Effects of acute prolonged exposure to high-altitude hypoxia on exercise-induced breathlessness

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ABSTRACT

The direct effects of hypoxia on exercise-induced breathlessness are unclear. Increased breathlessness on exercise is known to occur at high altitude, but it is not known whether this is related to the hypoxia per se, or to other ventilatory parameters. To examine the role of high-altitude hypoxia in exercise-induced breathlessness, studies were performed in 10 healthy, normal subjects at sea level and after acute exposure to an altitude of 4450 m. Although the perception of hand weights did not alter between sea level and high altitude, the intensity of exercise-induced breathlessness increased significantly at high altitude. This was associated with a higher minute ventilation and respiratory frequency for any given exercise level, whereas tidal volume was not significantly altered from sea level values. The increased intensity of breathlessness with exercise did not change significantly over the 5 days at high altitude. These results suggest that the increased intensity of exercise-induced breathlessness at high altitude is not related to peripheral mechanisms or the pattern of ventilation, or to the level of hypoxia per se, but to the level of reflexly increased ventilation.

INTRODUCTION

Increased breathlessness during exercise on exposure to high altitude (HA) is a common experience. However, it is unclear whether the sensation of breathlessness is truly increased at any given level of exercise, relative to sea level (SL), or whether the HA terrain demands greater effort. Furthermore, it is unknown whether the degree of breathlessness is greater because of an increased level of ventilation for any given effort or whether it is increased at iso-ventilation levels relative to SL.

The effects of hypoxia per se on the intensity of the sensation of breathlessness are unclear. At SL, acute exposure to hypoxia was initially reported to increase breathlessness on exercise [1]. However, later studies found the sensation of breathlessness during exercise to be more closely related to the level of reflexly stimulated ventilation rather than to the level of hypoxia itself [2].

The present study was undertaken to examine the relationship between breathlessness and exercise after acute exposure to HA hypoxia, and to assess whether the sensation of breathlessness with exercise is altered with prolonged exposure to HA hypoxia.

METHODS

Ten healthy, normal men (age range 19–46 years) were studied. Informed consent was obtained from each subject.
Studies were performed at 518 m, which for physiological purposes may be considered to be SL, and after rapid ascent (< 8 h) by car to HA (4450 m). The HA site was in the Khunjerab Pass in the Karakorum Mountains of Pakistan.

All subjects were medically examined to ensure that there was no history of significant medical illness or physical abnormality. The measurements described below were made on each subject at SL and on days 2, 4 and 5 after arrival at HA.

Arterial oxygen saturation (\(SaO_2\)) was measured by means of a pulse oximeter (CSI Corporation, Milwaukee, WI, U.S.A.).

Resting arterial \(PCO_2\) was derived from measurement of the mixed venous \(PCO_2\) by a standard rebreathing technique [3] using a CO\(_2\) gas analyser (Ohmeda Corporation, Englewood, CA, U.S.A.); the alveolar \(PO_2\) was derived from the calculated arterial \(PCO_2\) by the alveolar air equation. The alveolar \(PO_2\) allowed an estimation of the arterial \(PO_2\) and therefore acted as a check on the measured \(SaO_2\).

General sensory perception was measured by means of a series of hand weights [4]. The weights consisted of four plastic bottles weighing, respectively, 0.25 kg, 0.5 kg, 0.75 kg and 1.0 kg. The subjects had no visual or other indication of the weight of any bottle. On each occasion, the series of bottles were presented to the subject’s dominant hand and the subject was asked to assign a number to the perceived weight of each bottle. In each subject, on each occasion, weight perception was assessed by presentation of the series of four weights three times, in random order. The regression coefficient correlating the assigned number to each presented weight was calculated [5].

Exercise tests were performed on a cycle ergometer (Monark Inc., model 840, Varberg, Sweden). Initial measurements were made (Figure 1) after the subject was comfortably seated on the ergometer, breathing through a one-way, low-dead-space valve (Hans Rudolph Inc., Kansas City, MO, U.S.A.). A timed sample of the expired gas was collected in a Douglas bag and analysed; CO\(_2\) concentration was measured with a CO\(_2\) gas analyser (Ohmeda Corporation), \(O_2\) concentration was measured with two \(O_2\) analysers for accuracy (Instrumentation Laboratory, Model 406, Lexington, MA, U.S.A., and Kontron Inc., Everett, MA, U.S.A.), and the bag volume was also measured. From these measurements the \(O_2\) uptake (\(VO_2\)) and CO\(_2\) production (\(VCO_2\)) were calculated. A pneumotachograph on the inspiratory side of the one-way valve provided the inspiratory flow signal via a differential pressure transducer (Validyne Inc., PM15, Northridge, CA, U.S.A.), which was electronically integrated and recorded on a chart recorder (Gould electronics, model TA 550, Valley View, OH, U.S.A.). Inspired minute ventilation (\(V_i\)), adjusted to BTPS, tidal volume (\(V_t\)) and respiratory frequency (\(f\)) were calculated from the recorded signal. The pulse oximeter was attached for continuous recording of the \(SaO_2\) and pulse rate. After measurement of the resting values, the subjects exercised at 50 W for 2 min, at 100 W for 2 min, and at further 50 W increments for 2 min each to the maximum level possible for each individual. Measurements were recorded during the last 30 s at each exercise level, and expired gas samples were collected during the recordings in a series of Douglas bags (Figure 1), one for each exercise level.

The intensity of breathlessness was measured using a Borg scale [6, 7] to which the subject pointed; assessments of the degree of breathlessness were made at the same time as the other measurements, i.e. at rest and during the last 30 s at each exercise level.

The resting values of the various parameters at SL and HA were compared by repeated measures one-way ANOVA, with post-hoc Tukey’s test for significance of differences between days [5]. The regression coefficients of the relationship of breathlessness to exercise and of weight perception, at SL and HA, were similarly analysed by repeated measures one-way ANOVA [5].

**RESULTS**

The resting values for ventilation and blood gases are shown in Table 1. As expected, the significant decrease in atmospheric pressure at altitude resulted in significant \((P < 0.001)\) changes in alveolar \(PO_2\), \(SaO_2\) and \(PaCO_2\).

Table 2 and Figure 2 show the results of hand weight perception in terms of the mean regression coefficients for all subjects at SL and HA; the correlation coefficients
Table 1  Atmospheric pressure and blood gas values
Values are mean ± S.D. *P < 0.001 compared with SL.

<table>
<thead>
<tr>
<th>HA</th>
<th>SL</th>
<th>Day 2</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{atm}$ (mmHg)</td>
<td>706.5</td>
<td>445*</td>
<td>444*</td>
<td>445*</td>
</tr>
<tr>
<td>$PaCO_2$ (mmHg)</td>
<td>37.4 ± 1.9</td>
<td>25.9 ± 2.2*</td>
<td>25.9 ± 2.8*</td>
<td>25.5 ± 7*</td>
</tr>
<tr>
<td>$PaO_2$ (mmHg)</td>
<td>93.0 ± 2.2</td>
<td>52.0 ± 2.6*</td>
<td>52.2 ± 3.2*</td>
<td>52.7 ± 3.1*</td>
</tr>
<tr>
<td>$SaO_2$ (%)</td>
<td>96.7 ± 0.8</td>
<td>82.5 ± 4.6*</td>
<td>81.6 ± 3.4*</td>
<td>82.8 ± 4.6*</td>
</tr>
</tbody>
</table>

Table 2  Weight perception
Values are means ± S.D. There were no significant differences between regression coefficients.

<table>
<thead>
<tr>
<th>HA</th>
<th>SL</th>
<th>Day 2</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression coefficient</td>
<td>39.3 ± 17.1</td>
<td>28.3 ± 14.7</td>
<td>23.0 ± 16.2</td>
<td>27.1 ± 12.9</td>
</tr>
<tr>
<td>Intercept</td>
<td>−4.41</td>
<td>−1.17</td>
<td>2.27</td>
<td>−2.26</td>
</tr>
</tbody>
</table>

Figure 2  Relationship of hand weights to magnitude estimation at SL and on days 2, 4 and 5 at HA

for each regression coefficient were significant ($P < 0.02$). There were no significant ($P > 0.1$) changes in the regression coefficients, i.e. the perception of hand weights did not differ significantly between SL and HA.

Tables 3 and 4 and Figures 3 and 4 show the results of the studies of breathlessness and exercise. The slope of expired minute ventilation ($V_e$) to exercise did not alter significantly ($P > 0.05$) at HA, except on the last day; however, because resting $V_e$ was increased, the $V_e$ was significantly higher ($P < 0.05$) at any given exercise level (Table 4). This increase was almost entirely due to an increase in respiratory frequency (Table 4), since the slope of tidal volume relative to exercise did not change significantly with altitude, nor did the absolute values of $V_e$ (Table 4), except on the fifth day at HA. The regression coefficients of the breathlessness scores on the Borg scale and the exercise intensity, expressed in watts, increased significantly ($P < 0.05$) from SL to HA; however, the relationship of breathlessness to minute ventilation, tidal volume or respiratory frequency did not alter significantly at altitude, although there were significant increases in the regression coefficients of the Borg scores with $O_2$ uptake ($VO_2$) and $CO_2$ production ($VCO_2$). In all cases the correlations were significant ($P < 0.05$).
Table 3  Relationship of breathlessness to exercise ventilatory parameters

*P < 0.05 compared with SL; †P < 0.05 compared with HA day 2.

<table>
<thead>
<tr>
<th></th>
<th>Mean regression coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HA</td>
</tr>
<tr>
<td></td>
<td>SL</td>
</tr>
<tr>
<td>( V_e ) (l/min, BTPS) vs Work (W)</td>
<td>0.37</td>
</tr>
<tr>
<td>( V_t ) (l, BTPS) vs Work (W)</td>
<td>0.009</td>
</tr>
<tr>
<td>Borg score vs Work (W)</td>
<td>0.032</td>
</tr>
<tr>
<td>Borg score vs ( V_e ) (l/min, BTPS)</td>
<td>0.08</td>
</tr>
<tr>
<td>Borg score vs ( f ) (min(^{-1}))</td>
<td>3.22</td>
</tr>
<tr>
<td>Borg score vs ( V_{O_2} ) (l/min, STPD)</td>
<td>0.28</td>
</tr>
<tr>
<td>Borg score vs ( V_{CO_2} ) (l/min, STPD)</td>
<td>3.02</td>
</tr>
<tr>
<td>Borg score vs ( f ) (min(^{-1}))</td>
<td>2.27</td>
</tr>
</tbody>
</table>

Table 4  Values at an exercise level of 75 W

Values are means ± S.D.  *P < 0.05 compared with SL; †P < 0.05 compared with HA day 2.

<table>
<thead>
<tr>
<th></th>
<th>Borg score</th>
<th>( V_e ) (l/min, BTPS)</th>
<th>( V_t ) (l, BTPS)</th>
<th>( f ) (min(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SL</td>
<td>Day 2</td>
<td>Day 4</td>
<td>Day 5</td>
</tr>
<tr>
<td></td>
<td>2.62 ± 1.02</td>
<td>38.1 ± 3.8</td>
<td>1.50 ± 0.23</td>
<td>24.0 ± 4.4</td>
</tr>
<tr>
<td></td>
<td>HA</td>
<td>Day 2</td>
<td>Day 4</td>
<td>Day 5</td>
</tr>
<tr>
<td></td>
<td>4.87 ± 1.14*</td>
<td>52.6 ± 12.1*</td>
<td>1.63 ± 0.43</td>
<td>31.0 ± 6.2*</td>
</tr>
<tr>
<td></td>
<td>4.23 ± 1.27*</td>
<td>59.4 ± 3.4*</td>
<td>1.82 ± 0.44</td>
<td>33.7 ± 5.0*</td>
</tr>
<tr>
<td></td>
<td>4.01 ± 1.55*</td>
<td>64.0 ± 6.8*†</td>
<td>1.90 ± 0.33*</td>
<td>31.4 ± 3.9*</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Our results indicate that acute exposure to hypoxia at HA increases the intensity of breathlessness on exercise, and that this is related to the increased ventilation; however, general sensory perception is not altered.

While the sensation of breathlessness or dyspnoea remains a subject of study, the mechanisms underlying this important and common sensation are imperfectly understood. One problematic aspect is that of definition [8]: it is important to define as clearly as possible the sensation under study. Dyspnoea, or ‘the sensation of unpleasant breathlessness in disease’, has been distinguished from exercise-induced breathlessness in normal subjects [8]; the present study specifically examined the latter sensation.

Studies [6,7,9] of breathlessness during exercise have used either the modified Borg scale or visual analogue scale. We chose to use the modified Borg scale because of its ease of use, its previously demonstrated good correlation with the visual analogue scale, and its reproducibility on repeated testing [6,10]; it has been shown to have a lower variance than the visual analogue scale [6]. In addition, the time duration between tests has not been shown to affect the repeatability [10].

Previous studies [6,7,9,10] have shown that in normal subjects there is a linear relationship between ventilation and the Borg breathlessness score with exercise, and our findings agree with this. Furthermore, there is a wide inter-subject variability [9], which was also observed in the present study. Studies [6] have also shown a linear relation between the oxygen uptake (\( V_{O_2} \)) on exercise and the Borg score, and the present study confirmed this relationship, both during sea-level normoxia as well as HA hypoxia.

Although the precise mechanism of the sensation of breathlessness induced by exercise remains unclear, it is now generally accepted to involve central, peripheral and chemoreceptor mechanisms [11,12]. It is believed that the sensation of breathlessness arises as an awareness of the reflexly stimulated central motor command to the respiratory anterior horn cells in the spinal cord [12,13].

Studies of the role of chemoreceptor stimulation in the genesis of breathlessness have shown that the perception of breathlessness during exercise is directly related to the level of ventilation, and not specifically to the arterial \( P_{CO_2} \) level itself [2,14]. However, studies at rest have suggested that the arterial \( P_{CO_2} \) is itself a dyspnogenic stimulus [15–17]. Whether the \( P_{CO_2} \) level during exercise also has a specific effect on the intensity of breathlessness, unrelated to its ventilatory stimulus, remains to be demonstrated.

Previous studies in normal subjects have provided conflicting data on the role of hypoxia in breathlessness:
earlier SL studies with induction of transient acute hypoxia during exercise [1] suggested an increase in the intensity of perceived breathlessness in the absence of any specific effect on ventilation. Later studies [2] indicated that it was the level of stimulated ventilation rather than hypoxia per se which correlated with the intensity of breathlessness on exercise. More recently, the same workers, using a technique of continuous measurement of breathlessness during exercise and transient hypoxia [18], have indicated that hypoxia may indeed be dyspnogenic. In hypoxaemic patients with obstructive lung disease, some workers have reported a decrease in exercise-induced breathlessness with supplemental oxygen [19,20], whereas others have reported no effect of oxygenation during exercise on the intensity of breathlessness [21,22].

The present study supports previous hypotheses [2] that the intensity of breathlessness is related to the degree of reflex stimulation of ventilation, rather than to the hypoxia per se. Thus, there were no significant changes in the relationship of breathlessness intensity to ventilation, tidal volume or respiratory frequency between the normoxaemic sea-level state and hypoxaemic HA state, and the increased intensity of breathlessness with exercise correlated with the increased ventilation at any given exercise level. It could be argued that the number of subjects in the present study was insufficient to detect a significant change. However, calculations indicate that the power [5] of the present study to detect a significant change ($P < 0.05$) in the slopes of breathlessness intensity (Borg scale) to ventilation or tidal volume was 86% and 75% respectively, making it unlikely that a significant
difference would have been detected with a larger number of subjects. The increased intensity of exercise-induced breathlessness may also reflect a generalized increase in sensory perception related to adrenergic mechanisms which are known to be stimulated in response to hypoxia [23]. However, the absence of any significant change in the magnitude perception of hand weights during exposure to HA argues against such a mechanism.

We have previously shown that changes occur in the resting ventilatory pattern on exposure to HA hypoxia [24] and the present study shows that these changes extend to exercise at HA. The respiratory frequency was higher and tidal volume was unchanged for any given exercise level during the first few days of exposure to HA, although by the fifth day at HA there was a significant increase in tidal volume. It has been suggested that the individual ventilatory pattern is adjusted so as to minimize the sense of effort, which is related to the sensation of breathlessness [25,26]. Increases in tidal volume increase the sense of effort by increasing the generated intrathoracic pressure. In normal subjects, optimization of ventilatory pattern appears to occur reflexly [25], and it is likely that this also occurs at rest in response to HA hypoxia, where it has been shown that the increased ventilation occurs primarily due to an increase in respiratory frequency [24]. On the other hand, in the present study, the Borg breathlessness score increased while tidal volume remained unchanged for any given exercise level at HA, and the intensity of breathlessness was related to the absolute level of reflexly stimulated ventilation, even though the increased ventilation was primarily achieved by an increase in res-
piratory frequency. Thus, in the setting of HA hypoxia, it is the level of reflexly stimulated ventilation that is primarily related to the intensity of breathlessness, rather than the pattern by which that ventilation is achieved. This would imply that central rather than peripheral mechanisms are primarily involved in the increased exercise-induced breathlessness at HA. It is tempting to speculate that in this situation, where the two stimuli – an increased sense of effort related to increased intrathoracic pressure changes, and hypoxic reflex stimulation – could have been additive, the wisdom of the body mitigates in a lower intensity of breathlessness than might otherwise have been the case.

In conclusion, the present study has shown that acute exposure to HA hypoxia results in an increase in the intensity of exercise-induced breathlessness, which is related to the increase in ventilation. These results are compatible with the hypothesis that breathlessness is related to the level of reflexly increased ventilation rather than to the level of hypoxia per se. Furthermore, this increased breathlessness does not appear to be related to changes in peripheral mechanisms, such as an increased sense of effort, but is primarily related to central mechanisms.

REFERENCES


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