Cerebral oxygenation at high altitude and the response to carbon dioxide, hyperventilation and oxygen

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ABSTRACT

Cerebral oxygenation is likely to be of critical importance in determining function at high altitude. The present study has used the technique of near-IR spectroscopy to monitor changes in cerebral regional oxygenation in response to inhaled carbon dioxide, hyperventilation and supplementary oxygen on ascent to 4680 m over 3 days. At sea level, inhaled CO_2 resulted in a significant rise in cerebral regional oxygenation [from mean 69.6% (S.D. 2.4% to 71.1 $\pm$ 2.3%; means $\pm$ S.D.; $P < 0.001$). At 4680 m, CO_2 increased regional cerebral oxygenation (63.8 $\pm$ 2.5% to 65.9 $\pm$ 2.2%; $P < 0.001$) and also increased peripheral oxygen saturation (75.1 $\pm$ 6.1% to 83.6 $\pm$ 4.0%; $P < 0.001$). Voluntary hyperventilation resulted in improved peripheral oxygen saturation at 2770 m, 3650 m and 4680 m, whereas cerebral regional oxygenation was reduced at sea level and at 2770 m, unchanged at 3650 m and increased at 4680 m. Supplementary oxygen (6 litres/min) at 4680 m resulted in greater improvements in peripheral oxygen saturation (76.7 $\pm$ 7.9% to 98.1 $\pm$ 1.5%; $P < 0.001$) and cerebral regional oxygenation (64.6 $\pm$ 3.3% to 70.6 $\pm$ 2.9%; $P < 0.001$) than were found with CO_2 or hyperventilation. We conclude that attempts to increase CO_2 inhalation or ventilation at high altitude are likely to be beneficial for cerebral oxygenation in the short term.

INTRODUCTION

Oxygenation of the brain is critical in determining performance and illness at high altitude. Cerebral oxygenation is dependent upon a number of factors, including arterial oxygenation, oxyhaemoglobin (HbO_2) dissociation, haemoglobin (Hb) concentration and cerebral blood flow. Many of these factors are affected by altitude, and also by physiological events such as sleep and exercise. The precise relationship between reduced arterial oxygen pressures and the development of acute mountain sickness (AMS) is controversial, with some studies showing a direct correlation with PaO_2 (arterial partial pressure of O_2) or oxygen saturation [1] and others not [2]. Such discrepancies could be explained by the timing of the measurements of blood gases in relation to the development of AMS or to imprecision in the quantification of AMS, but could also reflect differences in cerebral oxygenation that are dependent upon factors other than PaO_2. There could also be differences in the

Key words: carbon dioxide administration, cerebral oxygenation, high altitude, hyperventilation, near-IR spectroscopy.

Abbreviations: AMS, acute mountain sickness; Hb, haemoglobin; $HbDO_2$, deoxyhaemoglobin; HbO_2, oxyhaemoglobin; NIRS, near-IR spectroscopy; PaO_2 and $PaCO_2$, arterial partial pressure of O_2 and CO_2 respectively; P_{ETCO_2}, end-tidal partial pressure of CO_2.

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function of cerebral capillaries or cerebral tissues in response to hypoxia. In some reports, AMS has been shown to be more closely related to $PaCO_2$ [3], suggesting that a poor ventilatory response to hypoxia is an important factor. In support of this hypothesis are the findings in some studies that climbers with a good hypoxic ventilatory response tolerate extreme altitude better than those with a more modest response [4].

As early as 1885, Miescher-Rusch [4a] recognized that "over the oxygen supply of the body, carbon dioxide spreads its protecting wings – especially as it cares for the brain which, for unknown reasons, may lack air in warm blooded animals, whereas skin and muscle may tolerate the ischaemia of a tourniquet for more than half an hour". Based on the hypothesis that a deficiency in oxygen induces hypernoea and acapnia, and therefore subnormal respiration, Angelo Mosso in 1898 [4b] administered CO_2 mixtures to relieve hypoxic symptoms in subjects exposed to pressures as low as 250 torr (33 kPa; $\sim$ 8800 m) in a hypobaric chamber. The importance of hypocapnia was re-emphasized earlier this century [5,6], with the suggestion that inhaled CO_2 might be useful when climbing to great altitudes. Our own more recent studies have shown that part of the improvement in oxygenation when subjects are pressurized in a portable compression bag at altitude is due to CO_2 accumulation (C. H. E. Imray, T. Clarke, P. J. G. Forster, T. C. Harvey, H. Hoar, S. Walsh and A. D. Wright, unpublished work). However, the beneficial effects of CO_2 alone in relieving symptoms of AMS [7] have not been confirmed by other studies [8].

The beneficial effect of CO_2 in the management of cerebral hypoxia may be due to a more complex mechanism than a simple increase in ventilation with a consequent increase in PaO_2. The addition of CO_2 has a powerful vasodilator effect on the cerebral resistance vessels, increasing blood flow and hence oxygen delivery. In sheep at a simulated altitude of $\sim$ 6000 m, an increase in cerebral blood flow of 54% was found in comparison with that at sea level; however, with additional 3% CO_2, cerebral blood flow increased to 288% [9]. Similar rises in cerebral blood flow have been reported in clinical studies carried out at altitude [10,11].

The development of reflected near-IR spectroscopy (NIRS) has allowed the continuous, non-invasive monitoring of cerebral oxygenation. The technique was first described in adults in 1991 [12], and has already developed widespread research and clinical applications [13,14]. The NIRS method is particularly suitable for multiple measurements of trends rather than single absolute measurements of cerebral oxygenation. We have reported the changes observed on ascent to high altitude and found that the equipment was robust and suitably sensitive for use in the field [15]. In the present study the acute effects of CO_2-enriched air on peripheral and cerebral regional oxygenation at high altitude are reported, and the results obtained with CO_2 are compared with the effects of hyperventilation and administration of oxygen.

METHODS

Subjects

A total of 20 healthy, non-smoking subjects (17 males; three females) aged 24–59 years were studied. Baseline measurements of cerebral regional oxygenation were made at 150 m above sea level in 17 subjects 1 month before ascent. Subjects were randomly allocated to groups taking placebo or medroxyprogesterone 60 mg daily, which was started 1 week before departure for Chile. A series of daily studies was then carried out on the morning after arrival at sea level (La Serena), and on ascent to 2770 m, 3560 m and 4680 m (Paso del Agua Negra). Travel was by minibus. Subjects rested for 10–15 min before each study. Baseline measurements of cerebral regional oxygenation and the effects of hyperventilation were obtained at each altitude. The effect of CO_2 was assessed at sea level and at 4680 m, and the oxygen study was performed after a second night sleeping at 4680 m.

Approval for the studies was given by the South Birmingham Local Research Ethics committee, and written informed consent was obtained from all subjects.

Peripheral oxygen saturation

Peripheral pulse oximetry and heart rate were measured at 1 min intervals using a hand-held digital oximeter (model 3770; Ohmeda; BOC Group). This was applied after warming the hand in woollen clothing and excluding extraneous light.

Cerebral regional oxygen saturation

Continuous non-invasive NIRS was performed using a Critikon 2020 instrument (Johnson and Johnson UK Ltd). The sensor position was standardized to a point over the right fronto–parietal region, with the sensor margin 30 mm from the midline and 30 mm above the orbital crest, taking care to avoid the saggital sinus. The Critikon disposable pads were unsatisfactory, and a Blue-line Tubifast bandage (Seton Healthcare Group, Turbiton, Oldham, Lancashire, U.K.) was used to keep the sensor in place. Recordings were made of HbO_2, deoxyhaemoglobin ($HbDO_2$), total Hb and cytochrome a_3. Cerebral regional oxygenation was derived from HbO_2/total Hb $\times$ 100. Data sampled every 1 s were logged on to a Toshiba Satellite 200 CDS laptop computer. The interlock hold time was set at 120 s.

End-tidal partial pressure of CO_2 (P_{ETCO_2})

A BOC face-mask was positioned on the face of the subject, with a Clausen harness ensuring a good seal. A

capnograph (Hewlett Packard 78356A) was attached to the mask inlet in order to measure the partial pressure of CO_2 in the inspired air and P_{ETCO_2} at 1 min intervals.

Carbon dioxide

To obtain CO_2-enriched air, 97 vol. of ambient air was mixed with 3 vol. of CO_2 in a 500 litre Douglas bag. The gas mixture was validated by checking the partial pressure of CO_2 in the inspired air on the capnograph. Initial attempts to 'blind' subjects to the administration of CO_2 were abandoned, because subjects were aware almost immediately of the increased ventilatory drive. Subjects inhaled the CO_2 mixture for 7 min.

Hyperventilation

Hyperventilation studies were performed when baseline recordings were stable, which at sea level and 4680 m was 5–10 min after the CO_2 study. Subjects were asked to breathe as hard and fast as possible for 1 min, being 'counted down' through the 60 s by an observer. Measurements were recorded at the end of hyperventilation.

Oxygen

After baseline measurements in ambient air, supplementary oxygen was given at 6 litres/min for 3 min.

Statistics

The statistical significance of results obtained was assessed by repeated-measures analysis of variance. Other comparisons were made by paired t test (StatView for Windows; Abacus Concepts, Berkley, CA, U.S.A.). P values of < 0.05 were considered significant.

RESULTS

CO_2 studies

Sea level

P_{ETCO_2} rose in all subjects while breathing CO_2-enriched air (5.1 ± 0.4 kPa to 5.9 ± 0.5 kPa; means $\pm$ S.D.; $P < 0.001$) (Figure 1a). Baseline P_{ETCO_2} was not significantly different in subjects on medroxyprogesterone (4.91 ± 0.37 kPa) compared with those on placebo (5.37 ± 0.25 kPa), and the rise in P_{ETCO_2} at 7 min was also similar in the two groups (0.69 ± 0.3kPa and 0.85 ± 0.29kPa respectively). Peripheral oxygen saturation did not change significantly (98.1 ± 0.83 % to 98.3 ± 0.58 %) (Figure 1d). Cerebral regional oxygenation rose from 69.6 ± 2.4 % to 71.1 ± 2.3 % ($P < 0.001$) (Figure 1g) while breathing CO_2-enriched air, with no significant difference in the responses of subjects on medroxyprogesterone (1.38 ± 0.7 %) compared with those taking placebo (1.69 ± 0.9 %).

High altitude

At 4680 m, P_{ETCO_2} rose in all subjects while breathing CO_2-enriched air (3.1 ± 0.3 kPa to 3.4 ± 0.5 kPa; $P < 0.001$) (Figure 1a). Baseline P_{ETCO_2} was not significantly different in subjects on medroxyprogesterone (2.98 ± 0.23 kPa) compared with those taking placebo (3.18 ± 0.21 kPa), and the rise in P_{ETCO_2} at 7 min was also similar in the two groups (0.32 ± 0.16 kPa and 0.36 ± 0.16 kPa respectively). Peripheral oxygen saturation increased from 75.1 ± 6.1 % to 83.6 ± 4.0 % ($P < 0.001$) while breathing CO_2-enriched air (Figure 1d), with similar increases in subjects on medroxyprogesterone (mean 8.6 %) and placebo (mean 8.5 %). Changes in peripheral oxygen saturation in response to CO_2 were not related to baseline P_{ETCO_2} measured at sea level or at 4680 m. While breathing CO_2-enriched air, cerebral regional oxygenation increased in all but two subjects (mean $\pm$ S.D. 63.8 ± 2.5 % to 65.9 ± 2.2 %; $P < 0.001$) (Figure 1g), with similar rises in those on medroxyprogesterone (1.96 ± 1.2 %) and placebo (2.13 ± 1.1 %). Changes in cerebral regional oxygenation in response to CO_2 were not related to baseline P_{ETCO_2} measured at sea level or at 4680 m.

Hyperventilation studies

P_{ETCO_2} was reduced by a similar proportion of baseline (48–56 %) at the end of 1 min of hyperventilation (Figure 1b) at sea level, 2770 m, 3560 m and 4680 m. The decrease in P_{ETCO_2} caused by hyperventilation was similar in subjects on medroxyprogesterone and in those taking placebo (e.g. at 4680 m: from 2.94 ± 0.28 kPa to 1.61 ± 0.17 kPa and from 3.27 ± 0.21 kPa to 1.81 ± 0.20 kPa respectively; means $\pm$ S.D.). However, at 4680 m the P_{ETCO_2} at baseline and at the end of hyperventilation was lower in subjects taking medroxyprogesterone than in those taking placebo ($P < 0.02$). Peripheral oxygen saturation rose significantly on hyperventilation at 2770 m ($P < 0.001$), 3650 m ($P < 0.05$) and 4680 m ($P < 0.001$), with similar responses in subjects on medroxyprogesterone and in those taking placebo (Figure 1e). Cerebral regional oxygen saturation was reduced by hyperventilation at sea level (from 69.6 ± 2.5 % to 68.1 ± 2.9 %; $P < 0.001$) and at 2770 m (from 67.7 ± 3.2 % to 66.8 ± 4.2 %; $P < 0.001$), but was unchanged at 3650 m (Figure 1h). At 4680 m cerebral regional oxygen saturation increased on hyperventilation, from 64.4 ± 2.5 % to 66.3 ± 3.5 % ($P < 0.001$). The increase in cerebral regional oxygen saturation at 4680 m was similar in subjects on medroxyprogesterone (65.3 ± 2.2 % to 67.5 ± 2.7 %) and in those taking placebo (63.5 ± 2.7 % to 65.1 ± 3.9 %).

Oxygen study

P_{ETCO_2} did not change significantly during inhalation of oxygen-enriched air at 4680 m (Figure 1c), but both

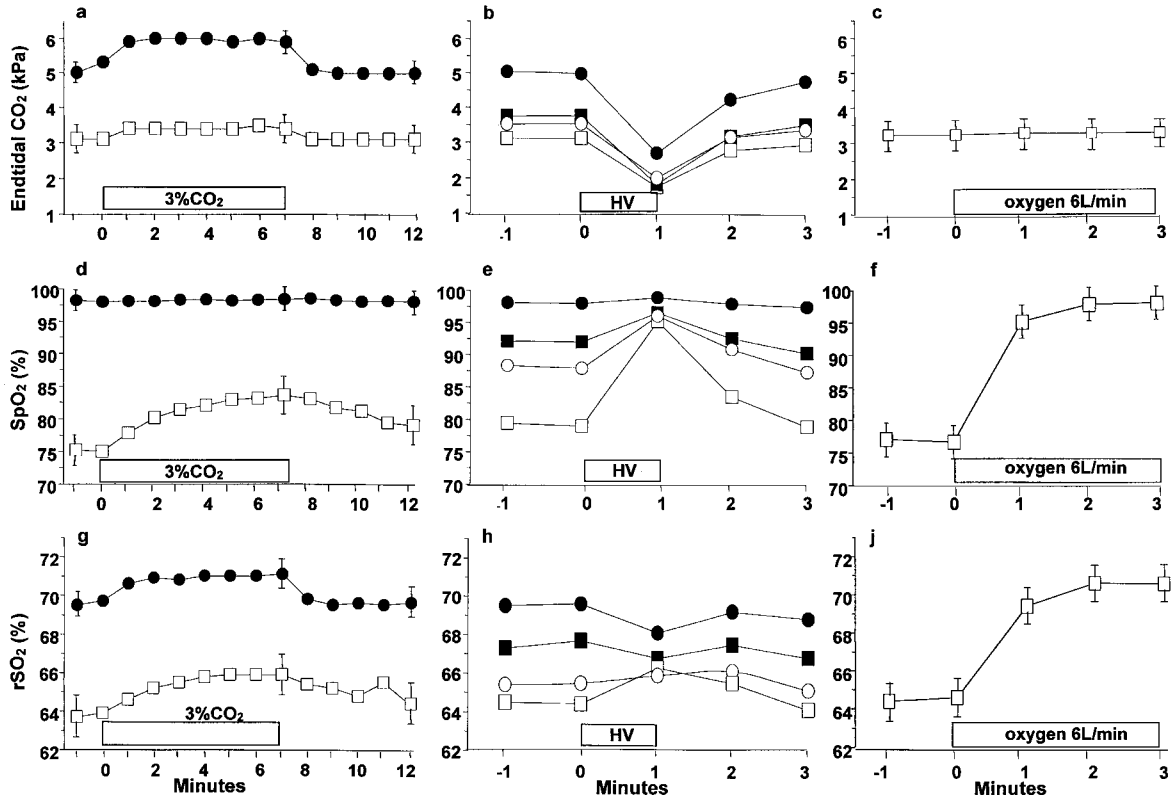

Figure 1 Changes in P_{ETCO_2}, peripheral O_2 saturation and cerebral regional O_2 saturation in response to CO_2, hyperventilation and oxygen

Panels (a), (b) and (c) show changes in P_{ETCO_2} in response to CO_2, hyperventilation (HV) and oxygen respectively; panels (d), (e) and (f) show changes in peripheral oxygen saturation (SpO_2) in response to CO_2, hyperventilation and oxygen respectively; and panels (g), (h) and (j) show changes in cerebral regional saturation (rSO_2) in response to CO_2, hyperventilation and oxygen respectively. Altitude: ●, sea level; ■, 2770 m; ○, 3560 m; □, 4680 m. All responses to CO_2 were analysed by repeated-measures analysis of variance. All other comparisons were made by paired *t* test; $n = 20$ for all experiments.

peripheral oxygen saturation ($76.7 \pm 7.9\%$ to $98.1 \pm 1.5\%$) (Figure 1f) and cerebral regional oxygen saturation ($64.6 \pm 3.3\%$ to $70.6 \pm 2.9\%$) (Figure 1j) rose significantly ($P < 0.001$).

DISCUSSION

This study enabled changes in cerebral regional oxygenation to be monitored at altitude following physiological manipulation for the first time. Increasing altitude resulted in an overall fall in cerebral HbO_2, a rise in cerebral $HbDO_2$ and a slight rise in cerebral total Hb. Changes in total Hb may be due to differing positions of the probe or changes in haemocrit or blood volume, and calculation of cerebral regional oxygen saturation allows for these. The equipment was robust, portable and easy to use in the field. Stable baseline measurements and sensitive responses to physiological manoeuvres were obtained. Concerns have been raised with regard to the reliability of the technique and the equipment [16], particularly during carotid endarterectomy, where contamination of the intracranial with extracranial signals could occur, with potentially devastating results [17]. However, the two-channel detection system theoretically enables the signal passing through the scalp and skull to be eliminated, and our own experience with carotid artery surgery under local anaesthetic using the Johnson and Johnson Critikon 2020 equipment supports this hypothesis. There were no wide variations in temperature at the different altitudes, and the use of the Tubifast bandage standardized probe application. The technique has also been validated in studies comparing NIRS with PET (positron-emission tomography) scanning [18], with ^{133}Xe washout techniques [19], with jugular venous saturation [20] and with internal carotid artery stump pressures [14]. The effect of medroxyprogesterone, which was being assessed as a respiratory stimulant, was to lower P_{ETCO_2} at all altitudes. This, however, did not alter the responses to CO_2, hyperventilation or oxygen. Further details on the medroxyprogesterone trial will be published elsewhere.

Breathing CO_2-enriched air caused a rise in P_{ETCO_2} both at sea level and at 4680 m, but, because the same

percentage enrichment was used, the rise in P_{ETCO_2} was less at high altitude. The associated rise in ventilatory drive was not measured. The increase in cerebral regional oxygenation at sea level was presumably due mainly to cerebral vasodilation, but at high altitude we were unable to distinguish between the effects on cerebral blood flow and effects on ventilation with increased peripheral oxygen saturation. However, these studies of cerebral regional oxygenation showed significant improvements in cerebral oxygenation, at least in the short term, while breathing CO_2, and are in keeping with the historical data and recommendations. The modest improvement in regional cerebral oxygenation was not nearly as great as that observed when oxygen was given.

Hyperventilation, both at sea level and at 2770 m, caused a marked fall in P_{ETCO_2}, a small rise in peripheral oxygen saturation and a small fall in cerebral regional oxygenation. The latter finding was presumably a result of cerebro-vasoconstriction. Hyperventilation at 4680 m increased both peripheral oxygen saturation and cerebral regional oxygenation. The almost normal peripheral oxygen saturation that was achieved on forced hyperventilation was only demonstrated in short-term studies, and it is unlikely that such respiratory drive could be sustained. The importance of these observations lies in the difference in responses to hyperventilation at different altitudes. The beneficial effect on cerebral regional oxygenation at 4680 m presumably was due to the increased arterial oxygen saturation (from 78% to 95%) having a greater effect than the small decrease in cerebral blood flow secondary to the relatively small further decrease in P_{aCO_2}.

The effects of oxygen were studied at 4680 m only; as expected, it had marked effects, improving peripheral oxygen saturation with no significant rise in P_{ETCO_2}. Other studies have demonstrated a fall in cerebral blood flow with supplemental oxygen, but all observe an improvement in symptoms. Cerebral regional oxygenation rose markedly on oxygen supplementation, reaching levels higher than those seen in the baseline sea level experiments, but not as high as those observed in the subjects at sea level on breathing 3% CO_2. Clearly there are considerable benefits of oxygen at altitude, although no attempt to assess AMS symptoms was made during these short-term studies.

In conclusion, cerebral oxygenation during physiological manipulations has been measured by NIRS for the first time at high altitude, and a fall in cerebral oxygenation was demonstrated with increasing altitude. However, this fall was less marked than the fall in peripheral oxygen saturation; this is likely to be due, at least in part, to the increase in cerebral blood flow seen at altitude. The use of NIRS has enabled us to study cerebral oxygen in response to physiological and therapeutic manoeuvres. Future studies should determine the optimum CO_2 concentrations to obtain maximum cerebral oxygenation at various altitudes, in both short-term and longer-term studies, and relate these changes to symptom scores of AMS.

ACKNOWLEDGMENTS

We are grateful for support given by the Mount Everest Foundation and the Arthur Thomson Trust.

REFERENCES

1 BMRES Mountain Sickness Study Group (1981) Acetazolamide in control of acute mountain sickness. Lancet **i**, 180–183
2 Hackett, P. H., Hollingshead, K. F., Roach, R. B. et al. (1987) Arterial saturation during ascent predicts subsequent acute mountain sickness. In Cold and Hypoxia (Sutton, J. R., Harrison, C. S. and Coates, G., eds.), p. 544, Praeger, New York
3 Sutton, J. R., Bryan, A. C., Gray, G. W. et al. (1976) Pulmonary gas exchange in acute mountain sickness. Aviat. Space Environ. Med. **47**, 1032–1037
4 Moore, L. G., Harrison, G. L., McCullough, R. E. et al. (1986) Low acute hypoxic ventilatory response and hypoxic depression in acute mountain sickness. J. Appl. Physiol. **60**, 1407–1412
4a Miescher-Rusch, F. (1885) Bemerkungen zur Lehre von der Athembewegungen. Arch. Anat. Physiol. Physiol. Abt. **9**, 355–361
4b Mosso, A. (1898) in Life of Man on the High Alps, pp. 287–307, Fischer Unwin, Stuttgart
5 Douglas, C. G., Haldane, J. S., Henderson, Y. and Schneider, E. C. (1913) Physiology observations made on Pike's peak. Philos. Trans. R. Soc. London **B203**, 185–318
6 Childs, S. B., Hamlin, H. and Henderson, Y. (1935) Possible value of inhalation of carbon dioxide in climbing great altitudes. Nature (London) **135**, 457–458
7 Harvey, T. C., Winterborn, M. H., Lassen, N. A. et al. (1988) Effect of carbon dioxide in acute mountain sickness: a rediscovery. Lancet **ii**, 639–641
8 Bartsh, P., Baumgartner, R. W., Waber, U., Maggiorini, M. and Oelz, O. (1990) Comparison of carbon dioxide enriched, oxygen enriched and normal air in treatment of acute mountain sickness. Lancet **336**, 772–775
9 Yang, S.-P., Bergo, G. W., Krasey, E. and Krasey, J. A. (1994) Cerebral pressure-flow and metabolic responses to substained hypoxia: effect of CO_2. J. Appl. Physiol. **76**, 303–313
10 Jensen, J. B., Wright, A. D., Lassen, N. A. et al. (1990) Cerebral blood flow in acute mountain sickness. J. Appl. Physiol. **69**, 430–433
11 Baumgartner, R. W., Bartsch, P., Maggiorini, M., Waber, U. and Oelz, O. (1994) Enhanced cerebral blood flow in acute mountain sickness. Aviat. Space Environ. Med. **65**, 726–729
12 McCormick, P. W., Stewart, M., Goetting, M. G. and Balakrishnam, G. (1991) Regional cerebrovascular oxygen saturation by optical spectroscopy in humans. Stroke **22**, 596–602
13 Kirkpatrick, P. J., Smielewski, P., Lam, J. M. K. and al-Rawi, P. (1996) Use of near infrared spectroscopy for the clinical monitoring of the adult brain. J. Biomed. Optics **1**, 363–372
14 Williams, I. M., Mortimer, A. J. and McCollum, C. N. (1996) Recent developments in cerebral monitoring: near-infrared light spectroscopy. An overview. Eur. J. Vasc. Endovasc. Surg. **12**, 263–271
15 Imray, C. H. E., Barnett, N. J., Walsh, S. et al. (1998) Near-infrared spectroscopy in the assessment of cerebral oxygenation at high altitude. Wilderness Environ. Med. **9**, 198–203

16 McKeating, E. G., Monjardino, J. R., Signorini, D. F., Souter, M. J. and Andrews, P. J. D. (1997) A comparison of the Invos 3100 and the Critikon 2020 near-infrared spectrophotometers as monitors of cerebral oxygenation. Anaethesia **52**, 136–140
17 Grubhofer, G., Lassnigg, A., Manlik, F., Marx, E., Trubel, W. and Hiesmayr, M. (1997) The contribution of extracranial blood oxygenation on near-infrared spectroscopy during carotid thromboendarterectomy. Anaesthesia **52**, 116–120
18 Villringer, K., Minoshima, S., Hock, C. et al. (1997) Assessment of local brain activation. A simultaneous PET and near-infrared spectroscopy study. Adv. Exp. Med. Biol. **413**, 149–153
19 Holzschuh, M., Woertgen, C., Metz, C. and Brawanski, A. (1997) Comparison of changes in cerebral blood flow and cerebral oxygen saturation measured by near-infra spectroscopy (NIRS) after acetazolamide. Acta Neurochir. **139**, 58–62
20 Henson, L. C., Calalang, C., Temp, J. A. and Ward, D. S. (1998) Accuracy of a cerebral oximeter in healthy volunteers under conditions of isocapnic hypoxia. Anaesthesiology **88**, 58–65

Received 25 June 1999/16 August 1999; accepted 4 October 1999