Effects of fenoterol on ventilatory responses to hypoxia and hypercapnia in normal subjects

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Abstract

Background – The effects of β_2 adrenergic agonists on chemoreceptors remain controversial. This study was designed to examine whether fenoterol, a β_2 adrenergic agonist, increases the ventilatory responses to hypercapnia (HCVR) and hypoxia (HVR) in normal subjects.

Methods – HCVR was tested with a re-breathing method and HVR was examined with a progressive isocapnic hypoxic method in 11 normal subjects. Both HCVR and HVR were assessed by the slope of occlusion pressure ($P_{0.1}$) or ventilation ($\dot{V}_E$) plotted against end tidal carbon dioxide pressure and arterial oxygen saturation, respectively. Respiratory muscle strength, spirometric values and lung volume were measured. After a single oral administration of 5 mg fenoterol or placebo HCVR and HVR were evaluated.

Results – Fenoterol treatment did not change the specific airway conductance or forced expiratory volume in one second. Respiratory muscle strength did not change. Fenoterol increased the slope of the HCVR of both $P_{0.1}$ (from 0.251 (0.116) to 0.386 (0.206) kPa/kPa, average increase 71%) and $\dot{V}_E$ (from 10.7 (3.4) to 15.1 (4.2) l/min/kPa, average increase 52%), and shifted the response curves to higher values. For the HVR fenoterol increased the slopes of both $P_{0.1}$ and $\dot{V}_E$ (from $-4.06 (2.00) \times 10^{-3}$ to $-7.99 (4.29) \times 10^{-3}$ kPa/l/min, an average increase of 83%, and from $-0.221 (0.070)$ to $-0.313 (0.112)$ l/min/%, a 44.5% increase, respectively), and shifted the response curves to higher values.

Conclusion – Acute administration of fenoterol increases the ventilatory responses to both hypercapnia and hypoxia in normal subjects.

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Keywords: fenoterol, β adrenergic agonist, hypercapnic ventilatory response, hypoxic ventilatory response.

Lahiri *et al*⁶ directly measured the carotid chemoreceptor activity and showed that isoprenaline excited the carotid body. Thus, isoprenaline acts on the β adrenergic receptors of the carotid body and increases ventilation.

The effects of β_2 adrenergic agonists on the central chemoreceptors remain controversial. Some studies^{7,8} showed that β_2 adrenergic agonists potentiate ventilatory chemosensitivity, but this was not a universal finding⁹ and this discrepancy may result from a species difference. Furthermore, little is known about the effects of β_2 adrenergic agonists on the ventilatory response to hypoxia. It may be necessary to consider the effects of β_2 agonists on ventilatory control when treating patients with airways obstruction. The purpose of the present study was to investigate the quantitative effects of fenoterol, a β_2 adrenergic agonist, on ventilatory responses to hypercapnia and hypoxia in normal subjects.

Methods

SUBJECTS

Eleven healthy non-smoking men whose mean (SD) age was 29.0 (6.2) years (range 24-46 years) participated in the study. All were medical personnel and had no history of chronic respiratory or circulatory diseases. All gave informed consent and the study was approved by the institution's committee on investigation in humans.

PULMONARY FUNCTION TESTS

Spirometric measurements (forced expiratory volume in one second (FEV₁) and vital capacity (VC)) were performed using a dry seal spirometer (OST-80, Chest Co, Tokyo) and body plethysmography (Autobox 2800, Gould, USA) was used to measure specific airway conductance (sGaw) and functional residual capacity (FRC).

VENTILATORY RESPONSES TO HYPERCAPNIA AND HYPOXIA

Chemical control of breathing was assessed by measuring minute ventilation ($\dot{V}_E$) and occlusion pressure ($P_{0.1}$) responses to hypercapnia or hypoxia. Response to hypercapnia (HCVR) was measured by a modification of the Read technique.¹⁰ The circuit used was similar to that of Whitelaw *et al*.¹¹ A two way non-rebreathing valve (Hans-Rudolph no. 1400, Kansas City, USA) was attached to the mouthpiece; both inspiratory and expiratory sides of the valve

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Isoprenaline, a potent β adrenergic agonist, is known to induce hyperpnoea¹⁻⁴ although the mechanisms underlying this are disputed. Heistad *et al*¹ and Winn *et al*⁴ showed that intravenous isoprenaline increased ventilation by stimulation of the peripheral chemoreceptors and ventilation was augmented by moderate hypoxia. Wasserman *et al*⁵ found that bilateral sectioning of the carotid sinus nerves substantially decreased the ventilatory response to isoprenaline. Eldridge and Gill-Kumar⁵ and

were connected to the rebreathing bag. Mouth pressure was measured from the side tap of the mouthpiece using a differential pressure transducer (MP-45 Validyne, Northridge, USA). Airflow was measured with a Fleisch pneumotachograph (Fleisch no. 1, Lausanne, Switzerland) placed between the mouthpiece and the two way valve. The volume was obtained from electrical integration of the flow signal. The inspiratory side of the two way valve was connected with a solenoid valve which was capable of occluding the side of the valve. The solenoid valve was closed during expiration and opened no later than 200 ms after the beginning of inspiration using an analog electrical circuit, by which a breathing cycle for measurement of occlusion pressure was manually selected. Occlusion pressure ($P_{0.1}$) was obtained from the 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 by a mass spectrometer (WSMR-1400; Westron, Chiba, Japan). The resistance of the inspiratory side was 0.059 kPa/l/s, while that of the expiratory circuit was 0.049 kPa/l/s. Subjects wearing nose clips were seated comfortably in front of the rebreathing circuit and held the mouthpiece in position. Initially they breathed air by a bypass of the rebreathing bag to room air until the circuit was equilibrated. They then rebreathed a gas mixture of 7% carbon dioxide and 93% oxygen from a six litre bag. During rebreathing the inspiratory side of the circuit was occluded randomly every 4–6 breaths. Rebreathing was continued until the end tidal partial pressure of carbon dioxide ($PETCO_2$) reached about 8.7 kPa or the subject complained of dyspnoea. The test was usually terminated within 3–4 minutes. Minute ventilation ($\dot{V}_E$) was calculated as the average of the two successive breaths preceding the one used for occlusion. Simultaneously the $PETCO_2$ was measured. Hypercapnic response was assessed by the slopes of linear regressions between $\dot{V}_E$ and $PETCO_2$ and between $P_{0.1}$ and $PETCO_2$ ($\Delta\dot{V}_E/\Delta PETCO_2$ and $\Delta P_{0.1}/\Delta PETCO_2$, respectively), calculated by the least squares method. Fifteen to 20 breath pairs were used for analysis.

Hypoxic ventilatory response (HVR) was measured by a modification of the progressive isocapnic hypoxia method of Rebuck and Campbell.¹² Subjects rebreathed using the same rebreathing circuit as for the hypercapnic response, except the rebreathing bag contained eight litres of a gas mixture of 3.5% carbon dioxide, 23% oxygen, and 73.5% nitrogen and a bypass carbon dioxide absorber was used. During the test arterial oxygen saturation (SaO_2) was monitored with a pulse oximeter (Biox 3700, Ohmeda, Boulder, USA). During rebreathing $PETCO_2$ was kept constant at the baseline resting level by removal of 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 hypoxic response was obtained from the slopes of linear regressions between $\dot{V}_E$ and SaO_2 and between

$P_{0.1}$ and SaO_2 ($\Delta\dot{V}_E/\Delta SaO_2$ and $\Delta P_{0.1}/\Delta SaO_2$, respectively).

RESPIRATORY MUSCLE STRENGTH

As we had previously found that fenoterol increased the strength of the fatigued canine diaphragm,¹³ respiratory muscle strength was assessed by measuring mouth pressures during maximal static inspiratory (P_{imax}) and expiratory (P_{emax}) efforts against a closed valve with a small air leak to prevent glottic closure.¹⁴ P_{imax} was measured at FRC and residual volume (RV) and P_{emax} was measured at FRC and total lung capacity (TLC) with a differential pressure transducer (Validyne MP – 45 $\pm$ 250 mm Hg). The determinations of P_{imax} and P_{emax} were repeated until three measurements varying by <5% and sustained for >2 seconds were recorded; the highest value thus obtained was reported.

PROTOCOL

The study was performed at the same time of day on two different days at least two days apart and within a seven day interval. Subjects were instructed to refrain from caffeine-containing beverages, alcohol, and other drugs for 24 hours before the study. HCVR was examined in all subjects while HVR was measured in seven of the 11 subjects. On each test day the baseline measurements of pulse rate (PR), blood pressure (BP), ventilation and $PETCO_2$ were performed at rest. Either 5 mg fenoterol (Boehringer Ingelheim of Japan, Kawanishi, Japan) or placebo was then administered orally in a randomised, double blind, crossover design on the first or second day. Two hours after fenoterol or placebo administration, pulmonary function tests, respiratory muscle strength, heart rate, blood pressure, ventilation, and $PETCO_2$ were measured and HCVR and HVR were then calculated. For HVR $PETCO_2$ was controlled at the baseline level before administration of fenoterol or placebo because fenoterol could decrease $PETCO_2$. The order of the tests (HCVR and HVR) was randomised and at least 10 minutes was allowed between tests.

DATA ANALYSIS

HCVR and HVR varied by approximately 20% and the sample size required to discern a significant difference from the drug was 10. All values are expressed as the mean (SD). Statistical analysis was performed using the Wilcoxon signed rank test and the two way analysis of variance (ANOVA). A p value of <0.05 was considered significant.

Results

Fenoterol did not affect $FEV_{1.0}$, VC, FRC, or sGaw. Heart rate was increased by 8.0 (10.5)% (ANOVA, $p < 0.05$) although systemic blood pressure did not change. Baseline minute ventilation while breathing air and $\dot{V}_T/TI$ were both increased by 15% with fenoterol ($p < 0.01$).

Figure 1 Mean (A) hypercapnic and (B) hypoxic ventilatory responses (HCVR and HVR). Fenoterol treatment (dashed line) increased both HCVR and HVR compared with placebo (solid line). Average response curves were calculated from slope means ($\Delta\dot{V}_E/\Delta P_{ETCO_2}$ and $\Delta\dot{V}_E/\Delta SaO_2$), and mean $\dot{V}_E$ values (at P_{ETCO_2} of 8 kPa with HCVR and at 80% SaO_2 with HVR, respectively). Mean responses and 95% confidence intervals are represented by thick and thin lines, respectively.

Figure 2 Hypercapnic ventilatory response (HCVR). (A) Slope of $\dot{V}_E$ versus P_{ETCO_2} curve ($\Delta\dot{V}_E/\Delta P_{ETCO_2}$) with placebo and fenoterol. (B) Slope of $P_{0.1}$ versus P_{ETCO_2} curve ($\Delta P_{0.1}/\Delta P_{ETCO_2}$) with placebo and fenoterol. Open boxes and bars represent the 95% confidence interval and mean value, respectively. Fenoterol increased the slopes of the response curve of $\dot{V}_E$ by 56% ($p < 0.01$) and that of $P_{0.1}$ by 104% ($p < 0.01$).

Figure 3 Hypoxic ventilatory response (HVR). (A) Slope of $\dot{V}_E$ versus SaO_2 curve ($\Delta\dot{V}_E/\Delta SaO_2$) with placebo and fenoterol. (B) 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. Both slopes of the hypoxic response curve increased ($p < 0.05$).

However, after drug treatment P_{ETCO_2} did not differ between those given placebo and those given fenoterol (5.05 (0.38) v 4.89 (0.62) kPa). Further, the $P_{0.1}$ during breathing air did not differ between treatments (0.197 (0.105) v 0.243 (0.153) kPa). There was no difference in P_{imax} or P_{Emax} between the two treatments.

For HCVR fenoterol increased the slope of $\dot{V}_E$ to P_{ETCO_2} ($\Delta\dot{V}_E/\Delta P_{ETCO_2}$) by 52 (43)% ($p < 0.01$) and that of $P_{0.1}$ to P_{ETCO_2} ($\Delta P_{0.1}/\Delta P_{ETCO_2}$) by 71 (104)% compared with placebo ($p < 0.05$) (figs 1 and 2). $\dot{V}_E$ at P_{ETCO_2} of 60 mm Hg (≈ 8 kPa) was 39.6 (12.6) l/min with fenoterol, which was higher than the value with placebo (31.2 (7.6) l/min) ($p < 0.01$). $P_{0.1}$ at P_{ETCO_2} of 8 kPa (0.70 (0.35) kPa) after fenoterol was higher than after placebo (0.54 (0.21) kPa) ($p < 0.05$).

For HVR fenoterol increased the slope of $\dot{V}_E$ to SaO_2 ($\Delta\dot{V}_E/\Delta SaO_2$) by 44.5 (53.4)%; $p < 0.05$ (fig 1). It also increased the slope of $P_{0.1}$ to SaO_2 ($\Delta P_{0.1}/\Delta SaO_2$) (-4.1 (2.0) $\times 10^{-3}$ with placebo v -8.0 (4.3) $\times 10^{-3}$ kPa/% with fenoterol, $p < 0.05$) (fig 3). The position of the $\dot{V}_E$ v SaO_2 curve at SaO_2 of 80% was higher than that of placebo (16.7 (1.8) v 19.5 (3.5) l/min, $p < 0.05$). Similarly, fenoterol shifted the $P_{0.1}$ curve to a higher $P_{0.1}$ at SaO_2 of 80% (0.29 (0.17) v 0.38 (0.20) kPa, $p < 0.02$).

Discussion

We have demonstrated that a single oral dose of 5 mg fenoterol enhanced the ventilatory responses to both hypercapnia and hypoxia in normal subjects. Respiratory muscle strength and specific airway conductance were not changed. These data suggest that fenoterol stimulates both central and peripheral chemoreceptors, although it is unknown whether its action is direct or indirect.

We measured the ventilatory response two hours after oral administration of the drug to allow the plasma concentration of fenoterol to reach a maximum.¹⁵ Since $\dot{V}_E$ reflects the neural output to inspiratory muscles poorly when thoracic mechanics change,¹⁶ we used occlusion pressure ($P_{0.1}$) as a reflection of respiratory output.¹¹ Occlusion pressure may be affected by inspiratory muscle strength or lung volume.¹⁷ Fortunately, in this study neither FRC nor inspiratory muscle strength was affected by fenoterol treatment. Therefore, it is possible that both occlusion pressure and minute ventilation reflected the neural output of the respiratory centre in this study.

Fenoterol is a potent bronchodilator and may increase FEV₁ and sGaw even in normal subjects. Resistive unloading with helium/oxygen breathing decreased $P_{0.1}$ but inhalation of atropine did not change $P_{0.1}$ in spite of a reduction in airways resistance.¹⁸ The increase in sGaw after fenoterol could therefore reduce the neural output such as $P_{0.1}$ or ventilation. In the present study, however, fenoterol caused no change in sGaw or FEV₁. Thus fenoterol may not affect $P_{0.1}$ by changing airway mechanics. It is likely that fenoterol increases the neural output to the inspiratory muscles.

Fenoterol increased the slopes of $\dot{V}_E$ and $P_{0.1}$ in HVR. The activity of the carotid body chemoreceptors increases with decreasing P_{aO_2} .¹⁹ Isoprenaline is known to stimulate the carotid body through a β adrenergic mechanism.^{1-3,5,6} Fenoterol is a selective β_2 adrenergic agonist but also has weak β_1 activity.²⁰ In the present study fenoterol did not affect the resting level of P_{ETCO_2} so that the level of carbon dioxide did not affect HVR. It is therefore possible that fenoterol augmented the response of the carotid body in hypoxia, probably through β_1 activity. The heart rate increased by 8% after fenoterol, which is also known to increase cardiac output,²¹ and this in turn may increase ventilation.²²

Fenoterol increased HCVR as measured by $P_{0.1}$ and $\dot{V}_E$. Response to carbon dioxide inhalation is thought to occur through the stimulation of the medullary chemoreceptors in hyperoxia. Carbon dioxide also stimulates the peripheral chemoreceptors, but their contribution to overall stimulation by carbon dioxide is thought to be small in the presence of hyperoxia.²³ It is possible that fenoterol stimulates the central chemoreceptors, thereby increasing HCVR.

β adrenergic agonist actions are accompanied by an increase in metabolic activity.²⁴ Although we did not measure oxygen consumption in our study, fenoterol increased resting $\dot{V}_E$ without any changes in P_{ETCO_2} and $P_{0.1}$, suggesting that it raises the metabolic activity thus increasing resting $\dot{V}_E$. It is known that the increased metabolic rate, which is associated with hyperthyroidism, exercise, or feeding, may stimulate peripheral and/or central chemoreceptors.²⁵⁻²⁷

In conclusion, fenoterol stimulates ventilatory chemosensitivity although it is unknown whether the mechanisms are the direct β receptor mediated effects on peripheral and/or central chemoreceptors, or the indirect effects on factors such as metabolic rate. Fenoterol is a potent bronchodilator and may be beneficial in patients with chronic obstructive pulmonary disease who have a tendency toward hypercapnia. However, further clinical studies are needed.

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