Effect of acute alterations in inspired oxygen tension on methacholine induced bronchoconstriction in patients with asthma


Abstract

Background – Recent in vitro and in vivo studies in animals have suggested that ambient oxygen tension may influence airway responsiveness to bronchoconstrictor stimuli. These observations may have relevance to the management of acute exacerbations of asthma. The present studies were designed to examine the influence of inspired oxygen tension (FiO₂) on methacholine induced bronchoconstriction in patients with asthma.

Methods – In a dual study two groups of asthmatic patients performed methacholine inhalation challenges breathing either air (FiO₂ 0.21) or a hypoxic gas mixture (FiO₂ 0.15) in study 1 and air (FiO₂ 0.21) or hyperoxia (FiO₂ 1.0) in study 2. The gases were administered through a closed breathing circuit in a randomised double blind fashion. The PC₂₀ values (dose of methacholine causing a 20% fall in forced expiratory volume in one second (FEV₁)) were calculated after each methacholine challenge by linear interpolation from the logarithmic dose response curve. Plasma catecholamine levels were measured before and after methacholine challenges as well as heart rate, oxygen saturation, and percentage end tidal carbon dioxide levels.

Results – The mean geometric PC₂₀ value for methacholine was significantly lower on the hypoxic study day than on the normoxic day in study 1 (mean difference in PC₂₀ values 2.88 mg/ml (95% CI 1.4 to 5.3); p<0.05), but there was no significant difference in the geometric mean PC₂₀ value for methacholine between the hypoxic and normoxic study days in study 2 (mean difference in PC₂₀ values 1.45 mg/ml (95% CI 0.83 to 2.51)).

Conclusions – Acute hypoxia potentiates methacholine induced bronchoconstriction and acute hyperoxia has no effect in mild to moderate patients with stable asthma.

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Keywords: hyperoxia, hypoxia, bronchoconstriction, methacholine, asthma.

Little is known about the effect of acute alterations in oxygen tension on the responsiveness of the airways to bronchoconstrictor stimuli. Recent in vitro and in vivo studies in animals suggest that hypoxia potentiates and hyperoxia attenuates the airway constrictor response to certain stimuli. Similar in vivo studies in man, however, have produced conflicting findings.

If airway responsiveness is increased by a fall in oxygen tension during acute exacerbations of asthma, then the administration of high concentrations of inspired oxygen may act to reduce this effect.

The present studies were designed to investigate the effect of acute hyperoxia and hypoxia on methacholine induced bronchoconstriction in patients with asthma.

Methods

Patients

Study 1

Eleven mild asthmatic patients (five men) of mean (SD) age 42 (12) years were recruited into the study (table 1). All were receiving inhaled β₂ agonists as required, 10 were receiving regular inhaled corticosteroids, two were taking regular inhaled salmeterol, and one a long acting oral theophylline.

Study 2

Fourteen adult mild asthmatic patients (five men) of mean (SD) age 36 (9.2) years were recruited into the study (table 1). All received inhaled β₂ agonists on an as required basis, 10 were receiving regular inhaled corticosteroids, two were taking regular oral theophyllines, and one inhaled salmeterol.

In both studies on each study day inhaled β₂ agonists were discontinued for eight hours, salmeterol for 24 hours, and oral theophyllines for 48 hours prior to attendance. Patients were asked to continue their inhaled corticosteroids as usual. They were asked to refrain from caffeine containing products for eight hours before each study day. All patients had been

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Mean (SD) age (years)</th>
<th>Mean (SD) FEV₁ (Litres % predicted)</th>
<th>PC₂₀ methacholine (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lines</td>
<td>Geometric mean (range)</td>
</tr>
<tr>
<td>Study 1</td>
<td>11</td>
<td>42 (12)</td>
<td>2.76 (0.49) 86 (7.7)</td>
<td>1.13 (0.04–7.90)</td>
</tr>
<tr>
<td>Study 2</td>
<td>14</td>
<td>36 (9.2)</td>
<td>2.80 (0.60) 90 (8.6)</td>
<td>0.84 (0.04–7.90)</td>
</tr>
</tbody>
</table>

FEV₁ = forced expiratory volume in one second; PC₂₀ methacholine = concentration of methacholine provoking a fall in FEV₁ of 20%.
stable for a period of two months before entry into the study with no significant change in their asthma symptoms or medication. All patients gave informed consent to the studies which had the approval of the West ethics committee.

STUDY DESIGN
For both study 1 and study 2 patients attended the laboratory on three separate days at approximately the same time each day. Patients were excluded from the study if there was any significant change in their asthma symptoms or medication between visits. The maximum period between each visit was seven days. During the initial screening visit each patient underwent a methacholine inhalation challenge test to determine the PC_{20} – that is, the concentration of methacholine causing a 20% fall in forced expiratory volume in one second (FEV1). On the subsequent two days, after 30 minutes of supine rest, the patients were commenced on a closed breathing circuit. Following a 10 minute run-in period breathing air (F_{iO2} 0.21) baseline measurements of FEV1, respiratory rate (RR), heart rate (HR), oxygen saturation (SaO2%), inspired oxygen and carbon dioxide levels (insp O2%, insp CO2%), and expired oxygen and carbon dioxide levels (PETO2%, PETCO2%) were made. Venous blood was also taken for assay of plasma catecholamines.

In study 1 patients then received either air (F_{iO2} 0.21) or a hypoxic gas mixture (F_{iO2} 0.15) and in study 2 either air (F_{iO2} 0.21) or oxygen (F_{iO2} 1.0) for the remainder of the study day. All gases were administered in a randomised double blind manner by a second person obscured from the vision of both the patient and the doctor administering the methacholine challenge. The methacholine inhalation challenge was performed 10 minutes after starting the study gas. All measurements, except venous blood sampling, were repeated before commencing the methacholine inhalation challenge. The study day was terminated when a PC_{20} value had been obtained and the measurements made at baseline repeated.

MEASUREMENTS
Heart rate, oxygen saturation, inspired and expired oxygen and carbon dioxide levels
Heart rate and oxygen saturation were measured using a pulse oximetry probe (Datex Division of Instrumentarium Corp, Helsinki, Finland). A side port on the face mask allowed continuous sampling of the inspired and expired gases and monitoring of respiratory rate. The gases were analysed using an OSCARoxy TM multigas monitor (Datex Instrumentarium Corp, Helsinki, Finland). Recordings were made every 10 seconds for one minute and automatically printed by a Hewlett Packard Think Jet printer in a blind fashion. Results were analysed after completion of the study.

FEV1 was measured using a dry wedge spirometer (Vitalograph S, Vitalograph, Buckingham, UK) and the best of three attempts was taken for analysis.

Results
There were no significant differences in baseline measurements between study days in either study (table 2). Analysis for period and order effects showed no significant differences for any measurements.
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Table 2 Mean (SE) baseline respiratory rate, heart rate and plasma catecholamine levels for patients in study 1 (hypoxia versus normoxia, n = 11) and study 2 (hyperoxia versus normoxia, n = 14)

<table>
<thead>
<tr>
<th>Baseline measurement</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normoxia</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>FEV1 (l)</td>
<td>2.67 (0.14)</td>
<td>2.63 (0.16)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>71.0 (4.0)</td>
<td>71.0 (4.7)</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>15.0 (1.5)</td>
<td>16.0 (1.6)</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>96.5 (0.2)</td>
<td>96.3 (0.2)</td>
</tr>
<tr>
<td>Inspired O2 (%)</td>
<td>20.8 (0.2)</td>
<td>21.0 (0.0)</td>
</tr>
<tr>
<td>End tidal CO2 (%)</td>
<td>4.66 (0.11)</td>
<td>4.64 (0.14)</td>
</tr>
<tr>
<td>Plasma noradrenaline (nmol/l)</td>
<td>1.72 (0.14)</td>
<td>1.61 (0.29)</td>
</tr>
<tr>
<td>Plasma adrenaline (nmol/l)</td>
<td>0.10 (0.02)</td>
<td>0.10 (0.02)</td>
</tr>
</tbody>
</table>

FEV₁ = forced expiratory volume in one second.

No significant differences were found between study days in either study.

STUDY 1
Methacholine PC20 values
The geometric mean PC20 methacholine value was significantly lower (p < 0.05) on the hypoxic study day than on the normoxic day (fig 1A) with a mean difference between the hypoxic and normoxic study days of 2.88 mg/ml (95% CI 1.40 to 5.3).

Oxygen saturation
Oxygen saturation was significantly lower (p < 0.01) following hypoxia (mean (SE) SaO₂% at baseline 96.3 (0.24)%, pre-methacholine 91.0 (0.56)%, post-methacholine 90.5 (1.0)%% than following normoxia (mean (SE) SaO₂% at baseline 96.5 (0.16)%%, pre-methacholine 96.3 (0.27)%, post-methacholine 96.0 (0.43)%; fig 2A).

Heart rate
There was no significant difference in heart rate when the hypoxia and normoxia study days were compared at any time point (data not shown).

Oxygen saturation
Oxygen saturation was significantly lower (p < 0.01) following hypoxia (mean (SE) SaO₂% at baseline 96.7 (0.35)%%, pre-methacholine 98.1 (0.23)%, post-methacholine 98.1 (0.20)%% than during the normoxic study day (mean (SE) SaO₂% at baseline 96.5 (0.33)%%, pre-methacholine 96.7 (0.37)%%, post-methacholine 96.0 (0.52)%; fig 2B).

Heart rate
The heart rate was significantly lower (p < 0.05) on the hyperoxic study day both before and after the methacholine inhalation test than on the normoxic study day. The mean (SE) heart rate on the hyperoxic study day was: baseline 75 (4) bpm, pre-methacholine 71 (4) bpm, post-methacholine 71 (4) bpm and on the normoxic study day: baseline 77 (4) bpm, pre-methacholine 75 (5) bpm, post-methacholine 77 (4) bpm.

There were no significant differences in respiratory rate, percentage end tidal carbon di-

Figure 1 Effect of (A) hypoxia and normoxia (n = 11) and (B) hyperoxia and normoxia (n = 14) on PC20 methacholine values in patients with asthma.
Dagg, Thomson, Clayton, Ramsay, Thomson

Figure 2 Effect of (A) hypoxia and normoxia (n = 11) and (B) hyperoxia and normoxia (n = 14) on oxygen saturation in patients with asthma. *p < 0.01.

Discussion

We found that acute hypoxia (FiO₂ 0.15) potentiated methacholine induced bronchoconstriction in asthma whereas acute hyperoxia (FiO₂ 1.0) had no effect.

The changes in oxygen saturation we observed in both studies and the fall in heart rate⁸⁻¹⁰ seen on the hypoxic study day would suggest that our closed breathing circuit has achieved significant alterations in vascular oxygen tension. Both hypoxia and hyperoxia in vivo may cause a rise in minute ventilation and subsequent fall in end tidal carbon dioxide levels.⁹⁻¹⁰ Hypocapnia in vivo is associated with increased airway tone.¹¹⁻¹⁴ We have shown no significant difference in percentage end tidal carbon dioxide levels between study days which suggests that an increase in airway tone due to hypocapnia has not influenced our results. Nebuliser output may be affected by the molecular weight of the gas used to drive the nebuliser. Before both studies the nebuliser output was calculated on two occasions for each study gas. In study 1 the nebuliser output for both air (FiO₂ 0.21) and the hypoxic gas mixture (FiO₂ 0.15) was 0.13 ml/min at a flow rate of 7 l/min and in study 2 the output for air (FiO₂ 0.21) and hyperoxia (FiO₂ 1.0) was 0.12 ml/min at 6 l/min. Circulating catecholamines have effects on airway smooth muscle tone.¹⁵ Any alteration in circulating levels of catecholamines due to changes in oxygen tension and inhalation of methacholine could potentially alter airway reactivity to methacholine. We have not, however, observed any significant differences in circulating catecholamine levels in either study.

Our double blind study has demonstrated an increase in airway reactivity to methacholine following acute hypoxia, in keeping with a previous single blind study reported by Denjean et al.⁷ Previous animal studies have suggested that the potentiation of methacholine induced bronchoconstriction by hypoxia is attenuated by prior surgical chemodenervation,¹⁶ suggesting that the effect is mediated via peripheral chemoreceptors. This does not, however, explain why potentiation of methacholine constriction by hypoxia in bovine bronchial rings¹ is observed in vitro in the absence of circulating humoral factors and neural innervation. In our study we have been unable to detect an increase in airway tone following 10 minutes of hypoxia as one would expect if this effect occurred as a consequence of bronchoconstriction due to hypoxia alone. Other animal studies have shown that potentiation of histamine and carbachol induced bronchoconstriction in sheep is significantly reduced by both intravenous cromolyn sodium¹⁷ and FPL57231,¹⁸ a leukotriene receptor antagonist, suggesting that alveolar hypoxia may stimulate release of inflammatory mediators. Hypoxia may also act directly on smooth muscle cells, altering signal transduction pathways and causing smooth muscle contraction, or it may act on vagal nerve endings to stimulate neurotransmitter release and hence cause bronchoconstriction. These findings are likely to have clinical relevance as the level of hypoxia we have induced is compatible with those seen in patients admitted to hospital with acute severe exacerbations of asthma or plasma catecholamine levels between study days in either study (table 3).

Table 3 Mean (SE) respiratory rate, end tidal carbon dioxide (%) and plasma catecholamine levels following methacholine inhalation in study 1 (hypoxia versus normoxia, n = 11) and study 2 (hyperoxia versus normoxia, n = 14).

<table>
<thead>
<tr>
<th>Measurement after methacholine inhalation</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normoxia</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>15.0 (1.6)</td>
<td>14.0 (2.0)</td>
</tr>
<tr>
<td>End tidal CO₂ (%)</td>
<td>3.70 (0.18)</td>
<td>3.86 (0.17)</td>
</tr>
<tr>
<td>Plasma noradrenaline (nmol/l)</td>
<td>1.60 (0.16)</td>
<td>1.40 (0.25)</td>
</tr>
<tr>
<td>Plasma adrenaline (nmol/l)</td>
<td>0.08 (0.02)</td>
<td>0.06 (0.02)</td>
</tr>
</tbody>
</table>

No significant differences were found between study days in either study.
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asthma. It would appear therefore that hypoxia occurs, not only as a consequence of acute severe asthma, but it may also increase airway responsiveness to bronchoconstrictor stimuli.

We have not demonstrated attenuation of methacholine induced bronchoconstriction in humans by hypoxia, in contrast to the findings of both the in vitro and in vivo animal studies. This difference may be explained by species variation between the studies or by hypoxia in vivo affecting bronchomotor tone via neural or humoral pathways and hence counteracting any direct effect of hypoxia alone on airway smooth muscle responsiveness. Our results support and extend those of Wollner et al. We have, however, also examined the potential influences of hypoxemia and circulating catecholamines on airway reactivity during hypoxia and have also found that our patients show the typical cardiovascular and respiratory responses to hypoxia. Our results differ from those of Inoue et al who found that hypoxia attenuated methacholine induced bronchoconstriction in asthmatic subjects. However, they used an inspired oxygen concentration of 30% whereas we used 100%. Six of their patients had arterial oxygen tensions below 10 kPa in keeping with resting hypoxaemia and, since inspiring 30% oxygen relieves hypoxic bronchoconstriction, this effect may have falsely influenced their results.

In conclusion, these results show that acute hypoxia potentiates methacholine induced bronchoconstriction in patients with stable asthma. They suggest that the administration of high concentrations of inspired oxygen to patients with acute exacerbations of asthma may not only improve gas exchange but may also reduce airway responsiveness to certain constrictor stimuli.

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11 O'Cain CF, Hensley MJ, McFadden ER, Ingram RH. Patients show the typical cardiovascular and respiratory responses to hypoxia. Our results differ from those of Inoue et al who found that hypoxia attenuated methacholine induced bronchoconstriction in asthmatic subjects.
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K D Dagg, L J Thomson, R A Clayton, S G Ramsay and N C Thomson

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