Hypoxia, hypocapnia and spirometry at altitude

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1. Both hypoxia and hypocapnia can cause bronchoconstriction in humans, and this could have a bearing on performance at high altitude or contribute to altitude sickness. We studied the relationship between spirometry, arterial oxygen saturation and end-tidal carbon dioxide (ETCO₂) concentration in a group of healthy lowland adults during a stay at high altitude, and then evaluated the response to supplementary oxygen and administration of a β₂ agonist.

2. We collected spirometric data from 51 members of the 1994 British Mount Everest Medical Expedition at sea level (barometric pressure 101.2–101.6 kPa) and at Mount Everest Base Camp in Nepal (altitude 5300 m, barometric pressure 53–54.7 kPa) using a pocket turbine spirometer. A total of 205 spirometric measurements were made on the 51 subjects during the first 6 days after arrival at Base Camp. Further measurements were made before and after inhalation of oxygen (n = 47) or a β₂ agonist (n = 39). ETCO₂ tensions were measured on the same day as spirometric measurements in 30 of these subjects.

3. In the first 6 days after arrival at 5300 m, lower oxygen saturations were associated with lower forced expiratory volume in 1 s (FEV₁; P < 0.02) and forced vital capacity (FVC; P < 0.01), but not with peak expiratory flow (PEF). Administration of supplementary oxygen for 5 min increased oxygen saturation from a mean of 81%–94%, but there was no significant change in FEV₁ or FVC, whilst PEF fell by 2.3% [P < 0.001; 95% confidence intervals (CI) -4 to -0.7%]. After salbutamol administration, there was no significant change in PEF, FEV₁ or FVC in 35 non-asthmatic subjects. Mean ETCO₂ at Everest Base Camp was 26 mmHg, and a low ETCO₂ was weakly associated with a larger drop in FVC at altitude compared with sea level (r = 0.38, P < 0.05). There was no correlation between either ETCO₂ or oxygen saturation and changes in FEV₁ or PEF compared with sea-level values.

4. In this study, in normal subjects who were acclimatized to hypobaric hypoxia at an altitude of 5300 m, we found no evidence of hypoxic bronchoconstriction. Individuals did not have lower PEF when they were more hypoxic, and neither PEF nor FEV₁ were increased by either supplementary oxygen or salbutamol. FVC fell at altitude, and there was a greater fall in FVC for subjects with lower oxygen saturations and probably lower ETCO₂.

INTRODUCTION

Studies undertaken 30 years ago demonstrated that acute hypoxia causes bronchoconstriction in experimental animals [1, 2]. More recently, investigators have demonstrated parallel development of airflow limitation and hypertrophy of airway smooth muscle in calves exposed to chronic (2 weeks) hypobaric hypoxia [3]. Bronchoconstriction has also been observed in individuals with chronic hypoxaemia from lung disease, and bronchodilation occurs in these individuals when breathing oxygen [4–8].

Bronchoconstriction also occurs in animals when carbon dioxide tension is reduced acutely [9, 10]. In humans, hyperventilation asthma has been recognized for at least half a century [11] and an acute fall in end-tidal carbon dioxide (ETCO₂) of 7.5 mmHg has also been shown to contribute to airflow obstruction in asthmatic patients [12] and patients undergoing hyperventilation (mean PaCO₂ 30.4 mmHg) because of neurological injury [13]. In normal subjects, acute hypocapnia (PaCO₂ 20–25 mmHg) also causes a consistent increase in flow resistance during sustained voluntary hyperventilation [14].

We have previously reported the change in peak expiratory flow (PEF) associated with low barometric pressure at altitude [15]. Hypobaria reduces resistance to flow in the airways and, consequently, PEF increases. In our study of 51 subjects at 5300 m, PEF rose by a mean of 25.5% and the average absolute PEF was 625 l/min (range 369–838) at sea level and 783 l/min (range 530–1117) at 5300 m [15].

The low-oxygen-tension environment of altitude leads to hypoxia, and acclimatization increases venti-
lation and causes hypocapnia. We postulated, therefore, that the combination of hypobaric hypoxia and hypocapnia at high altitude might produce bronchoconstriction in normal subjects.

**METHODS**

We collected spirometric data from 51 members of the 1994 British Mount Everest Medical Expedition (age range, 19–55; males/females, 36/15) at sea level (barometric pressure 101.2–101.6 kPa) in the U.K. (London and Stirling) and at Everest Base Camp in Nepal (altitude, 5300 m; barometric pressure, 53–54.7 kPa) after they had trekked from Lukla (altitude 2800 m) to base camp over a median of 12 days. Informed consent and ethical approval were obtained.

A total of 205 spirometric measurements were recorded from 51 subjects (median, 3 observations per subject; range 1–10) during the first 6 days after arrival at Base Camp, using a Micro Medical Microplus hand-held turbine spirometer (Micro Medical Ltd, Rochester, Kent, U.K.) which measures PEF, forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC). This spirometer had previously been validated for use at low barometric pressure and is unaffected by changes in barometric pressure and wide ranges of humidity [16] and temperature. At 5°C ambient temperature, the expired air temperature measured with a fast thermistor was 30°C at the turbine; at 20°C ambient, the expired air temperature was 31°C (Lawson C, Technical Department, Micro Medical, personal communication). In our study each forced expiration was performed in a large laboratory tent with an experienced observer, and measurements were made according to the recommendations of the British Thoracic Society for respiratory function tests [17]. The best lung function values from three expirations were recorded for each subject.

Spirometry was undertaken before and after supplementary oxygen was given (flow rate of 1 l/min) for 5 min using an open circuit system (Oxygen Systems, Moscow, Russia) via a face mask, to give an oxygen concentration of approximately 38% (measured in the tubing connecting the regulator to the face mask using a Normocap 200 Oxy; Datex, Vickers Medical, Sidcup, Kent, U.K.) at 5300 m. The exact concentration delivered was not known, as the mask did not give a perfect seal at the prevailing low barometric pressure. The delivery time of 5 min was long enough for arterial oxygen saturation to reach a steady state, but it did not exhaust the supply of bottled oxygen available at such a remote location.

In 39 subjects (four with asthma) spirometry was undertaken before and 10 min after a dose of 200 mg of salbutamol, given by prewarmed metered dose inhaler using a volumatic spacer (Allen and Hanburys, Uxbridge, U.K.) in 20 subjects, or after 5 mg of salbutamol given by ultrasonic nebulizer (Easimist, Medix Ltd, Lutterworth, U.K.) in 19 subjects. Two different delivery systems for the β2 agonist were used because of a technical problem and the data was analysed separately for the two groups.

Oxygen saturation was measured with a finger probe in all subjects, using a Nellcor N20P pulse oximeter (Nellcor Ltd, Warwick, U.K.). Pulse oximetry was performed in a tent during the daytime when the ambient temperature was comfortable (10–25°C) and peripheral vasoconstriction minimized. EtCO2 was measured on the same day as spirometric measurements (simultaneous measurements were not possible in this field study) using an infra-red carbon dioxide analyser (Normocap 200 Oxy; Datex, Helsinki, Finland), calibrated using standard 5% and 10% carbon dioxide at ambient pressure (British Oxygen Special Gases, Guildford, Surrey, U.K.).

Multivariate analysis was undertaken by general linear modelling of the percentage change in lung function from that sea level. The factors included in the model were the lung function parameters, number of days at base camp, subject identification number (subject ID), acute mountain sickness (AMS) score [18], time of day (morning or afternoon) and oxygen saturation (SaO2). Terms were removed from the model by backward stepwise regression, the least significant term being removed at each step and the model then re-analysed, until all remaining terms were significant [19]. By taking into account the inherent lung function of each subject, the model allowed repeated measures of lung function at different times after arrival at base camp to be analysed. The results are shown as coefficients relating the strength of association for each factor with respect to each of the lung function parameters, thus,

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\% \text{ change in } PEF = (m_1 \times \text{subject ID}) + (m_2 \times \text{SaO}_2) + (m_3 \times \text{AMS}) + \ldots
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where \(m_1, m_2, m_3\) are coefficients such that if the coefficient for \(\text{SaO}_2\) is, say 2.5, then the percentage change in PEF increases by 2.5 units for every 1 unit change in \(\text{SaO}_2\), other terms in the model being equal. To confirm that the data were appropriate for analysis by the general linear model, the residuals from the model were plotted to ensure that they were normally distributed and that the relationship between the residuals and the predictor values was linear. The data represented here satisfied these criteria for the use of the general linear model. Relationships with lung-function tests were tested with the raw data and again when calculated as standardized residuals to remove any bias from age, height or gender [17].

Regression lines of measurements from each individual subject were plotted against the fitted values from the linear model such that the relationship
between percentage change in spirometric measurements and oxygen saturation could be represented when the other significant term(s) in the final model had been taken into account.

The hypothesis that there was no change in lung function following administration of the supplemental oxygen or the bronchodilator were investigated using paired t-tests. The relationships between oxygen saturation or EtCO₂ and change in lung function from that at sea level were analysed by linear regression techniques. A probability of less than 5% was taken as significant.

RESULTS

The results of the analysis indicated a statistically significant relationship between oxygen saturation and changes in FEV₁ (Figure 1) or FVC (Figure 2) from sea level values, but no association between oxygen saturation and PEF (Figure 3). Lower oxygen saturations were associated with lower FEV₁ (coefficient 0.26; 95% CI, 0.25–0.28; \( P = 0.02 \)) and FVC (coefficient 0.31; 95% CI, 0.30–0.33; \( P = 0.005 \)), where the lung-function parameters were expressed as a percentage of their baseline (sea level) values. Analysis using standardized residuals of the spirometric data produced the same conclusions.

The factor in the model which produced the greatest variation was subject identification number. The relationship between spirometric values and AMS score and time of day were also included in the linear model but have been discussed elsewhere [15]. Lower PEF was related to higher AMS score and morning readings, and lower FVC was related to morning readings but not to the AMS score. The number of days spent at 5300 was not associated with any change in PEF.

After administration of supplementary oxygen for 5 min, oxygen saturations rose from a mean of 81% (range 66–91%) to 94% (range 88–98%).
by 2.3% (95% CI, -4% to -0.7%; \(P<0.001\)).

Following the administration of the \(\beta_2\) agonist no significant change in PEF, FEV1 or FVC in the 35 non-asthmatic subjects was observed. The lack of change in spirometric parameters was seen in both the group who received nebulized salbutamol and those who received the drug from a metered dose inhaler via a spacer device. In the four asthmatic subjects, all of whom were asymptomatic, there was, however, a mean increase of 5.4% in PEF, 10% in FEV1 and 2% in FVC. Oxygen saturations did not change significantly following the administration of salbutamol.

The mean \(\text{ETCO}_2\) measured in 30 of our subjects was 26 mmHg at Everest Base Camp, indicating that their steady-state acclimatization to 5300 m was near complete [21]. There was no significant relationship between \(\text{ETCO}_2\) and oxygen saturation. Subjects with a greater decrease in FVC at altitude compared with sea level tended to have a lower \(\text{ETCO}_2\), but the correlation was weak (\(r = 0.38\), slope 1.45; 95% CI, 1.21–1.69; \(P<0.05\)).

**DISCUSSION**

In this study, we found no relationship between oxygen saturations and PEF in a group of acclimatized normal subjects at 5300 m. Although some authors have clearly demonstrated hypoxic bronchoconstriction at sea level during acute hypoxia in normal humans [22] and animals [1–2], and as a result of chronic hypoxia due to chronic lung disease in infants and adults [5–8], others have found no change in airway mechanics during acute hypoxia in normal [23–25] or asthmatic [26] subjects. As our subjects were acclimatized to the ambient hypobaric hypoxia and had no underlying pulmonary pathology, our investigation differs from these other studies where the stimulus is either acute hypoxia or chronic hypoxaemia from pulmonary disease.

To test the hypothesis that hypoxia-related bronchoconstriction had occurred we exposed our chronically hypoxic subjects to supplementary oxygen, hoping to improve PEF. However, we were not able to show any change in PEF after 5 min of supplementary oxygen. In contrast, bronchodilation in hypoxaemic patients with chronic obstructive pulmonary disease (COPD) [3, 5–7] and in human infants with bronchopulmonary dysplasia [8] has been shown after the administration of supplementary oxygen.

Although we achieved a satisfactory increase in oxygen saturation from 81% to 94%, we were unable to measure directly the inspired oxygen concentration and to relate this to the concentration used in other studies (30–100%) which have demonstrated bronchodilation in patients with chronic obstructive lung disease [6, 7]. Libby et al. [6] used 20 min of supplementary oxygen [6] and Coe and Pride [7] administered supplementary oxygen until a constant oxygen saturation was achieved. In our acclimatized subjects, 5 min of supplementary oxygen was long enough to reach a steady state, and this 'artificial descent' reduced ventilation (as it does in exercise [27]) and caused \(\text{ETCO}_2\) to rise (D. J. Collier, unpublished work). Libby et al. [6] noted a similar increase in \(\text{ETCO}_2\) in their group of patients with COPD after the administration of 30% oxygen. Supplementary oxygen does not simply reverse hypoxia.

We actually found a small decrease in PEF (2.3%) measured on the first breath after removal of the oxygen. Previously, it has also been noted that breathing 100% \(O_2\) reduces forced expiratory flow in patients with COPD, which has been attributed to the increased density and viscosity of oxygen compared with air, which increases resistance and decreases flow [28].

It is not clear whether hypoxic bronchoconstric-
tion is mediated by a direct effect of oxygen on bronchial smooth muscle [24] or by an effect on the vagus nerve [4-6]. Coe and Pride [7] found that the bronchodilatation they achieved in 18 patients with COPD who were given 100% oxygen was independent of the response to a β-adrenoceptor agonist [7]. Based on these observations we included treatment with salbutamol in our study to show that any vagus nerve jects and in animals.

Based on these observations we included treatment with salbutamol in our study to show that any vagus nerve effects, but we were not able to demonstrate an improvement in PEF in non-asthmatic subjects. Broncho-provocative tests may have provided additional useful information, as bronchial responsiveness to methacholine is increased after acute hypoxia (15% oxygen) [29], and the response to atropine or ipratropium would have been interesting.

Despite accumulated evidence for hypocapnic bronchoconstriction in normal and asthmatic subjects and in animals [9-14] during acute hypocapnia, we were unable to demonstrate bronchoconstriction related to EtCO2 level in our chronically hypocapnic normal subjects. Newhouse et al. [14] found hypocapnic bronchoconstriction in normal subjects in whom the bronchoconstrictive effects of hypoxia were reduced by both atropine and isoproterenol. Conversely, administration of carbon dioxide relaxes tracheobronchial smooth muscle if the muscle is in a state of tone [9, 30]. As we did not administer carbon dioxide directly to our subjects, our data do not exclude this possibility, although the increase in EtCO2 associated with administration of oxygen did not improve PEF. In our subjects with higher oxygen saturations, ETCO2 tended to be lower, presumably because of greater polikilocapnic hypoxic ventilatory drive in those individuals.

We noted a decrease in FVC, which was related to lower oxygen saturations and was weakly correlated with lower EtCO2. Interstitial or intra-alveolar oedema may account for this fall in FVC, perhaps by bringing about early small airways closure [15, 31, 32]. Increased microvascular leakage in guinea pig trachea has been found in relationship to airway hypoxia, supporting this hypothesis [33].

We have previously reported the change in PEF associated with low barometric pressure at altitude [15]. Hypobaria reduces resistance to flow in the Airways and consequently PEF rises. In this study we have shown that those individuals with relatively lower PEF at high altitude do not have lower oxygen saturations, and that PEF is not improved by administration of 5 min of supplementary oxygen or a β2 agonist. Neither hypoxic nor hypocapnic bronchoconstriction seem to be important at altitude in acclimatized normal subjects.

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REFERENCES

20. Reference deleted.