Cough frequency and cough-receptor sensitivity are increased in man at altitude

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(Received 16 January/7 April 1997; accepted 24 April 1997)

INTRODUCTION

Ascent to high altitude exposes the mountaineer to a variety of environmental and physiological challenges. Climbers and travellers to high altitude have long complained of paroxysmal cough, which has not been previously investigated. We recorded overnight cough frequency and cough-receptor sensitivity to inhaled citric acid in a group of climbers travelling to 5300 m or higher.

METHODS

Subjects

Subjects for the study were recruited from members of the British Mount Everest Medical Expedition. Members of the Expedition travelled to Nepal to climb peaks of 6000 m or greater height while undertaking a series of medical and environmental research projects. Members of the Expedition flew from the United Kingdom to Lukla, altitude 2800 m, and then trekked over 10-14 days to Mount Everest Base Camp (5300 m), where the main research station was situated. Where their climbing itineraries allowed, members returned to the research station after 6-10 days spent at 5000 m or higher, for the experiments to be repeated.

Frequency of nocturnal cough was studied in ten subjects and citric acid cough threshold in 42. Nine subjects took carbonic anhydrase inhibitors for the prophylaxis of AMS, levels of oxygen and carbon dioxide and measurements of lung function.

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Ascent to high altitude exposes the mountaineer to a variety of environmental and physiological challenges. Climbers and travellers to high altitude have long complained of a debilitating dry cough [1], which may be severe enough to cause rib fractures [2]. In one study 42% of trekkers in the Everest region of Nepal complained of cough [3]. The cause of the increase in cough is not known, but it has been attributed to high-altitude pulmonary oedema or an effect on the cough centre of acclimatization to altitude, cannot be excluded.

Key words: Acute mountain sickness, altitude, citric acid, cough, respiratory tract.

Abbreviations: AMS, acute mountain sickness; FEVI, forced expiratory volume in 1 s; GMD, geometric mean difference; HAPE, high-altitude pulmonary oedema; PEF, peak expiratory flow.

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1. Travellers to high altitude often complain of paroxysmal cough, which has not been previously investigated. We recorded overnight cough frequency and cough-receptor sensitivity to inhaled citric acid in a group of climbers travelling to 5300 m or higher.

2. Cough frequency, monitored in ten subjects, increased from a median of 0 coughs at sea level (range 0–1) to 5 coughs at 5000 m (range 0–13) and to over 60 coughs in subjects ascending to 7000 m. Citric acid cough threshold, measured in 42 subjects, was unchanged on arrival at 5300 m compared with sea level (geometric mean difference 1.26, 95% confidence intervals 0.84–1.89, P = 0.25), but was significantly reduced after 6 days, or more, at altitude compared with sea level (geometric mean difference 2.2, 95% confidence intervals 1.54–3.15, P = 0.0002). Cough threshold was not related to symptoms of acute mountain sickness, oxygen saturation, carbon dioxide tension or lung function.

3. These results indicate an increase in cough and cough-receptor sensitivity after some days at altitude. This may be due to respiratory tract damage from breathing cold dry air at increased ventilatory rates. Other explanations, such as subclinical pulmonary oedema or an effect on the cough centre of acclimatization to altitude, cannot be excluded.

16
challenge has been described in one study of patients with chronic lung disease [5]. In view of the isolated site of our research facility, we decided *a priori* to exclude subjects with a history of asthma, exercise-induced cough or wheeze, bronchoconstriction or atopy from the study.

The study was approved by the Leicester Health Ethical Review Committee, and written informed consent was obtained from the subjects.

**Cough monitoring**

Frequency of nocturnal cough was measured using portable voice-activated tape recorders (Panasonic RQ-L317). A microphone was placed adjacent to each subject's head every night. The threshold for voice activation was adjusted to an appropriate sensitivity to be activated by coughing. Tapes were replayed the next day by the same observer and the total number of coughs noted. Coughs were easily distinguished from snoring and other extraneous noise. Cough monitoring was undertaken in the U.K. and at altitudes between 3400 m and 7000 m in Nepal. Subjects studied at altitudes up to 5300 m were those who accompanied one of us (P.W.B.) on the trek from Luklha (2800 m) to Base Camp (5300 m); they were studied on the first or second night after arrival at each new altitude. Data above 5300 m was obtained from climbers attempting to ascend Mount Everest, who were studied after they had been at 5300 m or higher for more than 28 days.

**Citric acid cough challenge**

Solutions of citric acid of increasing concentration were nebulized using a hand-held ultrasonic nebulizer (Easimist, Medix, Lutterworth, U.K.). Citric acid was chosen as it is less likely to cause bronchoconstriction than tussive agents such as capsaicin, is well tolerated by subjects and is easy to prepare. Subjects inhaled from residual volume to total lung capacity over 5 s. Subjects repeated the inhalation three times with each concentration.

The pattern of deposition of an aerosol within the airways changes with different inspiratory flow rates [6], and variations in the inspiratory flow rate alter the citric acid cough threshold [7]. To maintain a reproducible stimulus to the airways we administered citric acid aerosol using a single-breath technique from residual volume to total lung capacity over 5 s [8]. Other studies have used tidal breathing during inhalational challenge [9], but as breathing rate and tidal volume are altered at altitude, a standardized inspiratory manoeuvre was preferred for all tests. This single-breath technique has been reported to give a reproducible result for the citric acid cough threshold [10].

The citric acid challenge was given as successive inhalations of doubling concentrations of citric acid, beginning with a control solution of normal saline, then a 0.3125 g/l solution of citric acid in normal saline, and ceasing when the maximum concentration (160 g/l) or the cough threshold was reached. The cough threshold was defined as the lowest concentration of citric acid that provoked cough, provided that the following concentration also provoked cough [9]. The osmolality of these solutions ranged from 320 mosm/kg to >700 mosm/kg. All of the solutions were strongly acidic with a pH ranging from 3.0 to 1.6.

Cough challenges were undertaken in the U.K. before the Expedition, on arrival at 5300 m and after 6 days, or more, at 5000 m or higher. Forty-two subjects had challenges in the U.K. and on arrival at Base Camp, and 23 had a further challenge on their second visit to Base Camp. Challenges on any one subject were undertaken at the same time of day (morning or afternoon).

Before each cough challenge subjects recorded their AMS score [11]. This gives a score for six symptoms, and three clinical signs, from 0 (for not present) to three for mild, moderate and severe symptoms, giving a possible score from 0 to 27. A score greater than 3 indicates probable AMS, with increasing scores suggesting increasing severity of the illness. Forced expiratory volume in 1 s (FEV1) was measured before and after the cough challenge, using a hand-held turbine spirometer (Microloop, Micro Medical Ltd, Rochester, U.K.). The accuracy of this type of spirometer has been shown to be unaffected by changes in barometric pressure [12]. Oxygen saturation, using a Nellcor N20P oximeter (Nellcor UK Ltd, Coventry, U.K.), was monitored during the challenge. Capillary carbon dioxide tensions, measured on a Ciba Corning 248 blood-gas analyser, were recorded immediately after the second challenge at altitude in 18 of 23 subjects. Capillary samples were taken by puncture of the medial aspect of the thumb, warmed in a glove or by holding it in the axilla.

Barometric pressure at base camp was 53–54.7 kPa (sea level 101 kPa) and inspired oxygen tension was approximately 10 kPa, equivalent to breathing 10.5% oxygen at sea level. The temperature at base camp when the experiments were undertaken varied between 10 and 30°C and the relative humidity between 25 and 30%. The lowest night-time temperature recorded in the research tent was −15°C, and temperatures at camp 4 on the South Col (8000 m) fell to −40°C. The temperature and humidity of inspired air inside the subjects' tents at night is not known.

**Statistical analysis**

The distribution of cough threshold values was positively skewed, and was normalized by logarithmic transformation of the data. Cough thresholds for groups of subjects at each location are described by
Cough at altitude

The relationship between change in cough threshold from that at sea level and AMS score, oxygen saturation, capillary carbon dioxide tension and FEV1 were compared using a general linear model. The model allows multiple factors to be analysed to explain the observed change in cough threshold at altitude. Terms for AMS score [11], recent history of coryzal symptoms, carbonic anhydrase inhibitor therapy, FEV1, peak expiratory flow (PEF) and oxygen saturation were included in the model. Capillary carbon dioxide tension was included in the model used to analyse data from the second Base Camp visit. Terms were fitted to the model by backwards stepwise regression [13]. Statistical significance was assumed at \( P < 0.05 \).

RESULTS

Cough monitoring (Table 1)

Cough frequency increased in subjects 1–4 as they ascended from 2800 m to 5300 m, and was unchanged in subjects 5 and 6. Subjects 7–10 were first monitored after they had been at 5300 m or higher for 28 days. The cough monitors did not function reliably above Base Camp, due to battery failure in the extreme cold. Blank values in Table 1 are where the subject or the monitors were not available or did not go to that altitude.

Citric acid cough challenge (Figs. 1–3)

Cough threshold was unchanged on arrival at Base Camp compared with the sea level value \([n = 42, \text{ geometric mean difference (GMD, sea level minus Base Camp) 1.26, 95\% confidence intervals 0.84–1.89, } P = 0.25]\), but was significantly reduced on the second visit to Base Camp compared with the sea-level threshold \((n = 23, \text{ GMD 2.20, 95\% confidence intervals 1.54–3.15, } P = 0.0002)\) and with the first Base Camp visit \((n = 23, \text{ GMD 1.94, 95\% confidence intervals 1.54–3.25, } P = 0.023)\).

On arrival at 5300 m, the median AMS score was 1 (range 0–8), mean oxygen saturation 80.4\% (range 66–91\%), FEV1 was a mean 1.5\% (95\% confidence intervals -0.6 to 3.7\%) higher than at sea level, and PEF was a mean 27.1\% (95\% confidence intervals 22.4–31.7\%) higher than at sea level. On returning to Base Camp after 6 days, or more, climbing at 5000 m or higher, the median AMS score was 0 (range 0–5), mean oxygen saturation 83.4\% (range 76–90\%) and mean capillary carbon dioxide tension 3.33 kPa (range 2.51–4.15 kPa). FEV1 and PEF were a mean (95\% confidence intervals) 4\% (1.7–6.3\%) and 26.4\% (21.9–30.9\%) higher than at sea level, similar to the results of a parallel study undertaken during the expedition [14]. The general linear model showed that although a higher AMS score on arrival at 5300 m was associated with a greater reduction in cough threshold \((F = 6.52, P < 0.001, \text{ overall the reduction in cough threshold between sea level and arrival at 5300 m was not statistically significant. None of the other terms included in the model were significant.})\)

PEF fell immediately after the cough challenge by a mean (SD) of 2.54\% (6.85\%) in the U.K. \((P = 0.016)\), by 3.96\% (9.09\%) after the first challenge at altitude \((P = 0.013)\) and by 1.54\% (3.88\%) after the second challenge at altitude \((P > 0.05)\).

On the second visit to Base Camp, one subject coughed when inhaling the control solution of normal saline, and also when inhaling the lowest concentration of citric acid. In the analysis of the results this subject was assigned a threshold one-half the concentration of the weakest solution \((0.156 \text{ g/l})\). Removal of this subject from the analysis does not alter the overall results of the study.

Table 1. Number of coughs recorded by overnight cough monitoring at different altitudes. Subjects 1–6 were studied as they trekked to Base Camp, subjects 7–10 after they had been at Base Camp or higher for 4 weeks.

<table>
<thead>
<tr>
<th>Subject number</th>
<th>Altitude (m)</th>
<th>Sea-level (3–4) (\times 10^3)</th>
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*Cough monitor failed after approximately 1 h due to battery failure.
DISCUSSION

This study has shown an increase in the frequency of cough and a decrease in the citric acid cough threshold in a group of people ascending to 5300 m or higher, which are most apparent in those ascending to above 7000 m. To our knowledge, there have been no previous studies into cough frequency or cough threshold at altitude. The cause of the increased cough is not known, but a number of factors may account for it, including the low temperature and humidity of the inspired air at Base Camp, AMS or hypoxia.

Air is normally warmed and humidified in the upper airway before reaching the lungs. Pharyngeal air is conditioned to a lesser degree in cold and dry environments, and during increased ventilation [15]. Inspired air conditioning is also compromised by mouth breathing. We have shown that feelings of increased nasal blockage occur in subjects at Base Camp [16]. Partial nasal blockage encourages oral or oronasal breathing and we postulate that the prolonged inspiration of cold dry air, aggravated by very high levels of minute ventilation at altitude, especially during exercise [4], may have overcome the normal warming and humidifying capabilities of the upper respiratory tract, leading to drying of the airways and changes in the airway surface liquid, with resulting cough [17].

In one study [18], hyperpnoea with cold air induced cough and bronchoconstriction in patients with a history of exercise-induced cough, but did not induce significant cough in normal volunteers. Significant bronchoconstriction was not seen in our study, from which asthmatics were excluded, and peak expiratory flow fell by less than 5% after the cough challenge. Coughing after exercise has been related to respiratory water loss [19], and recent studies suggest that reflex bronchoconstriction and cough are
dissociated and mediated through different sensory pathways [20,21]. Furthermore bronchodilators do not increase the citric acid cough threshold in non-asthmatics [22]. Thus it is unlikely that the observed increase in cough at altitude is due to bronchoconstriction, but it may be due to the prolonged inhalation of poorly conditioned air.

Cough may occur in AMS and high-altitude pulmonary oedema (HAPE). Symptoms of AMS usually occur a few hours after ascent to altitude, and resolve after 1-3 days acclimatization if further ascent is not made. A small proportion of those with AMS go on to develop HAPE, which also normally occurs in the first few days of ascent. None of the subjects in this study needed to descend due to symptoms consistent with HAPE, and AMS scores were, in general, low, due to a long acclimatization period trekking to Base Camp. The general linear model suggests that AMS score was related to a decrease in cough threshold on arrival at Base Camp, but the small number of subjects with AMS scores (only two had AMS scores of five or more) and the lack of a significant fall in cough threshold on arrival at Base Camp in the group as a whole, suggest that AMS is unlikely to be the mechanism for high-altitude cough observed in this study. Another possible explanation is that cough-receptor sensitivity is a more sensitive indicator of AMS and HAPE, and sub-clinical pulmonary oedema cannot be excluded.

Ascent to altitude is characterized by hypoxia and an increase in ventilation, leading to hypocapnia. Mean oxygen saturation in our subjects on arrival at Base Camp was 80.4%. However, the change in cough thresholds of our subjects was not significant on arrival at Base Camp, but was on the second test at altitude, when the oxygen saturation was higher (mean 83.4%). Furthermore, the change in cough threshold was not related to the oxygen saturation in the general linear model, and our results do not suggest that hypoxia has a role in causing high-altitude cough.

Cough thresholds show marked inter-subject variability. It has been suggested that this is due to differences in the central control of cough and respiration, as individuals who have a greater hypercapnic ventilatory response also have lower cough thresholds [23]. Part of the process of acclimatization involves an increase in the hypercapnic ventilatory response [24], and previous studies have shown subjects with higher arterial carbon dioxide tensions to have worse AMS [25, 26]. From these observations, it might be hypothesized that subjects with lower carbon dioxide tensions at altitude (due to a greater hypercapnic ventilatory response) would have lower cough thresholds and lower AMS scores. Carbon dioxide tensions were measured in 18 of our subjects on the second visit to Base Camp, and there was no relation between carbon dioxide tensions and change in cough threshold. However, as we had very few subjects with high AMS scores, and did not measure carbon dioxide tensions in all our subjects at altitude, it is not possible to be certain about the part played by the hypercapnic ventilatory response to the change in citric acid cough threshold that we have observed, and the relationship between cough thresholds and the control of breathing deserves further study.

Stimulants of cough in disease include mucus production, release of inflammatory mediators and epithelial damage [27-29]. Non-asthmatics with chronic cough show evidence of airways inflammation [27]. Cough thresholds are reduced in upper respiratory-tract infections [30] and by the inhalation of inflammatory mediators [31]. Subjects in the present study were asked to note symptoms of a ‘cold’, such as ‘runny nose, sneezing, fever or chills’. Eight subjects reported such symptoms at some time in the month before arriving at Base Camp. Even when these subjects were removed from the analysis, cough thresholds were still significantly reduced after a stay at altitude. It is not certain that all of those excluded actually had upper respiratory-tract infections, as the symptoms described above could be attributed to other illnesses, such as AMS [4].

Deposition of inhaled aerosol in the airways may have been different at altitude, as the decreased air density at Base Camp will have altered the aerodynamic properties of the citric acid aerosol [32]. This does not explain our results, however, as there were significant differences between the cough thresholds on arrival at 5300 m and those undertaken under the same conditions 6 days, or more, later.

Overnight cough monitoring showed a dramatic increase in cough in those going to the highest altitudes, in whom the cough was at times debilitating. Subjects at Camp 4 on the South Col of Everest (8000 m) were unable to blow into a spirometer because inspiration resulted in paroxysmal cough. Cough counts in this group may have been even higher, but the extreme cold reduced battery life and the cough monitors functioned for a few hours only.

This study has quantified previous anecdotal reports of debilitating cough at altitude, and related this to a decrease in the citric acid cough threshold. The increased cough does not appear to be due to AMS, hypoxia, bronchoconstriction or infection. Further studies are required to determine the underlying mechanism and possible therapies.

ACKNOWLEDGMENTS

We thank the members of the British Mount Everest Medical Expedition for their co-operation; Mr N. Taub of the Department of Epidemiology, University of Leicester for statistical advice; Dr D. Collier, Research Co-ordinator British Mount Everest Medical Expedition and Dr C. Beardsmore of the Department of Child Health, University of
Leicester for their helpful comments on the manuscript; Nellcor Ltd for the loan of the oximeter; and Medix Ltd for financial support and loan of the nebulizer. P.W.B. is funded by the Astra Foundation.

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