **89:** 171–173.
23. Hay JG, Stone P, Carter J, Church S *et al.* Bronchodilator reversibility, exercise performance and breathlessness in stable chronic obstructive pulmonary disease. *Eur Respir J* 1992; **5:** 659–664.
24. O'Donnell DE, Webb KA. Exertional breathlessness in patients with chronic air flow limitation: the role of lung hyperinflation. *Am Rev Respir Dis* 1993; **148:** 1351–1357.
25. Gross NJ. Anticholinergic agents in chronic bronchitis and emphysema. *Postgrad Med J* 1987; **63** (Suppl. 1): 29–34.
26. Coleridge ITM, Coleridge JC. Reflexes evoke from tracheobronchial tree and lungs. In *Handbook of Physiology: Respiratory System: Control of Breathing.* Bethesda, MD: American Pysiological Society, 1986 (sec 3); V2 (pt1): 395–429.
27. Degaute JP, Domenighetti G, Naelije R, Vincent JL, Treyvand D, Perrel CI. Oxygen delivery in acute exacerbation of chronic obstructive pulmonary disease: effect of controlled oxygen therapy. *Am Rev Respir Dis* 1981; **124:** 26–30.