

Hypoxic ventilatory response and acute mountain sickness

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ABSTRACT: The acute ventilatory response to hypoxia (HVR) and to hypercapnia (CO_2VR) was measured in 32 members of two mountaineering expeditions prior to their departure. Both teams made rapid ascents to their base camps at 5200 m and 4300 m and remained there for at least four days. Symptom scores for acute mountain sickness (AMS) were collected daily for these four days. There was a range of AMS from the unaffected to severe sickness requiring evacuation, but there was no correlation between AMS scores and HVR or CO_2VR . When ascent to altitude takes a day or more, HVR (measured at sea level) is probably not the major determinant of ventilation and from our studies does not predict susceptibility to AMS. The rate of respiratory acclimatization is probably more important.

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It would seem obvious that subjects with a brisk acute hypoxic ventilatory response (HVR) on going to altitude would ventilate more, have a higher arterial oxygen tension (Po_2), and suffer less acute mountain sickness (AMS). The association of relative hypoventilation at altitude with AMS has been well documented in a number of studies [1-3]. However, the association of a low HVR with AMS is less well founded. Two chamber studies [1, 3] and a few retrospective studies of small numbers of subjects [4, 5], have addressed this problem but there have been no prospective studies in the field.

We report two prospective studies to investigate the correlation, if any, of AMS with the ventilatory response to acute hypoxia or hypercapnia. We took the opportunity of using two mountaineering expeditions when a total of 32 members would be going together rapidly to altitude and remaining at base camp for at least a few days. The first was an expedition to Mt. Everest (North Side) and the second to Mt. Kenya.

Subjects and methods

On the Everest expedition there were eleven male subjects and on the Kenyan expedition 21 subjects including two females. Ages ranged from 29-58 yrs (mean 41 yrs) and 21-56 yrs (mean 30 yrs), respectively. Mountaineering experience ranged from the highly experienced seasoned Himalayan climbers to subjects with no previous exposure to altitude, but the majority were competent alpinists with a few big peak expeditions behind them. The Everest group were more experienced than the members of the Kenyan expedition.

Subjects were asked not to take drugs likely to influence AMS symptoms. In particular acetazolamide was prohibited. If analgesics were taken for headache the symptom was scored according to the severity before taking the drug.

Altitude/time profiles of the two expeditions are shown in figure 1. On Mt. Everest, base camp at 5200 m was reached one week after leaving Beijing and on Mt. Kenya the base camp at 4300 m was reached approximately 30 h after leaving Nairobi (1500 m).

Hypoxic ventilatory response (HVR) and CO_2 (hypercapnic) ventilatory responses (CO_2VR) were measured in the laboratory during the three months prior to departure for China or Africa. Both responses were measured by rebreathing techniques modified from those described by REBUCK and CAMPBELL [6] for HVR and by READ [7] for CO_2VR . We used a circuit which included a dry rolling sleeve spirometer, the flow signal of which was rectified and damped to give a signal proportional to minute ventilation. This was applied to the Y axis on an X-Y plotter. Before each test the system was calibrated using a Harvard pump set to deliver $33 \text{ l}\cdot\text{min}^{-1}$. This in turn was initially checked by a timed collection into a Tissot spirometer.

During measurement of HVR, a CO_2 absorber with a variable bypass was placed in the breathing circuit enabling us to keep end tidal carbon dioxide tension (Pco_2) constant at the mixed venous Pco_2 , $6.3 \pm 0.25 \text{ kPa}$ ($47 \pm 2 \text{ mmHg}$). An infra-red CO_2 analyser monitored Pco_2 continuously downstream of the expiratory valves. An ear oximeter was used to measure arterial oxygen saturation and its output was applied to the X axis of the X-Y plotter so that the HVR (V/Sao_2) was plotted in real time. During measurement of CO_2VR the CO_2 absorber

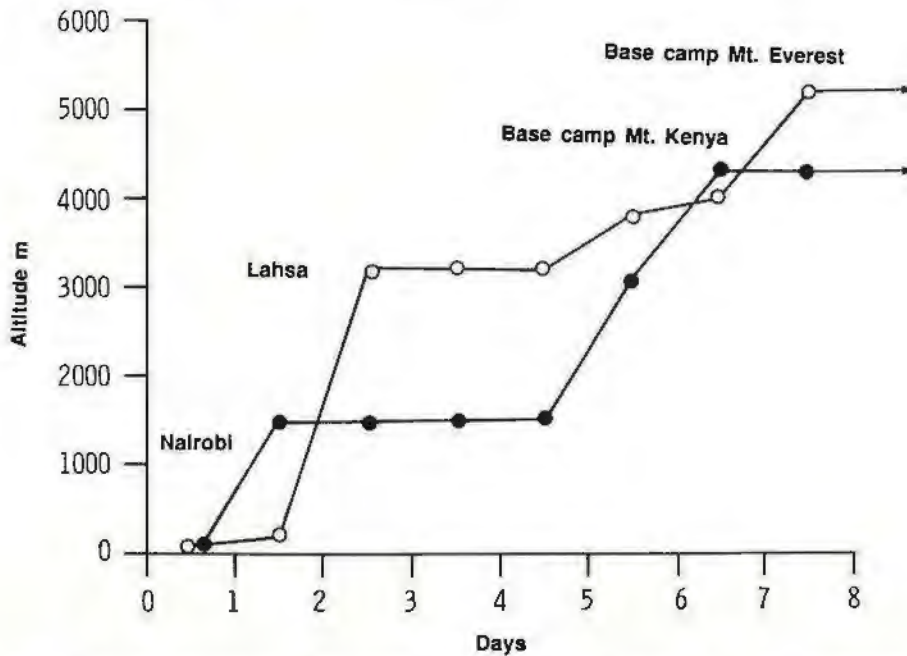


Fig. 1. - Altitude/time profile of the early part of the two expeditions (Mt. Everest open symbols, Mt. Kenya closed symbols). Symptoms of AMS were scored from arrival at base camp for four days.

and bypass were excluded from the breathing circuit. The output of the infra-red CO₂ analyser was applied to the X axis of a second X-Y plotter and the CO₂VR (\dot{V}/P_{CO_2}) was plotted in real time. The spirometer was charged with 6 l of 7% CO₂ in air for HVR and with 7% CO₂ in 50% oxygen, 43% nitrogen for the CO₂VR. The test was stopped when the ventilation reached 50 l·min⁻¹ or an oxygen saturation of 70% or a Pco₂ of 8.7 kPa (67 mmHg).

Subjects were studied in the semi-recumbent position and encouraged to read during the measurements. After at least 15 min rest, three estimates of CO₂VR were made. This was followed by three estimates of HVR. Best fit lines were drawn by eye by two observers who were not involved with later scoring for AMS. The slope of these lines was calculated. Where measurements of the response differed between the two observers by more than 0.5 U for any run, the results of that run were rejected. Eight out of 186 were rejected for this reason but not more than one run had to be rejected in any one subject. The mean of the satisfactory runs was taken as the response for each subject.

On arrival at altitude AMS symptom scores were collected by asking subjects to fill out a simple questionnaire each morning relating to the previous 24 h. Symptoms of headache, nausea, loss of appetite and loss of sleep were scored as: no symptoms 0, slight 1, definite 2, severe 3. On both expeditions the scores for each symptom for the first four days at base camp were totalled for each subject. A further symptom score was made by two observers giving a single overall score for each subject each day. These observer scores were found to correlate closely with the questionnaire scores ($p=0.01$ Everest expedition; $p=0.001$ Kenyan expedition; Kendall rank test). Since these scores were less detailed

(and give similar results) only the questionnaire scores are reported.

Results

During both expeditions there was a considerable incidence of AMS. Amongst the subjects we studied on Mt. Everest, 7 out of 11 had at least mild symptoms (a score of 4 or more). On Mt. Kenya 19 out of 21

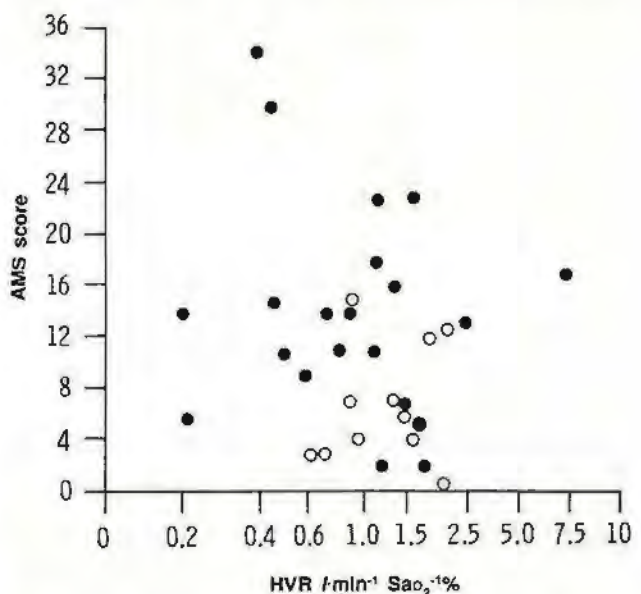


Fig. 2. - The results of AMS symptom scores and HVR measurements from the Mt. Everest (open symbols) and the Mt. Kenya (closed symbols) expeditions. There is no correlation between AMS and HVR.

subjects had at least mild AMS and one subject had to be evacuated due to severe AMS with signs of cerebral involvement.

HVR ranged from 0.2–6 $l \cdot \text{min}^{-1} \% \text{Sao}_2^{-1}$ (fig. 2) and CO_2VR from 0.67–3.89 $l \cdot \text{min}^{-1} \text{mmHg} \cdot \text{Pco}_2^{-1}$ with the expected skewed distribution towards lower values. There was a significant correlation between HVR and CO_2VR , $r=0.54$, $p<0.001$.

The results of AMS scoring and HVR are shown in figure 2 where HVR is shown on a log scale since its distribution is skewed. As can be seen, there was no correlation between the AMS score and HVR. Similarly there was no correlation between AMS scoring and CO_2VR (using Kendall's rank test).

Discussion

AMS affects otherwise healthy subjects of both sexes of all ages who ascend rapidly to high altitudes but there is a wide range of susceptibility. Generally, individuals respond consistently so that experience on one ascent is a good guide to subsequent performance [8]. This suggests that some constitutional factor must be important in determining susceptibility.

KING and ROBINSON [1] studied 24 men at a simulated altitude of 4200 m in a decompression chamber for six hours. There was a clear difference in the ventilatory response to altitude between the men most and least affected. Although all subjects increased their ventilation with altitude, those with most symptoms showed higher Pco_2 and lower Po_2 , *i.e.* relative hypoventilation, compared with those affected least. MOORE *et al.* [3] found similar results after 4.5 h in a chamber. HACKETT *et al.* [2], in 42 trekkers at 4243 m, found an association between AMS scores and arterial carbon dioxide tension (Paco_2) on arrival at that altitude. SUTTON *et al.* [9] also found a correlation of AMS with Paco_2 on the second day at altitude. These studies provide strong evidence for the association of AMS with relative hypoventilation on arrival at altitude compared with subjects free from symptoms.

Is this relative hypoventilation due to a blunted HVR in subjects susceptible to AMS?

The results of this study suggest that there is no correlation of HVR, measured at sea level, and AMS. Could we have failed to find a correlation between HVR and AMS scores because of technical or methodological problems? The measurement of HVR has its own variability which differs from subject to subject. The reproducibility between the three runs on an individual subject on one day is good. The slopes varied by an average of 14% about the mean. The day-to-day variability for one subject who is familiar with the test has a coefficient of variation of 8.5%, but presumably those tested for the first time, as our subjects were, would have rather more variability. However, the fact that we showed the expected correlation between HVR and CO_2VR [10] suggests that our testing methods were adequate and should have given a correlation with AMS if it truly existed.

Scoring AMS is obviously a subjective matter. We relied mainly on questionnaires which were administered by two observers. We also used an observer overall rating which gave similar results. In addition we calculated a score following the method of HACKETT *et al.* [2] which gives rather different weighting to symptoms from our scoring system. Nevertheless, the different scores produced rank scores which correlated closely with each other ($p=0.01$ to 0.001 , Kendall rank test) and none of them correlated with HVR or CO_2VR .

KING and ROBINSON [1] claimed that their most affected subjects had significantly lower HVR than their least affected subjects but from their published data the difference is not significant at the usual level ($p=0.064$ two-tailed, unpaired t-test). MOORE *et al.* [3] noted that the isocapnic HVR (Pco_2 allowed to fall during the test with increasing hypoxia) was significantly lower in their "ill" subjects. Two retrospective studies [4, 5] found low HVR in subjects who had had severe AMS but the numbers of subjects were small, comprising only one subject in the first study and four AMS subjects in the second.

There have been a few studies in which a brisk HVR correlated with a good performance at altitude and although this does not necessarily imply freedom from AMS it is usually associated with it. SCHOENE [11] reported that 14 high altitude climbers had higher HVR than control non-climbers. SCHOENE and co-workers [12] showed that on the American Research Expedition to Everest those with the highest HVR climbed higher on the mountain. MATSUYAMA *et al.* [13] claimed that their "high performance" group had higher HVR than their "low performance" climbers on Kangchenjunga but this was only true for the calculated parameter A (the shape parameter of the V/Pao_2 hyperbola); there was no significant difference in HVR measured by the V/Sao_2 slope. In contrast MILLEDGE *et al.* [14] found that four elite climbers had rather less HVR than four controls and SCHOENE *et al.* [15] also reported a blunted HVR in one of the two men who first climbed Everest without supplementary oxygen. Finally OELZ *et al.* [16] showed that six elite climbers who had all reached at least 8500 m without supplementary oxygen had HVRs no different from controls.

Peoples native to high altitude, who tend to acclimatize and perform better at altitude than do lowlanders, have been shown to have blunted HVR [17, 18], again suggesting that a brisk HVR is not essential to avoid AMS.

If HVR is not correlated with AMS, what is the mechanism of the relative hypoventilation in susceptible individuals?

After acclimatization, when the CO_2 response line has shifted to the left, much of the chemical drive to breathing is due to CO_2 and only some is due to hypoxia. The rate of this shift of CO_2 response has been little studied since the work of Kellogg [19]. He showed that the rate of shift of the CO_2 response line is roughly ex-

potential with time, about two-thirds of the eventual shift taking place in the first 24 h at altitude, although there is probably considerable individual variation in this rate. Recently it has been suggested that part of the ventilatory acclimatization may be due to an increase in the HVR during the first few days at altitude, at least in animals [20].

It is arguable, therefore, that under field conditions when the altitude stress is applied over a period of one to three days (see fig. 1) there is time for considerable respiratory acclimatization to take place. The major determinant of ventilation under these conditions may well be the speed of this adaptation rather than HVR (measured at sea level), whereas with very acute altitude stress, as in a decompression chamber, the sea level HVR may be the more important determinant of ventilation and so may be found to correlate with AMS.

In conclusion, we suggest that HVR (measured at sea level) is not an important factor in determining the susceptibility to AMS. Probably factors relating to the rate of respiratory acclimatization, about which very little is known, are more important in determining the level of ventilation and hence susceptibility to AMS.

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Réponse ventilatoire hypoxique et mal des montagnes aigu.
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RÉSUMÉ: La réponse ventilatoire aiguë à l'hypoxie (HVR) et à l'hypercapnie (CO₂VR) a été mesurée chez 32 membres de deux expéditions de montagne avant leur départ. Les deux équipes ont fait des ascensions rapides vers leur camp de base à 5.200 m et 4.300 m, et y sont restées pendant au moins quatre jours. Les scores de symptômes pour le mal des montagnes aigu ont été établis quotidiennement pendant ces quatre jours. On a observé toute une gamme de symptômes de mal des montagnes aigu, depuis les sujets non affectés, jusqu'à une maladie sévère exigeant l'évacuation, mais il n'y avait pas de corrélation entre les scores de symptômes de mal des montagnes aigu et la réponse ventilatoire à l'hypoxie et à l'hypercapnie. Lorsque l'ascension en altitude prend un jour ou davantage, la réponse ventilatoire à l'hypoxie mesurée au niveau de la mer n'est probablement pas le déterminant majeur de la ventilation et, selon nos études, ne permet pas de prédire la susceptibilité de développer un mal des montagnes aigu. Le degré d'acclimatation respiratoire est probablement plus important.

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