Effects of fenoterol on ventilatory response to hypercapnia and hypoxia in patients with chronic obstructive pulmonary disease

Shunsuke Suzuki, Yuuji Watanuki, Yasuhiro Yoshiike, Takao Okubo

Abstract

Background – It has previously been shown that fenoterol, a β_2 adrenergic agonist, increases the ventilatory response to hypoxia (HVR) and hypercapnia (HCVR) in normal subjects. The effects of β_2 adrenergic agonists on chemoreceptors in patients with chronic obstructive pulmonary disease (COPD) remain controversial. This study was designed to examine whether fenoterol increases the HVR and HCVR in patients with COPD.

Methods – The HCVR was tested in 20 patients using a rebreathing method and the HVR was examined using a progressive isocapnic hypoxic method. The HCVR and HVR were assessed by calculating the slopes of plots of occlusion pressure ($P_{0.1}$) and ventilation ($\dot{V}E$) against end tidal carbon dioxide pressure (P_{ETCO_2}) and arterial oxygen saturation (Sa_{O_2}), respectively. Spirometric values, lung volumes, and respiratory muscle strength were also measured. The HCVR and HVR were examined after the oral administration of fenoterol (15 mg/day) or placebo for seven days.

Results – Fenoterol treatment increased the forced expiratory volume in one second (FEV_1) and inspiratory muscle strength. In the HCVR the slope of $P_{0.1}$ versus P_{ETCO_2} was increased by fenoterol from 0.35 (0.23) to 0.43 (0.24) (p<0.01). Moreover, the $P_{0.1}$ at P_{ETCO_2} of 8 kPa was higher on fenoterol than on placebo (p<0.05) and the $\dot{V}E$ was also greater (p<0.01). In the HVR fenoterol treatment increased the $P_{0.1}$ at 80% Sa_{O_2} from 0.90 (0.72) to 0.97 (0.55) kPa (p<0.05) while the slopes of the response of $P_{0.1}$ and $\dot{V}E$ were not changed.

Conclusions – Fenoterol increases the ventilatory response to hypercapnia in patients with COPD, presumably by stimulation of the central chemoreceptor. The hypoxic ventilatory response is only slightly affected by fenoterol.

(*Thorax* 1997;**52**:125–129)

The First Department of Internal Medicine, Yokohama City University School of Medicine, 3–9 Fukura, Kanazawa-ku, Yokohama, Kanagawa 236, Japan
S Suzuki
Y Watanuki
Y Yoshiike
T Okubo

Correspondence to:
Dr S Suzuki.

Previous studies have shown that isoprenaline, a potent β adrenergic agonist, induces hyperpnoea[1–4] and its major effect on respiration is thought to be due to an action on the carotid body.[2–4] Some studies[5 6] have found that β_2 adrenergic agonists potentiate chemosensitivity whilst another study did not.[7] The ventilatory response to hypercapnia or hypoxia in patients with chronic obstructive pulmonary disease (COPD) continues to be debated. Patients with carbon dioxide retention were found to have a decreased response to carbon dioxide while non-hypercapnic patients had a normal response.[8 9] In another study there was no difference in the response to carbon dioxide between hypercapnic and non-hypercapnic patients.[10] In some studies hypoxaemic patients with COPD have been reported to have a decreased response to hypoxia,[11 12] while in one study they had an increased response.[13] The effects of β agonists on ventilation and its chemical control may therefore be important when β agonists are used to treat obstructive airway diseases. We have recently shown that fenoterol increases the ventilatory responses to both hypercapnia and hypoxia in normal subjects.[6] The purpose of this study was to investigate the effects of fenoterol on the ventilatory responses to hypercapnia and hypoxia in patients with COPD.

Methods

Twenty patients (19 men) with COPD of mean (SD) age 67.2 (7.8) years (range 50–80) participated in the study. The patients were diagnosed as having COPD according to the definition of the American Thoracic Society.[14] All patients were clinically stable and had given informed consent to participate. The study was approved by the Committee on Investigation in Humans of our hospital.

Spirometric tests were performed using a dry seal spirometer (OST-80, Chest Co, Tokyo) and lung volumes were measured using a body plethysmograph (Autobox 2800, Gould, USA). The vital capacity (VC), forced expiratory volume in one second (FEV_1), airway resistance (Raw), specific airway conductance (sGaw), and functional residual capacity (FRC) were obtained. Arterial blood was sampled by puncture of the radial artery with the subjects sitting, two hours after drug administration, and gas tensions and pH were analysed with appropriate electrodes (IL BGM-1312, Instrumentation Laboratory, Milan, Italy).

Chemical control of breathing was assessed by measuring minute ventilation ($\dot{V}E$) and occlusion pressure ($P_{0.1}$) during hypercapnia and hypoxia, as in our previous study.[6] The response to hypercapnia was measured by a modification of the Read technique.[15] The circuit

Table 1   Mean (SD) pulmonary function data of patients with chronic obstructive pulmonary disease

	%VC (%)	FEV$_1$/VC (%)	%FEV$_1$ (%)	FRC (l)	%FRC (%)	sGaw (kPa^{-1}·s^{-1})	PImax (kPa)	%PImax (%)	Pao$_2$ (kPa)	Paco$_2$ (kPa)
Placebo	90(20)	50(14)	63(25)	4.29(0.95)	131(28)	0.71(0.57)	8.7(3.6)	52(21)	10.8(1.8)	5.3(0.6)
Fenoterol	93(19)	51(18)	67(30)	4.22(0.97)	129(29)	0.71(0.53)	10.1(4.0)	58(21)	10.7(1.6)	5.1(0.5)
Difference	NS	p<0.05	p<0.05	NS	NS	NS	p<0.05	p<0.05	NS	NS

VC=vital capacity; FEV$_1$=forced expiratory volume in one second; FRC=functional residual capacity; sGaw=specific airway conductance; PImax=maximum inspiratory mouth pressure at FRC; Pao$_2$, Paco$_2$=arterial oxygen and carbon dioxide tensions; NS=not significant.
%VC, %FEV$_1$, and %FRC were calculated from the predicted values.[19]

used was similar to that of Whitelaw and co-workers.[16] Volume was obtained from electrical integration of the flow signal which was measured at the mouthpiece. The P$_{0.1}$ was obtained from a mouth pressure measured 100 ms after the onset of inspiration, as defined by the appearance of a negative mouth pressure. The expiratory side was sampled continuously using a mass spectrometer (WSMR-1400; Westron, Chiba, Japan). The subjects breathed air until they became accustomed to the circuit by bypassing the rebreathing bag to room air. They then rebreathed a gas mixture of 7% carbon dioxide and 93% oxygen from a six litre rebreathing bag. During rebreathing the inspiratory side of the circuit was occluded randomly every 4–6 breaths. Rebreathing was usually terminated within 3–4 minutes. The $\dot{V}E$ was obtained as the average for the two breaths that preceded the breath from which the P$_{0.1}$ was measured. Simultaneously, the end tidal partial pressure of carbon dioxide (PETCO$_2$) was measured. The ventilatory response to hypercapnia was assessed from the slope of the linear regression between $\dot{V}E$ and PETCO$_2$, and between P$_{0.1}$ and PETCO$_2$ ($\Delta\dot{V}E/\Delta$PETCO$_2$ and ΔP$_{0.1}/\Delta$PETCO$_2$, respectively).

The ventilatory response to hypoxia was measured by the progressive isocapnic hypoxia method of Rebuck.[17] The subjects used the same rebreathing circuit as for the ventilatory response to hypercapnia, except that a rebreathing bag containing eight litres of gas mixture (3.5% carbon dioxide, 23% oxygen, and 73.5% nitrogen) and a bypass carbon dioxide absorber were used. During the test the arterial oxygen saturation (Sao$_2$) was monitored with a pulse oximeter (Biox IIA, Biox Technology, Boulder, USA). During rebreathing the PETCO$_2$ was kept constant at the resting level of each subject during room air breathing by removing carbon dioxide from the circuit with a variable AC motor fan connected to a bypass carbon dioxide absorber. Rebreathing was continued until Sao$_2$ decreased to 75–80%. The ventilatory response to hypoxia was calculated from the slope of the linear regression of plots of $\dot{V}E$ versus Sao$_2$ and P$_{0.1}$ versus Sao$_2$ ($\Delta\dot{V}E/\Delta$Sao$_2$ and ΔP$_{0.1}/\Delta$Sao$_2$, respectively).

Respiratory muscle strength was assessed by measuring mouth pressures during maximal static inspiratory (PImax) and expiratory (PEmax) efforts against a closed valve with a small air leak to prevent glottic closure.[18] PImax was measured at FRC and residual volume, and PEmax at FRC and total lung capacity with a differential pressure transducer (Validyne MP-45 ± 250 mm Hg). The determinations of PI-

max and PEmax were repeated until three measurements varying by <5% and sustained for one second or longer were recorded. The highest value thus obtained was reported.

Placebo or fenoterol (15 mg) was administered as three divided doses in a double blind crossover design for a week and then changed to the alternative for a week with no washout period. The ventilatory response tests (HCVR and HVR) and the pulmonary function tests were examined at the same time on the seventh day of each treatment. Subjects were asked to refrain from other drugs such as other β adrenergic agonists, theophylline, sedatives, caffeine-containing beverages, and alcohol for 24 hours before the test day. On each test day the tests were performed two hours after taking the placebo or fenoterol. The baseline measurements of the lung function tests, respiratory muscle strength, heart rate, and blood pressure were measured at rest and then the ventilatory responses to hypercapnia and hypoxia were assessed. The order of the ventilatory tests was randomised with at least 10 minutes rest between each test.

All values are expressed as mean (SD) unless otherwise specified. Statistical analysis was performed using the Wilcoxon signed rank test. A p value of less than 0.05 was considered significant. A prestudy power calculation indicated that, with 21 subjects, this study had an 80% chance of detecting a true change in HCVR or HVR of more than 19%, which was calculated from data in our previous study.[6] The STATISTICA statistical software package (StatSoft, Tulsa, USA) was used.

Results

The patients had severe airway obstruction with a mean FEV$_1$/VC of 50 (14)% and increased lung volumes as shown in table 1. Hypoxaemia (Pao$_2$ <10 kPa) was observed in six of 20 patients and hypercapnia (Paco$_2$ >6 kPa) in only one. Fenoterol treatment for one week increased the mean FEV$_1$ from 1.66 (0.70) l to 1.79 (0.89) l (p<0.05) with no significant change in sGaw or FRC. The mean PImax at FRC was 52 (21)% of our normal value (see Appendix) and was increased by a mean of 16% following fenoterol treatment (p<0.02), whereas the PEmax was 58 (21)% of normal and did not change following fenoterol. The heart rate was increased by 7% from 74.5 (10.5) to 79.8 (9.1) beats/min (p<0.01) following fenoterol but there was no significant change in Paco$_2$, Pao$_2$, or blood pressure.

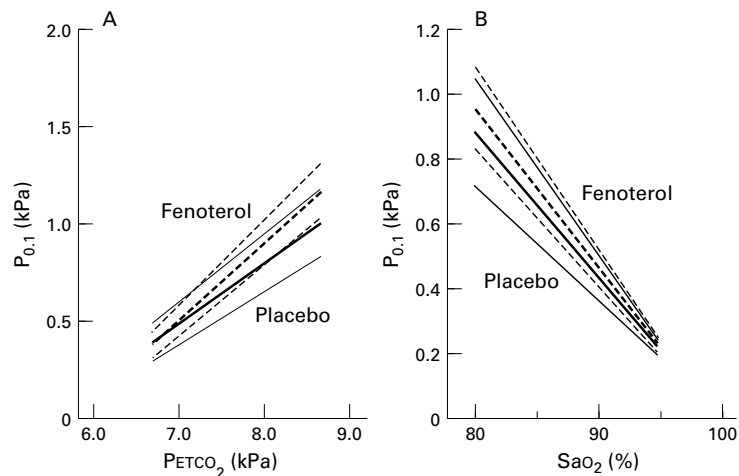The minute ventilation showed a trend to increase with fenoterol from a mean (SD) of

Figure 1 Mean occlusion pressure ($P_{0.1}$) responses to (A) the hypercapnic ventilatory response (HCVR) and (B) the hypoxic ventilatory response (HVR). Fenoterol treatment (dashed lines) increased HCVR (p<0.01) and the position of the mean $P_{0.1}$ at 80% SaO_2 (p<0.05) compared with placebo (solid lines). Mean response curves were calculated from individual slopes of $P_{0.1}$ in both HCVR and HVR. The mean responses and one standard error are represented by thick and thin lines, respectively.
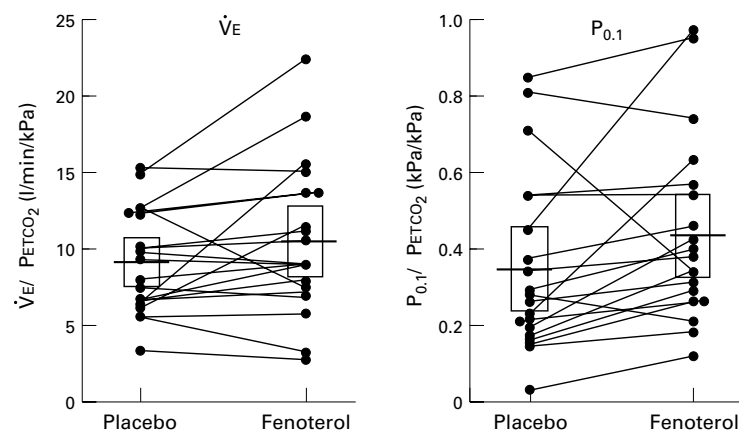

Figure 2 Hypercapnic ventilatory response (HCVR). Left: slope of $\dot{V}E$ versus $PETCO_2$ curve ($\Delta\dot{V}E/\Delta PETCO_2$) of placebo and fenoterol groups. Right: slope of $P_{0.1}$ versus $PETCO_2$ curve ($\Delta P_{0.1}/\Delta PETCO_2$) of placebo and fenoterol groups. Open boxes and bars represent the 95% confidence interval and mean value, respectively. Note that fenoterol increased the slopes of the response curve of $P_{0.1}$ by 23% (p<0.01) but did not affect the $\dot{V}E$.
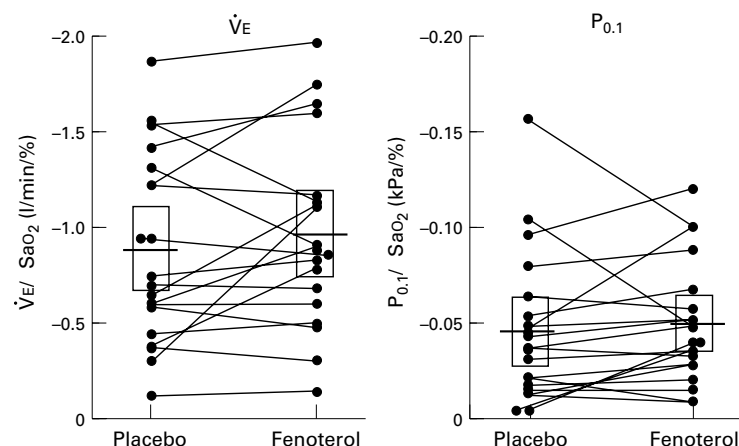

Figure 3 Hypoxic ventilatory response (HVR). Left: slope of $\dot{V}E$ versus SaO_2 curve ($\Delta\dot{V}E/\Delta SaO_2$) with placebo and fenoterol. Right: slope of $P_{0.1}$ versus SaO_2 curve ($\Delta P_{0.1}/\Delta SaO_2$) with placebo and fenoterol. Open boxes and bars represent the 95% confidence interval and mean value, respectively. Note that neither of the slopes changed.

12.9 (2.8) l/min with placebo to 14.2 (3.4) l/min after fenoterol (p=0.06), although neither the VT, breathing frequency, nor $PETCO_2$ showed any significant change. The $P_{0.1}$ during air breathing did not differ between the two treatments at 0.20 (0.09) versus 0.23 (0.09) kPa, whereas the VT/TI of 0.57 (0.12) l/min on fenoterol was significantly higher than the 0.52 (0.12) l/min when on placebo (p<0.02).

Our patients showed a wide range of ventilatory responses to hypercapnia (HCVR) and hypoxia (HVR). Fenoterol increased the slope of $P_{0.1}$ versus $PETCO_2$ ($\Delta P_{0.1}/\Delta PETCO_2$) by 23%, from a mean (SD) of 0.35 (0.23) kPa/kPa with placebo to 0.43 (0.24) kPa/kPa (p<0.01; fig 1). The slope of $\dot{V}E$ versus $PETCO_2$ ($\Delta\dot{V}E/\Delta PETCO_2$) showed a trend to increase with fenoterol from a mean (SD) of 9.2 (3.4) with placebo to 10.5 (4.9) l/min/kPa after fenoterol (p=0.08; fig 2). The $P_{0.1}$ at $PETCO_2$ of 8 kPa increased by 13% from 0.82 (0.57) kPa on placebo to 0.93 (0.45) kPa on fenoterol (p<0.05), and the $\dot{V}E$ at $PETCO_2$ of 8 kPa was also increased from 32.6 (13.8) on placebo to 34.9 (15.0) l/min on fenoterol (p<0.01). The slopes of the response curves to hypoxia ($\Delta P_{0.1}/\Delta SaO_2$ and $\dot{V}E/\Delta SaO_2$) were greater than for the normal subjects in our previous study[6] (both p<0.02). Fenoterol did not change the slope of either $\dot{V}E$ or $P_{0.1}$ versus SaO_2, as shown in fig 3, but from fig 1 it can be seen that the $P_{0.1}$ at an SaO_2 value of 80% was significantly increased from a mean of 0.90 (0.72) to 0.97 (0.55) kPa following fenoterol treatment (p<0.05) whereas $\dot{V}E$ was unchanged at 80% oxygen saturation.

Discussion

We have shown that fenoterol significantly increased the ventilatory response to hypercapnia in patients with COPD but caused a non-significant trend to increase their response to hypoxia. Fenoterol did significantly increase the FEV_1 and inspiratory muscle strength but these changes did not affect the resting ventilation and $P_{0.1}$. These results suggest that, in patients with COPD, fenoterol may stimulate the central chemoreceptor with a lesser effect on the peripheral chemoreceptor.

To be certain that these findings are true it is necessary to consider whether our experimental method or protocol could have influenced the result. Ventilatory responses were measured two hours after the last oral dose of fenoterol because plasma levels reach a maximum at this time[20] and, with a half life of only 6–7 hours, there was no need for a prolonged washout period. We therefore believe that the results truly reflect the effects of the drug and placebo. Blood levels were not checked but we had no reason to suspect that our subjects were not complying with the dose regimen.

The rebreathing techniques[15 17] used for HCVR and HVR were first designed for normal subjects based on the assumption that a relation between $\dot{V}E$ and $PETCO_2$ or between $\dot{V}E$ and SaO_2 is linear. One concern when using the $\dot{V}E$ response in patients with airway obstruction is that the response may no longer be linear. In our patients the correlation coefficient for $\dot{V}E$

with P_{ETCO_2} when taking placebo was 0.97 and for $\dot{V}_E$ with Sao_2 it was -0.93, indicating a close linear relationship in the range of P_{ETCO_2} and Sao_2 in our experiment. This close relationship was not affected by fenoterol and so we believe that the rebreathing techniques of Read and Rebuck were valid tests for our subjects. Because of the concern that $\dot{V}_E$ may be affected by the presence of airflow limitation, we also used $P_{0.1}$ as a measure of respiratory output. $P_{0.1}$ may be influenced by changes in muscle strength or lung volume[21] and in our subjects fenoterol increased P_{Imax} by 16% but did not alter FRC. However, we found that $P_{0.1}$ when breathing air was not changed by fenoterol and so we believe that this change in muscle strength was not affecting $P_{0.1}$ in our tests. We also found that fenoterol increased FEV_1 but had no effect on sGaw, and others have found that bronchodilation with atropine did not affect $P_{0.1}$ whereas resistive unloading with helium/oxygen reduced it.[22] It therefore seems that fenoterol is unlikely to influence $P_{0.1}$ by its effects on airway mechanics. For a given $P_{0.1}$ the mean inspiratory flow will increase if flow resistance decreases, and we found that the V_T/T_I whilst breathing air increased following fenoterol while the $P_{0.1}$ did not change. It has been reported in patients with COPD that the effective inspiratory impedance decreased after fenoterol only in those patients who had an increase in their FEV_1.[23] We found no difference in the effective impedance between our placebo and fenoterol groups, and so the recorded increase in FEV_1 after fenoterol in our subjects may have been too small to change the effective impedance.

Patients with COPD are characterised by increased neuromuscular inspiratory drive and increased effective inspiratory impedance.[24] In our patients with COPD the $P_{0.1}$ and V_T/T_I were comparable with that found in our normal subjects.[6] The effective inspiratory impedance, $P_{0.1}/(V_T/T_I)$, during air breathing did not differ from that of the normal subjects (0.40 (0.14) versus 0.38 (0.22) kPa/l/min) and this similarity suggests that our patients had no increased neuromuscular drive and that their airflow limitation was not sufficiently severe to increase the effective inspiratory impedance.

The abnormalities of control of breathing in patients with COPD remain controversial. Hypercapnic patients have a diminished HCVR, while the HCVR in non-hypercapnic patients is normal.[8 9] It has also been reported that the HCVR in patients with COPD is lower than in normal subjects, although there is no difference in the HCVR between hypercapnic and non-hypercapnic patients.[10] On the contrary, patients with COPD are reported to have a normal or increased response to hypercapnia when measured with diaphragmatic electromyography, although the $P_{0.1}$ response slope is decreased.[25] In the present study hypercapnia was observed in only one patient but the increase in $Paco_2$ was slight (6.4 kPa). His $\Delta P_{0.1}/\Delta P_{ETCO_2}$ was normal but he had a low $\Delta \dot{V}_E/\Delta P_{ETCO_2}$. The average values of $\Delta P_{0.1}/\Delta P_{ETCO_2}$ and $\Delta \dot{V}_E/\Delta P_{ETCO_2}$ in our patients were comparable with those of the normal subjects in our previous study.[6]

The HVR in COPD has been less well studied than HCVR and a range of HVR values have been reported for patients with COPD.[11–13 26] Those patients who were hypoxaemic were found by some authors to have a reduced ventilatory response to hypoxia,[11 12] whereas others have found these patients to have an increased HVR.[13] The HVR in our patients was greater than that of the normal subjects in our previous study[6] ($\Delta \dot{V}_E/Sao_2$ -0.22 (0.06) for normal subjects versus -0.87 (0.49) l/min/% for patients with COPD, p<0.01). In our study only the most hypoxaemic patient ($Pao_2 = 6.3$ kPa) had a decreased HVR; Pao_2 in the remaining patients was more than 8.3 kPa. In our previous study in normal subjects we found a reduced response to hypoxia compared with the results from some studies[11 26] but our finding was similar to that of others,[13] and it is accepted that there is a wide range of HVR responses in normal subjects. In those studies in which a reduced HVR response was found in patients with COPD[11 12] most of the patients were hypoxaemic and so the different finding in our study may be due to the fact that our patients were essentially normoxic.

Fenoterol increased the slopes of both $P_{0.1}$ and $\dot{V}_E$ during the HCVR, but that of $\dot{V}_E$ did not reach significance. The position of the $P_{0.1}$ and $\dot{V}_E$ response curves at P_{ETCO_2} of 8 kPa was moved to a higher value by fenoterol treatment. The increase in the $P_{0.1}$ response by fenoterol was similar to that found in normal subjects[6] and the smaller change in $\dot{V}_E$ compared with $P_{0.1}$ may be due to the effect of airflow limitation. The effect of fenoterol on HVR is weak and so its action on the peripheral chemoreceptors seems limited. The increased response to carbon dioxide with fenoterol could be due to an action on central chemoreceptors but this putative action remains controversial. Some, but not all, studies have shown that β_2 adrenergic agonists potentiate ventilatory chemosensitivity[5–7] and those studies undertaken on humans,[5 6] together with the current study, have shown that β_2 adrenergic agonists stimulate HCVR which suggests an effect on the central chemoreceptor.

The position of the $P_{0.1}$ response curve at 80% Sao_2 in the HVR was augmented by fenoterol treatment, although the slope of the response curve was not changed. The effect of fenoterol on the HVR may be weak in patients with COPD. In our previous study fenoterol increased both the slope and the position of $P_{0.1}$ at 80% Sao_2 of HVR in normal subjects.[6] The $Paco_2$ did not differ between placebo and fenoterol, suggesting that the level of carbon dioxide may not affect the HVR. Little is known about the effects of β_2 adrenergic agonists on the ventilatory response to hypoxia. Isoprenaline stimulates the carotid body through a β adrenergic mechanism[3 4] and fenoterol has weak β_1 activity in spite of being a relatively selective β_2 adrenergic agonist.[27] It is therefore possible that fenoterol increases the response of the carotid body to hypoxia through β_1 activity. The plasma potassium level is a putative po-

tentiator of carotid body response.[28] Salbutamol can induce hypokalaemia and its stimulant action on ventilation may be effected by a potassium shift from the extracellular to the intracellular space.[5] Fenoterol can also affect plasma potassium levels[29] and so its effect on the ventilatory response could be due to this mechanism. We did not measure plasma potassium levels in our patients and so cannot supply direct evidence to support this possibility.

Beta adrenergic agonists can lead to an increase in metabolic activity[30] and the raised metabolic rate associated with exercise or feeding may stimulate peripheral and/or central chemoreceptors.[31 32] In the current study we did not measure oxygen consumption but in our previous study we found fenoterol increased resting $\dot{V}E$ without any changes in $PETCO_2$ or $P_{0.1}$, suggesting the possibility that fenoterol increased the metabolic activity. If this was true then this may be a possible mechanism to explain the effect of fenoterol on the ventilatory responses to hypercapnia and hypoxia. Another possible mechanism could relate to changes in cardiac output. Isoprenaline stimulates ventilation and this was initially thought to be secondary to the consequent increase in cardiac output,[33] but a direct action on the carotid body has subsequently been proposed.[2] Fenoterol stimulates cardiac function[27] but we found only a 7% increase in heart rate, much less than that found with isoprenaline,[33] and $P_{0.1}$ was not changed by fenoterol when breathing air. Thus, a mechanism for the ventilatory action of fenoterol through changes in cardiac output seems unlikely.

In conclusion, we have shown that fenoterol stimulates the ventilatory responses to hypercapnia and hypoxia in patients with COPD but the exact mechanism is unclear. Patients with COPD whose disease progresses tend to become hypoxic and hypercapnic. Whilst fenoterol may benefit these patients by its bronchodilator action, it is possible that its effect on ventilatory responses may also be of benefit and this deserves further study.

Appendix

Mean (SD) normal values of respiratory muscle strength:

PImax at FRC; 16.6 (4.3) kPa (men), 11.3 (3.1) kPa (women)

PImax at RV; 18.4 (4.1) kPa (men), 12.6 (3.1) kPa (women)

PEmax at TLC; 25.1 (6.2) kPa (men), 14.7 (4.1) kPa (women)

PImax at FRC; 20.9 (5.8) kPa (men), 11.7 (3.34) kPa (women)

1 Heistad DD, Wheeler RC, Mark AL, Schmid PG, Abboud FM. Effects of adrenergic stimulation on ventilation in man. *J Clin Invest* 1972;**51**:1469–75.
2 Wasserman K, Mitchell RA, Berger AJ, Casaburi R, Davis JA. Mechanism of isoproterenol hyperpnea in the cat. *Respir Physiol* 1979;**38**:359–76.
3 Eldridge FL, Gill-Kumar P. Mechanisms of hyperpnea induced by isoproterenol. *Respir Physiol* 1980;**40**:349–63.
4 Lahiri S, Pokorski M, Davies RO. Augmentation of carotid body chemoreceptor responses by isoproterenol in the cat. *Respir Physiol* 1981;**44**:351–64.
5 Leitch AG, Clancy LJ, Costello JE, Flenley DC. Effect of intravenous infusion of salbutamol on ventilatory response to carbon dioxide and hypoxia and on heart rate and plasma potassium in normal men. *BMJ* 1976;**1**:365–7.
6 Yoshiike Y, Suzuki S, Watanuki Y, Okubo T. Effects of fenoterol on ventilatory responses to hypoxia and hypercapnia in normal subjects. *Thorax* 1995;**50**:139–42.
7 Folgering H. Central β-adrenergic effects on the control of ventilation in cats. *Respiration* 1980;**39**:131–8.
8 Altose MD, McCauley WC, Kelsen SG, Cherniack NS. Effects of hypercapnia and inspiratory flow-resistive loading on respiratory activity in chronic airways obstruction. *J Clin Invest* 1977;**59**:500–7.
9 Zackon H, Despas PJ, Anthonisen NR. Occlusion pressure responses in asthma and chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1976;**114**:917–27.
10 Lourenco RV, Miranda JM. Drive and performance of the ventilatory apparatus in chronic obstructive lung disease. *N Engl J Med* 1968;**279**:53–9.
11 Bradley CA, Fleetham JA, Anthonisen NR. Ventilatory control in patients with hypoxemia due to obstructive lung disease. *Am Rev Respir Dis* 1979;**120**:21–30.
12 Flenley DC, Franklin DH, Millar JS. The hypoxic drive to breathing in chronic bronchitis and emphysema. *Clin Sci* 1970;**38**:503–18.
13 Erbland ML, Ebert RV, Snow SL. Interaction of hypoxia and hypercapnia on respiratory drive in patients with COPD. *Chest* 1990;**97**:1289–94.
14 American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987;**136**:225–44.
15 Read DJC. A clinical method for assessing the ventilatory response to carbon dioxide. *Australas Ann Med* 1967;**16**:20–32.
16 Whitelaw WA, Derenne JP, Milic-Emili J. Occlusion pressure as a measure of respiratory centre output in conscious man. *Respir Physiol* 1975;**23**:181–99.
17 Rebuck AS, Campbell EJM. A clinical method for assessing the ventilatory response to hypoxia. *Am Rev Respir Dis* 1974;**109**:345–50.
18 Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 1969;**99**:696–702.
19 The Pulmonary Physiology Committee of Japan Society of Chest Diseases. Normal standards of pulmonary function tests for healthy Japanese adults. *Jpn J Thorac Dis* 1993;**31**(Suppl):1–25.
20 Rominger KL, Pollmann W. Comparative pharmacokinetic studies on fenoterol-hydrobromide in rat, dog and man. *Arzneim Forsch* 1972;**22**:1190–6.
21 Eldridge FL, Vaughn KZ. Relationship of thoracic volume and airway occlusion pressure: muscular effects. *J Appl Physiol* 1977;**43**:312–21.
22 DeWeese EL, Sullivan TY, Yu PL. Neuromuscular response to resistive unloading: helium vs. bronchodilatation. *J Appl Physiol* 1984;**56**:1308–13.
23 Appendini L, Molina G, Senis L, Garbagni L. Control of breathing in chronic obstructive pulmonary disease patients at rest and after beta-2 agonist inhalation. *Respiration* 1991;**58**:42–8.
24 Sorli J, Grassino A, Lorange G, Milic-Emili J. Control of breathing in patients with chronic obstructive lung disease. *Clin Sci Mol Med* 1978;**54**:295–304.
25 Scano G, Duranti R, Spenelli A, Gorini M, Conte CL, Gigliottie F. Control of breathing in normal subjects and in patients with chronic airflow obstruction. *Bull Eur Physiopathol Respir* 1987;**23**:209–16.
26 Light RW, Mahutte CK, Stansbury DW, Fischer CE, Brown SE. Relationship between improvement in exercise performance with supplemental oxygen and hypoxic ventilatory drive in patients with chronic airflow obstruction. *Chest* 1989;**95**:751–6.
27 Giles RE, Williams JC, Finkel MP. The bronchodilator and cardiac stimulant effects of Th1165a, salbutamol and isoproterenol. *J Pharmacol Exp Ther* 1973;**186**:472–81.
28 Linton RAF, Band DM. The effect of potassium on carotid chemoreceptor activity and ventilation in the cat. *Respir Physiol* 1985;**59**:65–70.
29 Wong CS, Pavord ID, Williams J, Britton JR, Tattersfield AE. Bronchodilator, cardiovascular, and hypokalaemic effects of fenoterol, salbutamol, and terbutaline in asthma. *Lancet* 1990;**336**:1396–9.
30 Amoroso P, Wilson SR, Moxham J, Ponte J. Acute effects of inhaled salbutamol on the metabolic rate of normal subjects. *Thorax* 1993;**48**:882–5.
31 Zwillich CW, Sahn SA, Weil JV. Effects of hypermetabolism on ventilation and chemosensitivity. *J Clin Invest* 1977;**60**:900–6.
32 Weil JV, Byrne-Quinn E, Sodal IE, Kline JS, McCullough RE, Filley GF. Augmentation of chemosensitivity during mild exercise in normal man. *J Appl Physiol* 1972;**66**:813–9.
33 Wasserman K, Whipp BJ, Castagna J. Cardiodynamic hyperpnea: hyperpnea secondary to cardiac output increase. *J Appl Physiol* 1974;**36**:457–64.