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

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Abstract
Background – The effects of β₂ adrenergic agonists on chemoreceptors remain controversial. This study was designed to examine whether fenoterol, a β₂ adrenergic agonist, increases the ventilatory responses to hypercapnia (HCVR) and hypoxia (HVR) in normal subjects.

Methods – HCVR was tested with a rebreathing 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 (P₀,₀) or ventilation (Ve) 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 P₀,₀ (from 0.251 (0.116) to 0.386 (0.206) kPa/kPa, average increase 71%) and Ve (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 P₀,₀ and Ve (from −4.06 (2.00) × 10⁻³ to −7.99 (4.29) × 10⁻³ kPa/l/min%, an average increase of 83%, and from −0.221 (0.070) to −0.313 (0.112) l/min%/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.

Keywords: fenoterol, β₂ adrenergic agonist, hypoxic ventilatory response, hyperoxic ventilatory response.

Isoprenaline, a potent β adrenergic agonist, is known to induce hyperpnoea although the mechanisms underlying this are disputed. Heistad et al. and Winn et al. showed that intravenous isoprenaline increased ventilation by stimulation of the peripheral chemoreceptors and ventilation was augmented by moderate hypoxia. Wasserman et al. found that bilateral sectioning of the carotid sinus nerves substantially decreased the ventilatory response to isoprenaline. Eldridge and Gill-Kumar and Lahiri et al. 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 β₂ adrenergic agonists on the central chemoreceptors remain controversial. Some studies showed that β₂ adrenergic agonists potentiate ventilatory chemosensitivity, but this was not a universal finding and this discrepancy may result from a species difference. Furthermore, little is known about the effects of β₂ adrenergic agonists on the ventilatory response to hypoxia. It may be necessary to consider the effects of β₂ 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 β₂ 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 (Ve) and occlusion pressure (P₀,₀) responses to hypercapnia or hypoxia. Response to hypercapnia (HCVR) was measured by a modification of the Read technique. The circuit used was similar to that of Whitelaw et al. 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...
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\textsubscript{o1}) 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\textsubscript{2}) reached about 8.7 kPa or the subject complained of dyspnoea. The test was usually terminated within 3–4 minutes. Minute ventilation (V\textsubscript{E}) was calculated as the average of the two successive breaths preceding the one used for occlusion. Simultaneously the PETCO\textsubscript{2} was measured. Hypercapnic response was assessed by the slopes of linear regressions between \textit{Ve} and PETCO\textsubscript{2} and between P\textsubscript{o1} and PETCO\textsubscript{2} (\textit{AVe}/\textit{ΔPETCO}_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 Reuback and Campbell.\textsuperscript{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\textsubscript{2}) was monitored with a pulse oximeter (Biox 3700, Ohmeda, Boulder, USA). During rebreathing PETCO\textsubscript{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\textsubscript{2} decreased to 75–80%. The hypoxic response was obtained from the slopes of linear regressions between \textit{Ve} and Sao\textsubscript{2} and between P\textsubscript{o1} and Sao\textsubscript{2} (\textit{AVe}/\textit{ΔSao}_2 and \textit{ΔP}_{o1}/\textit{ΔSao}_2, respectively).

**Respiratory Muscle Strength**

As we had previously found that fenoterol increased the strength of the fatigued canine diaphragm,\textsuperscript{13} respiratory muscle strength was assessed by measuring mouth pressures during maximal static inspiratory (P\textsubscript{imax}) and expiratory (P\textsubscript{emax}) efforts against a closed valve with a small air leak to prevent glottic closure.\textsuperscript{14} P\textsubscript{imax} was measured at FRC and residual volume (RV) and P\textsubscript{emax} was measured at FRC and total lung capacity (TLC) with a differential pressure transducer (Validyne MP - 45 ± 250 mm Hg). The determinations of P\textsubscript{imax} and P\textsubscript{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\textsubscript{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\textsubscript{2} were measured and HCVR and HVR were then calculated. For HVR PETCO\textsubscript{2} was controlled at the baseline level before administration of fenoterol or placebo because fenoterol could decrease PETCO\textsubscript{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\textsubscript{1}, 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 VT/Ti were both increased by 15% with fenoterol (p<0.01).
Effect of fenoterol on HCVR and HVR

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 (ΔVe/ΔPETCO2 and ΔVe/ΔSao2) and mean Ve values (at PETCO2 of 8 kPa with HCVR and at 80% Sao2 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 Ve versus PETCO2 curve (ΔVe/ΔPETCO2) with placebo and fenoterol. (B) Slope of PETCO2 curve (APetco2/ΔPETCO2) 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 Ve by 56% (p < 0.01) and that of P0.1, by 104% (p < 0.01).

Figure 3  Hypoxic ventilatory response (HVR). (A) Slope of Ve versus Sao2 curve (ΔVe/ΔSao2) with placebo and fenoterol. (B) 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. Both slopes of the hypoxic response curve increased (p < 0.05).

However, after drug treatment PETCO2 did not differ between those given placebo and those given fenoterol (5.05 (0.38) v 4.89 (0.62) kPa). Further, the P0.1 during breathing air did not differ between treatments (0.197 (0.105) v 0.243 (0.153) kPa). There was no difference in Pmax or PEmax between the two treatments.

For HCVR fenoterol increased the slope of Ve to PETCO2 (ΔVe/ΔPETCO2) by 52 (43)% (p < 0.01) and that of P0.1, to PETCO2 (APetco2/ΔPETCO2) by 71 (104)% compared with placebo (p < 0.05) (figs 1 and 2). Ve at PETCO2 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). P0.1 at PETCO2 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 Ve to Sao2 (ΔVe/ΔSao2) by 44.5 (53.4)%; p < 0.05 (fig 1). It also increased the slope of P0.1 to Sao2 (APetco2/ΔSao2) by 1.1 (2.0) × 10⁻³ kPa% with placebo v -0.8 (4.3) × 10⁻³ kPa% with fenoterol, p < 0.05 (fig 3). The position of the Ve v Sao2 curve at Sao2 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 P0.1 curve to a higher P0.1 at Sao2 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. Since Ve reflects the neural output to inspiratory muscles poorly when thoracic mechanics change, we used occlusion pressure (P0.1) as a reflection of respiratory output. Occlusion pressure may be affected by inspiratory muscle strength or lung volume. 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 P0.1, but inhalation of atropine did not change P0.1 in spite of a reduction in airways resistance. The increase in sGaw after fenoterol could therefore reduce the neural output input such as P0.1 or ventilation. In the present study, however, fenoterol caused no change in sGaw or FEV1. Thus fenoterol may not affect P0.1 by changing airway mechanics. It is likely that fenoterol increases the neural output to the inspiratory muscles.
Fenoterol increased the slopes of VE and PO.2 in HVR. The activity of the carotid body chemoreceptors increases with decreasing PaO2.19 Isoprenaline is known to stimulate the carotid body through a β adrenergic mechanism.20–23 Fenoterol is a selective β2 adrenergic agonist but also has weak β1 activity.20 In the present study fenoterol did not affect the resting level of PETCO2 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 β1 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 Po.1 and VE. 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 VE without any changes in PETCO2 and Po.1, suggesting that it raises the metabolic activity thus increasing resting VE. 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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