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

Shunsuke Suzuki, Yuji Watanuki, Yasuhiro Yoshiike, Takao Okubo

Abstract

Background - It has previously been shown that fenoterol, a β2 adrenergic agonist, increases the ventilatory response to hypoxia (HVR) and hypercapnia (HCVR) in normal subjects. The effects of β2 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 (P0.1) and ventilation (VE) against end tidal carbon dioxide pressure (PETCO2) and arterial oxygen saturation (Sao2), 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 (FEV1) and inspiratory muscle strength. In the HCVR the slope of P0.1 versus PETCO2 was increased by fenoterol from 0.35 (0.23) to 0.43 (0.24) (p<0.01). Moreover, the P0.1 at PETCO2 of 8 kPa was higher on fenoterol than on placebo (p<0.05) and the VE was also greater (p<0.01). In the HVR fenoterol treatment increased the P0.1 at 80% Sao2 from 0.90 (0.72) to 0.97 (0.55) kPa (p<0.05) while the slopes of the response of P0.1 and VE 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.

Keywords: fenoterol, β2 adrenergic agonist, hypercapnic ventilatory response, hypoxic ventilatory response, chronic obstructive pulmonary disease (COPD).

Methods

Twenty patients (19 men) with COPD of mean (SD) age 67.2 (7.8) years (range 50-80) participated in the study. 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 (FEV1), 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 (VE) and occlusion pressure (P0.1) during hypercapnia and hypoxia, as in our previous study. The response to hypercapnia was measured by a modification of the Read technique. The circuit
Table 1  Mean (SD) pulmonary function data of patients with chronic obstructive pulmonary disease

<table>
<thead>
<tr>
<th></th>
<th>%VC (%)</th>
<th>FEV1/VC (%)</th>
<th>%FEV1 (%)</th>
<th>FRC (l)</th>
<th>%FRC (%)</th>
<th>sGaw (kPa l⁻¹ s⁻¹)</th>
<th>Pmax (kPa)</th>
<th>%Pmax (%)</th>
<th>Pao2 (kPa)</th>
<th>Paco2 (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>90(20)</td>
<td>50(14)</td>
<td>63(25)</td>
<td>4.29(0.95)</td>
<td>131(28)</td>
<td>0.71(0.57)</td>
<td>10.1(4.0)</td>
<td>52(21)</td>
<td>10.8(1.8)</td>
<td>5.4(0.6)</td>
</tr>
<tr>
<td>Fenoterol</td>
<td>93(19)</td>
<td>51(18)</td>
<td>67(30)</td>
<td>4.22(0.97)</td>
<td>129(29)</td>
<td>0.71(0.53)</td>
<td>10.1(4.0)</td>
<td>58(21)</td>
<td>10.8(1.8)</td>
<td>5.3(0.6)</td>
</tr>
<tr>
<td>Difference</td>
<td>NS</td>
<td>p&lt;0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

%VC = vital capacity; FEV1 = forced expiratory volume in one second; FRC = functional residual capacity; sGaw = specific airway conductance; Pmax = maximum inspiratory mouth pressure at FRC; Pao2, Paco2 = arterial oxygen and carbon dioxide tensions; NS = not significant.

VC, %FEV1, and %FRC were calculated from the predicted values.16

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 P0.1 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 inspiratory 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 litre re-breathing 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 Ve was obtained as the average for the two breaths that preceded the breath from which the P0.1 was measured. Simultaneously, the end tidal partial pressure of carbon dioxide (PETCO2) was measured. The ventilatory response to hypercapnia was assessed from the slope of the linear regression between Ve and PETCO2, and between P0.1 and PETCO2 (∆Ve/∆PETCO2 and ∆P0.1/∆PETCO2, 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 (SaO2) was monitored with a pulse oximeter (Biox IIA, Biox Technology, Boulder, USA). During rebreathing the PETCO2 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 SaO2 decreased to 75–80%. The ventilatory response to hypoxia was calculated from the slope of the linear regression of plots of Ve versus SaO2 and P0.1 versus SaO2 (∆Ve/∆SaO2 and ∆P0.1/∆SaO2, respectively).

Respiratory muscle strength was assessed by measuring mouth pressures during maximal static inspiratory (Pmax) and expiratory (Pmax) efforts against a closed valve with a small air leak to prevent glottic closure.18 Pmax was measured at FRC and residual volume, and Pmax at FRC and total lung capacity with a differential pressure transducer (Validyne MP-45 ± 250 mm Hg). The determinations of Pmax and Pmax 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 beta 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.15 The STATISTICA statistical software package (StatSoft, Tulsa, USA) was used.

Results

The patients had severe airway obstruction with a mean FEV1/VC of 50 (14)% and increased lung volumes as shown in table 1. Hypoxaemia (Pao2 <10 kPa) was observed in six of 20 patients and hypercapnia (Paco2 >6 kPa) in only one. Fenoterol treatment for one week increased the mean FEV1 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 Pmax 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 Pmax 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 Paco2, Pao2, or blood pressure.

The minute ventilation showed a trend to increase with fenoterol from a mean (SD) of
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SaO₂) with placebo and fenoterol. Open boxes and bars represent the 95% confidence interval and mean value, respectively. Note that neither of the slopes changed.

The P₀.₁ at an SaO₂ 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 Ve was unchanged at 80% oxygen saturation.

Figure 1 Mean occlusion pressure (P₀.₁) responses to (A) the hypacemic 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 P₀.₁ at 80% SaO₂ (p<0.05) compared with placebo (solid lines). Mean response curves were calculated from individual slopes of P₀.₁ in both HCVR and HVR. The mean responses and one standard error are represented by thick and thin lines, respectively.

Figure 2 Hyperacemic ventilatory response (HCVR). Left: slope of Ve versus PETCO₂ curve (ΔVe/ΔPETCO₂) of placebo and fenoterol groups. Right: slope of P₀.₁ versus PETCO₂ curve (ΔP₀.₁/ΔPETCO₂) 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 P₀.₁ by 23% (p<0.01) but did not affect the Ve.

Figure 3 Hypoxic ventilatory response (HVR). Left: slope of Ve versus SaO₂ curve (ΔVe/ΔSaO₂) with placebo and fenoterol. Right: slope of P₀.₁ versus SaO₂ curve (ΔP₀.₁/ΔSaO₂) with placebo and fenoterol. Open boxes and bars represent the 95% confidence interval and mean value, respectively. Note that neither of the slopes changed.

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 FEV₁ and inspiratory muscle strength but these changes did not affect the resting ventilation and P₀.₁. 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 time²² 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 techniques¹⁵,¹⁷ used for HCVR and HVR were first designed for normal subjects based on the assumption that a relation between Ve and PETCO₂ or between Ve and SaO₂ is linear. One concern when using the Ve response in patients with airway obstruction is that the response may no longer be linear. In our patients the correlation coefficient for Ve...
with PetCO₂ when taking placebo was 0.97 and for Vₑ with SaO₂ it was −0.93, indicating a close linear relationship in the range of PetCO₂ and SaO₂ in our experiment. This close relationship was not affected by fenoterol and so we believe that the rebreathing techniques of Read and Reubuck were valid tests for our subjects. Because of the concern that Vₑ may be affected by the presence of airflow limitation, we also used P₀.₁ as a measure of respiratory output. P₀.₁ may be influenced by changes in muscle strength or lung volume¹¹ and in our subjects fenoterol increased Pmax by 16% but did not alter FRC. However, we found that P₀.₁ when breathing air was not changed by fenoterol and so we believe that this change in muscle strength was not affecting P₀.₁ in our tests. We also found that fenoterol increased FEV₁ but had no effect on sGaw, and others have found that bronchodilation with atropine did not affect P₀.₁ whereas resistive unloading with helium/oxygen reduced it.¹² It therefore seems that fenoterol is unlikely to influence P₀.₁ by its effects on airway mechanics. For a given P₀.₁, the mean inspiratory flow will increase if flow resistance decreases, and we found that the Vₑ/Tᵣ whilst breathing air increased following fenoterol while the P₀.₁ 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 FEV₁.²³ We found no difference in the effective impedance between our placebo and fenoterol groups, and so the recorded increase in FEV₁ 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 P₀.₁ and Vₑ/Tᵣ were comparable with that found in our normal subjects.²⁵ The effective inspiratory impedance, P₀.₁/(Vₑ/Tᵣ), 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.⁶ ⁸ 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 P₀.₁ response slope is decreased.²⁶ In the present study hypercapnia was observed in only one patient but the increase in PacO₂ was slight (6.4 kPa). His ΔP₀.₁/ΔPetCO₂ was normal but he had a low ΔVₑ/ΔPetCO₂. The average values of ΔP₀.₁/ΔPetCO₂ and ΔVₑ/ΔPetCO₂ 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 ¹² 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 study²⁶ (ΔVₑ/SaO₂ = 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 (PaO₂ = 6.3 kPa) had a decreased HVR; PaO₂ 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 studies¹¹ ¹² 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 COPD¹¹ 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 P₀.₁ and Vₑ during the HCVR, but that of Vₑ did not reach significance. The position of the P₀.₁ and Vₑ response curves at PetCO₂ of 8 kPa was moved to a higher value by fenoterol treatment. The increase in the P₀.₁ response by fenoterol was similar to that found in normal subjects¹⁰ and the smaller change in Vₑ compared with P₀.₁ 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 β₂ adrenergic agonists potentiate ventilatory chemosensitivity²⁷ and those studies undertaken on humans,⁶ ⁷ together with the present study, have shown that β₂ adrenergic agonists stimulate HCVR which suggests an effect on the central chemoreceptor.

The position of the P₀.₁ response curve at 80% SaO₂ 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 P₀.₁ at 80% SaO₂ of HVR in normal subjects.¹¹ The PacO₂ 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 β₂ adrenergic agonists on the ventilatory response to hypoxia. Isoprenaline stimulates the carotid body through a β adrenergic mechanism¹⁴ and fenoterol has weak β₁ activity in spite of being a relatively selective β₂ adrenergic agonist.²⁸ It is therefore possible that fenoterol increases the response of the carotid body to hypoxia through β₁ activity. The plasma potassium level is a putative po-
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tentiator of carotid body response. Salbutamol can induce hypokalaemia and its stimulant action on ventilation may be effected by a potassium shift from the extracellular to the intracellular space. Fenoterol can also affect plasma potassium levels 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 and the raised metabolic rate associated with exercise or feeding may stimulate peripheral and/or central chemoreceptors. The increase in metabolic rate associated with exercise or feeding may stimulate peripheral and/or central chemoreceptors. In the current study we did not measure oxygen consumption but in our previous study we found fenoterol increased resting V̇E without any changes in P aCO 2 or P aO 2 , 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. Iso- prenaline stimulates ventilation and this was initially thought to be secondary to the consequent increase in cardiac output, but a direct action on the carotid body has subsequently been proposed. Fenoterol stimulates cardiac function but we found only a 7% increase in heart rate, much less than that found with isoprenaline, and P aO 2 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 increase resting V̇E without any changes in P aCO 2 or P aO 2 .

Appendix

Mean (SD) normal values of respiratory muscle strength:

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pmax at FRC</td>
<td>16.6 (4.3) kPa (men), 11.3 (3.1) kPa (women)</td>
</tr>
<tr>
<td>Pmax at RV</td>
<td>18.4 (4.1) kPa (men), 12.6 (3.1) kPa (women)</td>
</tr>
<tr>
<td>Pmax at TLC</td>
<td>25.1 (6.2) kPa (men), 14.7 (4.1) kPa (women)</td>
</tr>
<tr>
<td>Pmax at FRC</td>
<td>20.9 (5.8) kPa (men), 11.7 (3.34) kPa (women)</td>
</tr>
</tbody>
</table>

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