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ORIGINAL ARTICLE

Near-infrared spectroscopy in the assessment of cerebral oxygenation at high altitude

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Hypoxia plays a key role in the pathogenesis of acute mountain sickness (AMS), but individual susceptibility is variable and cerebral symptoms do not always correlate with PaO_2 measurements. Cerebral hypoxia may be more relevant than PaO_2. We studied trends in cerebral regional oxygen saturation by the technique of near-infrared spectroscopy in 20 subjects ascending rapidly to 4680 m. Subjects were enrolled in a placebo-controlled, double-blind trial of medroxyprogesterone for the prevention of AMS. The fall in cerebral oxygen saturation was less than in the periphery. At 4680 m, cerebral oxygenation correlated with peripheral saturation but not with $PaCO_2$ or with cerebral symptoms scores. At 4680 m, subjects on medroxyprogesterone had higher cerebral and peripheral saturation compared with those on a placebo. We conclude that cerebral oxygenation monitored with the Critikon 2020 system provided important information on the complex relationship of hypoxia to AMS and that other factors, such as changes in blood flow or capillary permeability, may be equally important.

Key words:
brain, oxygenation, measurement technique, near-infrared spectroscopy, high altitude, acute mountain sickness

Introduction

Death from cerebral hypoxia induced by ascent to high altitude was described as early as 1874, when three balloonists lost consciousness at 23 000 feet and two of them died [1]. Wheel-well passengers are the modern equivalent, and a similar mortality has been reported of stowaways from flights up to 39 000 feet [2]. Today, high-altitude cerebral edema is a rare but still potentially fatal syndrome reported in trekkers, mountaineers, workers, and military personnel [3], especially when time has not been allowed for acclimatization. Symptoms of the more benign self-limiting syndrome of acute mountain sickness (AMS) with headache, anorexia, nausea, and vomiting also probably result from cerebral edema. Why individual susceptibility to high-altitude cerebral edema and to AMS is so variable is unknown. PaO_2 tends to be lower in those individuals suffering from AMS [4], perhaps as a consequence of a poor ventilatory response to hypoxia [5] or as a result of a ventilation-perfusion mismatch. The lower PaO_2 may, in those circumstances, be the direct cause of reduced cerebral oxygenation. Alternatively, increased capillary permeability [6] in response to a given degree of cerebral hypoxia may be greater in susceptible individuals. Changes in cerebral blood flow [7] and intracranial pressure [8] are unlikely to be prime factors in the pathogenesis of cerebral edema. Measurements of cerebral oxygenation would therefore contribute to our understanding of the mechanisms involved.

The introduction of reflected near-infrared light spectroscopy allows continuous, noninvasive monitoring of cerebral oxygenation. The technique was first described in adults in 1991 [9] and has already developed widespread clinical applications [10,11]. The aim of this field study was to investigate the effect of acute exposure to altitudes up to 4700 m on cerebral oxygenation and to relate these changes to the development of AMS.

Subjects and methods

Twenty healthy, nonsmoking subjects (17 males, 3 females) aged 24–59 years were studied. Baseline mea-

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surements of cerebral oxygenation were made at 150 m in 17 subjects 1 month before ascent. Subjects were taking part in a placebo controlled trial of medroxyprogesterone, 60 mg daily, for the prevention of AMS. After random allocation, the active drug and placebo were started 1 week before ascent to high altitude. Studies were made at sea level (La Serena, Chile) and then on consecutive days at 2770 m, 3650 m, and 4680 m (Paso del Agua Negra). Travel to each altitude was made in a minibus. All studies were made after overnight stay at that altitude, and an additional study was made after a second night at 4680 m. Clinical AMS scores were obtained from the Lake Louise questionnaires [12], which were completed morning and evening. A score of three points or more on a questionnaire indicated AMS. A total AMS score was calculated by addition of all the scores in the questionnaires above sea level. Subjects were also interviewed and examined each morning by two physicians experienced in altitude sickness. A central nervous system score was calculated by addition of the score for headache and gastrointestinal symptoms in the morning questionnaire and the change in mental status and ataxia noted in the clinical assessment.

In 10 of the 20 subjects, $PaCO_2$ and pH were measured in arterialized capillary blood with a Medical Analyser model 348 (Chiron Diagnostics) at sea level and at 2770 m and 4680 m. Data were incomplete in the other 10 subjects. PaO_2 was measured in arterialized capillary blood in all subjects at 2770 m. Peripheral oxygen saturation (SpO_2) and heart rate were measured at 1-min intervals with a hand-held digital pulse oximeter (model 3770, Ohmeda, BOC Group) that was applied after warming the hand in woollen clothing. A BOC face mask was positioned on the face of the subject with a Clausen harness ensuring a good seal. A Capnograph (Hewlett Packard 78356 A) was attached to the mask inlet to measure Pi CO_2 and Pe′ CO_2 at 1-min intervals.

CEREBRAL REGIONAL OXYGEN SATURATION (rSO_2)

Subjects rested supine for 10–15 min before each study. Continuous noninvasive near-infrared spectroscopy was performed with Critikon 2020 (Johnson and Johnson Medical Ltd, UK). The sensor position was standardized to a point over the right frontoparietal region with the sensor margins 3 cm from the midline and 3 cm above the orbital crest. The Critikon disposable adhesive pads were unsatisfactory, and a Blue-line tubifast bandage (Seton Healthcare Group plc, Turbiton House, Oldham, Lancashire, UK) was used to keep the sensor in place. Data sampled every second were logged on to a Toshiba Satellite 200 CDS laptop computer. The interlock hold time was set at 120 seconds. Measurements were made of oxygenated hemoglobin (HbO_2), deoxygenated hemoglobin ($HbDO_2$), and total hemoglobin. Cerebral regional oxygenation (rSO_2) was derived from ($HbO_2 \div$ total Hb) $\times$ 100.

STATISTICS

Statistical significance of results obtained during ascent (sea level to first measurement at 4680 m) was assessed by repeated measures analysis of variance. Other comparisons were made by paired *t*-test and by simple linear regression (Stat View for Windows, Abacus Concepts, Inc, Berkeley, CA). A *p*-value of <0.05 was considered significant. Approval for the studies was given by the South Birmingham Local Research Ethics Committee and informed consent was given by all subjects.

Results

OXYGENATION

Mean rSO_2 was similar at 150 m and sea level before ascent to high altitude and fell progressively during ascent (Table 1; Fig 1). The fall in SpO_2 was greater (23%) compared with the fall in rSO_2 (8%). At 4680 m, a significant correlation occurred between rSO_2 and SpO_2 ($r = 0.74$, $p < 0.001$). The rise in rSO_2 and SpO_2 on the second day at 4680 m was not significant. PaO_2 measured at 2770 m did not correlate with the corresponding cerebral HbO_2 or rSO_2 but correlated with SpO_2 ($r = 0.52$, $p < 0.05$).

CARBON DIOXIDE

End tidal CO_2 and $PaCO_2$ fell progressively during ascent (Table 1) and were correlated at 2770 m ($r = 0.6$, $p < 0.01$) but not at 4680 m ($r = 0.34$). rSO_2 was not correlated with corresponding measures of $PaCO_2$ at 2770 m ($r = -0.23$) or at 4680 m ($r = -0.44$, $p > 0.05 < 0.1$).

AMS AND MEDROXYPROGESTERONE

Mild or moderate symptoms of AMS occurred in all subjects, and a score of three points or more on at least one of the AMS self-reported questionnaires was recorded by 16 (80%) subjects. One subject on placebo required treatment with acetazolamide and dexamethasone after measurements were made on the first morning at 4680 m. Total AMS scores in subjects on medroxyprogesterone (16.0 $\pm$ 9.2 SD) were not different from those on placebo (20.7 $\pm$ 8.8 SD). Total AMS scores did not

Table 1. Oxygen saturation and blood gas data during ascent to high altitude

Altitude (m): *Days of expedition*	*150* *(pre)*	*Sea level* *1*	*2770* *2*	*3650* *3*	*4680* *4*	*4680* *5*
Near-infrared spectroscopy						
HbO_2 μmol/L tissue	79.3 (9.2)	73.8 (8.9)	78.9 (13.0)	70.3 (11.0)	72.3 (11.3)*	75.5 (11.6)
$HbDO_2$ μmol/L tissue	33.4 (3.8)	32.0 (4.2)	37.3 (5.1)	36.8 (4.8)	42.7 (6.3)§	41.5 (6.7)
Total Hb	112.3 (11.6)	105.2 (11.8)	115.9 (17.3)	106.8 (15.5)	117.6 (16.6)§	116.8 (16.6)
rSO_2%	70.2 (2.4)	69.5 (2.4)	67.3 (3.4)	65.4 (2.7)	63.6 (2.3)§	64.4 (3.3)
Pulse oximetry						
SpO_2%	98.1 (0.9)	97.3 (1.1)	92.0 (1.5)	88.3 (2.7)	75.1 (5.9)§	76.9 (7.8)
Heart rate/min	62.7 (9.1)	63.1 (8.0)	72.9 (10.5)	73.3 (13.4)	75.1 (5.8)§	78.8 (9.7)
Blood gases						
PaO_2kPa		—	7.9 (0.54)	—	—	
$PaCO_2$		4.8 (0.6)	4.0 (0.3)‡	—	3.6 (0.3)‡	
pH		7.418 (0.013)	7.460 (0.018)†	—	7.485 (0.029)§	
End tidal CO_2kPa		5.9 (0.6)	3.7 (0.3)	3.5 (0.3)	3.4 (0.3)§	3.2 (0.3)
Blood pressure						
Systolic mm Hg		134.0 (5.9)	132.0 (10.2)	139.2 (10.3)*	145.0 (15.9)†	133.8 (15.3)
Diastolic mm Hg		73.6 (8.2)	79.8 (8.9)*	80.1 (10.6)	77.0 (9.1)	82.4 (9.2)†

Results are given as mean (SD). $n = 20$ except for blood gases, where $n = 10$. Changes in near-infrared spectroscopy and endtidal CO_2 were assessed by repeated analysis of variance days 1 to 4. $PaCO_2$, pH, and systolic and diastolic blood pressure changes were assessed by paired t-test comparing each altitude result against sea level.

* $p < 0.05$.

† $p < 0.01$.

‡ $p < 0.001$.

§ $p < 0.0001$.

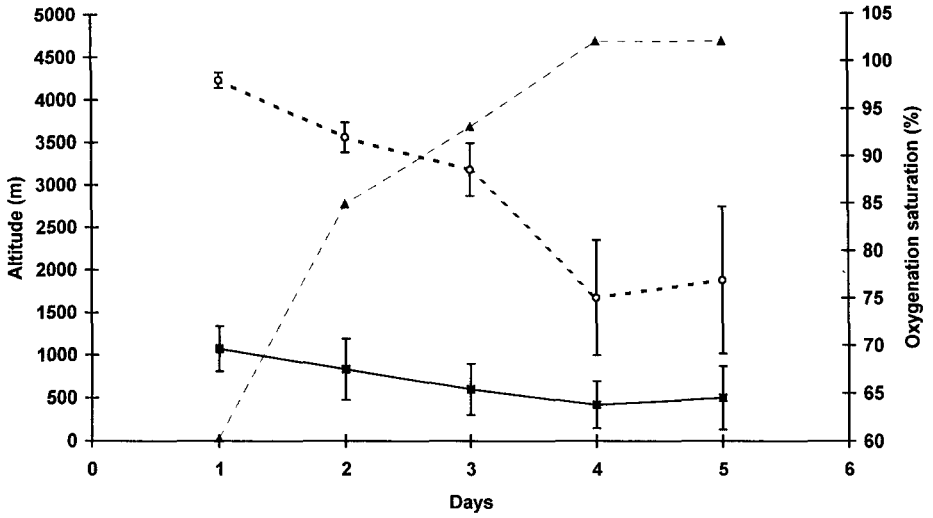

Fig 1. The fall in peripheral oxygen hemoglobin saturation (SpO_2 mean ± SD, open circles with dotted line) and cerebral regional oxygen saturation (rSO_2 mean ± SD, squares and thick solid line). The route profile is shown (triangles and dotted line).

correlate with rSO_2 or SpO_2 measurements at 4680 m. Cerebral AMS scores tended to be higher as rSO_2 fell ($r = -0.41$, $p > 0.05 < 0.1$; Fig 2). At high altitude, subjects on medroxyprogesterone had higher rSO_2 (64.8% ± 2.3 SD) compared with those on placebo (62.4% ± 2.0 SD, $p < 0.05$). Subjects on medroxyprogesterone had a consistently lower (0.27 kPa) endtidal CO_2 throughout the expedition except on the second day at 4680 m, when there was no difference from subjects on placebo.

Discussion

This study showed that the noninvasive technique of reflected near-infrared spectroscopy can be used successfully in the field and at high altitude. The equipment was robust and portable, and the results were easy to monitor and record. Stable baseline measurements were obtained on each occasion, and highly reproducible rSO_2 measurements were recorded on the two separate occasions before ascent. Sensitive responses occurred following

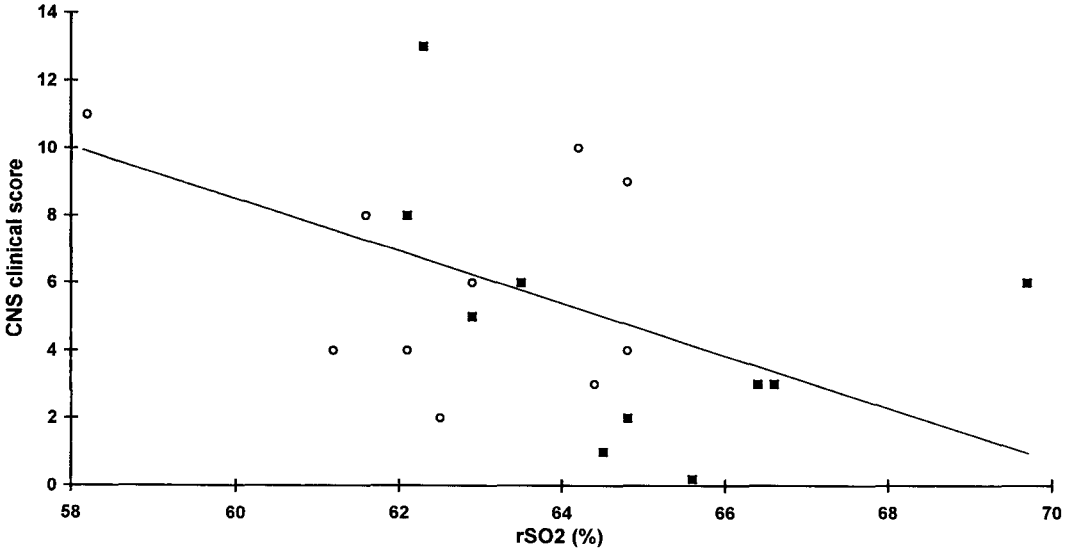

Fig 2. The relationship of rSO_2 at 4680 m and cerebral acute mountain sickness scores for the 10 subjects on medroxyprogesterone in solid squares and the 10 subjects on placebo in open circles ($y = 43.1 - 0.59x$, $r = -0.41$, $p > 0.05 < 0.1$).

physiological manipulations (unpublished observations). To date, all measurements of cerebral perfusion in human subjects at altitude have been based upon radioisotopes or transcranial Doppler techniques, and these have shown an increase in cerebral blood flow or velocity [13]. This study enabled cerebral oxygenation to be monitored at altitude for the first time. Regional cerebral oxygenation measured in this way was a mixed venous result [14], hence the lower values than SpO_2 and the smaller fall with increased altitude. Increased altitude resulted in an overall fall in cerebral HbO_2, a rise in cerebral $HbDO_2$, and a small rise in cerebral total Hb. The fall in HbO_2 corresponded with the observed fall in SpO_2, with the inverse being shown in the $HbDO_2$. The greater variation in HbO_2 was possibly due to changes in hematocrit occurring with changes in hydration. rSO_2 is a derived figure (HbO_2/total Hb $\times$ 100) and therefore takes into account changes in hematocrit. Changes in rSO_2 can follow changes in arterial or venous saturation, altered proportions of blood within the arterial, capillary, or venous compartments, or a combination of these. The normal distribution of cerebral blood volume is 25% arterial, 5% capillary, and 70% venous [15], and thus the fall in rSO_2 at altitude was less than the fall in SpO_2.

Studies investigating the use of near-infrared spectroscopy during carotid surgery have demonstrated a strong association between this noninvasive technique and invasive methods such as jugular bulb oximetry and stump pressures [16,17]. However, concerns have been raised over the specificity of the near-infrared technology, in particular when assessing the proportion of the signal arising from extracranial tissues supplied by the external carotid artery and brain tissue supplied by the internal carotid artery. Clearly, this differential is crucial in carotid surgery. Temporary interruption of scalp blood flow with an inflatable tourniquet caused no change in cerebral hemodynamics measured by near-infrared spectroscopy in adult volunteers, despite a significant fall in scalp blood flow measured by laser Doppler velocimetry [18]. Other studies have shown that extracranial tissue oxygenation has negligible influence on near-infrared measures of cerebral oxygenation [19]. The extracranial contribution is deleted to a large extent with a two-channel detector [20]. Our experience with local anesthetic carotid surgery with the Critikon 2020 supports this hypothesis (unpublished observations). Nevertheless, some contamination of cerebral oxygenation may have occurred from the extracranial component. In an individual subject, any such error may be constant, allowing valid assessment of changes in cerebral oxygenation [21].

SpO_2 fell as expected with increased altitude. Few problems were experienced with poor signals once the subject's hand was warmed adequately and protected from extraneous light. Peripheral pulse oximetry can be unreliable at low readings. The Ohmeda 3770 equipment has an accuracy (1 SD) of 1.5% at 90%–100%, 2.1% at 80%–89%, and 2.4% at 60%–100% saturation. The lowest reading obtained in the individuals studied at high altitude was 59%, so the greater range seen at high altitude must reflect a true spread of response to ascent. The small rise in mean rSO_2 and SpO_2 after 24 hr at high altitude was not significant, but we would have expected further rises as acclimatization occurred.

Measurement of rSO_2 did not separate subjects suffering from AMS from those with few or no symptoms. However there was a trend for subjects with high scores of cerebral symptoms to have lower rSO_2 readings, and with greater numbers and more refined clinical scoring, a more positive relationship might have been found. This possibility is supported by the finding of greater rSO_2 measurements at high altitude in subjects on medroxyprogesterone.

In conclusion, cerebral oxygenation has been monitored by near-infrared spectroscopy for the first time at high altitude. The fall in rSO_2 was less marked than the fall in SpO_2 because the measurement was mixed arterio-venous and perhaps because of increases in cerebral blood flow. Further assessment of the relative importance of these factors is required.

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