Cerebral haemodynamics in man: Clinical and applied observations.

Christopher H E Imray

MB BS, University of London, 1983

FRCS, Edinburgh, 1986

Diploma in Mountain Medicine, University of Leicester, 2004

A submission presented in fulfilment of the requirements of the
University of Glamorgan/Prifysgol Morgannwg
for the degree of

Doctor of Philosophy

by publication

November 2005

An overview of publications

Overview of publications

Acknowledgements:

To Sylvia, my wife and companion, for her unstinting support over many years. Without her understanding much of the research would not have been possible.

To my three children Caitlin, Oliver and Cameron.

To my parents for their encouragement, particularly in the early days.

To Alex Wright, Jo Bradwell, Kyle Pattinson and the Birmingham Medical Research Expeditionary Society for friendship, support, ideas and being willing subjects for many of the studies.

To Professor Bruce Davies and Professor Damian Bailey for support and guidance.

Abbreviations:

AMS	Acute mountain sickness
CBF	Cerebral blood flow
COC	Cerebral oxygen consumption
COD	Cerebral oxygen delivery
CNS	Central nervous system
$CMRO_2$	Cerebral metabolic rate of oxygen consumption
CPP	Cerebral perfusion pressure
CSF	Cerebrospinal fluid
CVR	Cerebrovascular resistance
EEG	Electro-encephalogram
HACE	High altitude cerebral oedema
HAPE	High altitude pulmonary oedema
HbO_2	Oxygenated haemoglobin
HDO_2	Deoxygenated haemoglobin
HITS	High intensity transient signals
ICAS	Internal carotid artery stenosis
ICP	Intracranial pressure
MCA	Middle cerebral artery
MES	Microembolic signals
MRI	Magnetic resonance imaging
NIRs	Near infrared spectroscopy
PaO_2	Partial pressure of arterial oxygen
$PaCO_2$	Partial pressure of arterial carbon dioxide
PET	Positive emission tomography
rSO_2	Regional cerebral oxygenation
SaO_2	Arterial haemoglobin oxygen saturation
SCUBA	Self-contained underwater breathing apparatus
TCD	Trans-cranial Doppler
TIA	Transient ischaemic attack
TotHb	Total haemoglobin
VEGF	Vascular endothelial growth factor

1) Abstract

This overview reviews seventeen publications between 1995 and 2005. CHE Imray was the first author of eleven of the papers, the senior author of four and a major contributor to two of the publications. The overview should be read in conjunction with the full copies of the seventeen publications (Appendix 2).

The brain is exquisitely sensitive to oxygen requiring a constant supply of adequately oxygenated blood to function normally. Cerebral oxygen delivery is dynamic, and alters rapidly in response to changes in physiological and pathological stimuli. Interference with cerebral oxygen delivery, either as a result of decreased cerebral blood flow, decreased arterial oxygenation or particulate matter (cerebral microemboli) within the blood can all rapidly result in temporary or permanent loss of function within minutes.

The author has used non-invasive cerebral perfusion imaging techniques, initially in the clinical setting (in clinic, at the bedside and in the operating theatre) and later transferring these methods to the field setting at high altitude. As a result of these studies, new insights into cerebral perfusion have been gained. Novel concepts such as 'virtual altitude' and 'partitioning of arterial and venous volumes' have been developed. New equipment has been designed and developed, such as the recumbent, collapsible, portable exercise bike. Finally new clinical treatments have been developed, including an apparently safe way to treat the high-risk group of patients with crescendo transient ischaemic attacks or mini-strokes, greatly reducing the risk of developing a subsequent major stroke.

The work submitted for consideration for a PhD by publication represents ten years of investigation in two closely inter-related fields. The aim of the submission is to provide a background to the seventeen publications (Appendix 2) allowing them to be seen in context to existing knowledge. Appendix 3 contains twelve additional communications that have either been published, or accepted for publication after the original list of seventeen publications was submitted to the University of Glamorgan. They confirm the author's ongoing interest and contributions to this field of research.

2) Chronological list of publications

a) Altitude related publications

1. Intracranial pressure at high altitude and acute mountain sickness.
AD Wright, **CHE Imray**, MSC Morrisey, RJ Marchbanks and AR Bradwell
Clinical Science 1995; **89**: 201-204.

2. Near-infrared spectroscopy in the assessment of cerebral oxygen at high altitude.
CHE Imray, NJ Barnett, S Walsh, T Clarke, J Morgan, D Hale, H Hoar, D Mole, I Chesner, AD Wright.
Wilderness and Environmental Medicine 1998; **9**: 198-203.

3. Cerebral oxygen at high altitude and the response to carbon dioxide, hyperventilation and oxygen.
CHE Imray, S Brearey, T Clarke, S Walsh, J Morgan, AD Wright.
Clinical Science 2000; **98**:159-164.

4. Carbon dioxide contributes to the beneficial effect of pressurisation in a portable hyperbaric chamber.
CHE Imray, S Brearey, T Clarke, S Walsh, J Morgan, AD Wright.
Clinical Science 2001; **100**: 151-157.

5. The effect of supplementary carbon dioxide, oxygen, and a mix of carbon dioxide and oxygen on arterial blood gases and on peripheral, muscle and cutaneous oxygenation at 150m and 3459m.
CHE Imray, S Walsh, T Clarke, J Morgan, H Hoar, T Harvey, AR Bradwell, AD Wright.
Clinical Science 2003; **104**: 1-8.

6. Perfusion cerebrale en haute altitude (High Altitude Cerebral Perfusion).
CHE Imray, C Chan, AW Wright.
'Sang, Thrombose, Vaisseaux' (Blood, thrombosis, vessels) 2003; **15**: 17-27.

7. Partitioning of arterial and venous volumes in the brain under hypoxic conditions.
CB Wolff, **CHE Imray**
Advances in Experimental Medicine and Biology. 2003; **540**: 19-32.

8. Medoxyprogesterone at high altitude and in the prevention of acute mountain sickness.
AD Wright, MF Beazley, AR Bradwell, IM Chesner, RN Clayton, PJG Forster, P Hillenbrand, **CHE Imray**.
Wilderness and Environmental Medicine 2004; **15(1):** 25-31.

9. Effect of exercise on cerebral perfusion in humans at high altitude
C.H.E Imray, S. D. Myers, K.T.S. Pattinson, A.R. Bradwell, C. W. Chan, S.Harris, P.Collins, A.D.Wright and the Birmingham Medical Research Expeditionary Society.
Journal of Applied Physiology 2005; **99(2)**: 699-706.

b) Carotid surgery related publications

10. 'A comparison of the Invos 3100 and the Critikon 2020 near-infrared spectrophotometers as monitors of cerebral oxygenation'
CHE Imray and C Knickenberg.
Anaesthesia 1997; **52(8)**: 805.

11. Near-infra red cerebral spectroscopic monitoring of patients undergoing carotid endarterectomy under loco-regional anaesthesia.
D Williams, P Laws, **CHE Imray**, S Lambert, P Horrocks.
Annals of the Royal College of Surgeons of England 1999:**81**; 431-432.

12. Blood pressure manipulation during loco-regional anaesthetic carotid surgery.
CHE Imray, M Mead, A Thacker and W Dimitri.
British Journal of Anaesthesia, 2002; **88(2)**: 303-304.

13. Crescendo TIAs: The use of pre-operative TCD directed I.V. Dextran therapy to control symptoms and emboli prior to elective carotid endarterectomy.
N Lennard, C Vijayasekar, C Tiivas, D Higman and **CHE Imray**.
British Journal of Surgery 2003; **90**: 166-170.

14. Timing of surgery in symptomatic carotid disease.
CHE Imray, DJ Higman, C Tiivas.
Lancet 2004; **363(9420)**:1553-4.

15. Validity of near-infrared cerebral spectroscopy.
K Pattinson, Clutton-Brock, **CHE Imray**
Anaesthesia. 2004; **59(5)**:507-8.

16. Screening for carotid disease and 'stroke prevention units'
CHE Imray and K Pattinson. British Medical Journal, 2004; **329(7478)**: 1344.

17. Are some strokes preventable? A potential role for transcranial Doppler in TIAs of carotid origin.
CHE Imray and C Tiivas. Lancet Neurology 2005; **4(9)**: 580-6.

3) List of figures with acknowledgements

Figure 6 Page 21

Metabolic regulation

From: *Lou HC, Edvinsson L, MacKenzie ET. The concept of coupling blood flow to brain function: revision required? Ann.Neurol. 1987;* ***22****: 289-297*

Figure 7 Page 23

Near infrared cerebral spectroscopy:

From: *Williams IM, Vohra R, Farrel A, Picton AJ, Mortimer AJ, McCollum CN. Cerebral oxygen saturation, transcranial Doppler ultrasonography and stump pressure in carotid surgery. British Journal of Surgery. 1994;* ***81(7)****: 960-64*

Figure 8 Page 24

Relationship between altitude and barometric pressure:

From: *Heath D and Williams DR. High altitude medicine and pathology. 4th Edition. Oxford University Press, Oxford.* 1995

Figure 9 a, b Page 30

Oxygen apparatus for 1924 British Everest Expedition:

From: *West JB. 'High Life' p184, 185 ISBN 0-19 512194-5*

Figure 10 Page 33

Pathogenesis of atheroma

Artwork by *CW Chan*

Figure 11 a, b Page 36

Transcranial Doppler: Platelet micro embolus:

From: ***CHE Imray****, C Tiivas. Are some strokes preventable? A potential role for transcranial Doppler in TIAs of carotid origin. Lancet Neurology 2005;* ***4(9)****: 580-6*

Figure 12 Page 42

Sequential changes in tympanic membrane displacement with altitude:

From: *AD Wright, **CHE Imray**, MSC Morrisey, RJ Marchbanks and AR Bradwell. Intracranial pressure at high altitude and acute mountain sickness. Clinical Science 1995; **89**: 201-204*

Figure 13 Page 44

Reduction in cerebral NIRs and peripheral arterial saturations with increasing altitude

From: ***CHE Imray**, NJ Barnett, S Walsh, T Clarke, J Morgan, D Hale, H Hoar, D Mole, I Chesner, AD Wright..Near-infrared spectroscopy in the assessment of cerebral oxygen at high altitude. Wilderness and Environmental Medicine 1998; **9**: 198-203*

Figure 14 Page 48

Changes in $PiCO_2$, $PeCO_2$, peripheral arterial and cerebral oxygenation in a portable hyperbaric chamber at altitude

From: ***CHE Imray**, S Brearey, T Clarke, S Walsh, J Morgan, AD Wright Carbon dioxide contributes to the beneficial effect of pressurisation in a portable hyperbaric chamber..Clinical Science 2001; **100**: 151-157.*

Figure 15 Page 50

Changes in arterial saturations and blood gases with supplementary carbon dioxide, oxygen and a mix of carbon dioxide/oxygen at 150m and 3459m

From: *The effect of supplementary carbon dioxide, oxygen, and a mix of carbon dioxide and oxygen on arterial blood gases and on peripheral, muscle and cutaneous oxygenation at 150m and 3459m..**CHE Imray**, S Walsh, T Clarke, J Morgan, H Hoar, T Harvey, AR Bradwell, AD Wright.Clinical Science 2003; **104**: 1-8*

Figure 16 Page 56-57

Alticycle™

From: ***C.H.E Imray**, S. D. Myers, K.T.S. Pattinson, A.R. Bradwell, C. W. Chan, S.Harris, P.Collins, A.D.Wright and the Birmingham Medical Research Expeditionary Society. Effect of exercise on cerebral perfusion in humans at high altitude Journal of Applied Physiology 2005; **99(2)**: 699-706.*

Figure 17 Page 70

Change in MCAV with exercise at SL, 3,610m, 4,750m and 5,260m

From: ***C.H.E Imray**, S. D. Myers, K.T.S. Pattinson, A.R. Bradwell, C. W. Chan, S.Harris, P.Collins, A.D.Wright and the Birmingham Medical Research Expeditionary Society. Effect of exercise on cerebral perfusion in humans at high altitude Journal of Applied Physiology 2005; **99(2)**: 699-706.*

Figure 18 Page 71

Change in $rSO_2$with exercise at SL, 3,610m, 4,750m and 5,260m

From: ***C.H.E Imray**, S. D. Myers, K.T.S. Pattinson, A.R. Bradwell, C. W. Chan, S.Harris, P.Collins, A.D.Wright and the Birmingham Medical Research Expeditionary Society. Effect of exercise on cerebral perfusion in humans at high altitude Journal of Applied Physiology 2005; **99(2)**: 699-706.*

Figure 19 Page 73

Change in cerebrovascular resistance with exercise at SL, 3,610m, 4,750m and 5,260m

From: ***C.H.E Imray**, S. D. Myers, K.T.S. Pattinson, A.R. Bradwell, C. W. Chan, S.Harris, P.Collins, A.D.Wright and the Birmingham Medical Research Expeditionary Society. Effect of exercise on cerebral perfusion in humans at high altitude Journal of Applied Physiology 2005; **99(2)**: 699-706.*

Figure 20 Page 75

Change in cerebral oxygen delivery with exercise at SL, 3,610m, 4,750m and 5,260m

From: ***C.H.E Imray**, S. D. Myers, K.T.S. Pattinson, A.R. Bradwell, C. W. Chan, S.Harris, P.Collins, A.D.Wright and the Birmingham Medical Research Expeditionary Society. Effect of exercise on cerebral perfusion in humans at high altitude Journal of Applied Physiology 2005; **99(2)**: 699-706.*

Figure 21 Page 78

Composite schematic of symptomatic carotid artery stenosis

From: ***CHE Imray**, C Tiivas. Are some strokes preventable? A potential role for transcranial Doppler in TIAs of carotid origin. Lancet Neurology 2005; **4(9)**: 580-6*

Figure 22 Page 82

Surgical technique and carotid plaque appearance

From: ***CHE Imray**, C Tiivas. Are some strokes preventable? A potential role for transcranial Doppler in TIAs of carotid origin. Lancet Neurology 2005; **4(9)**:*

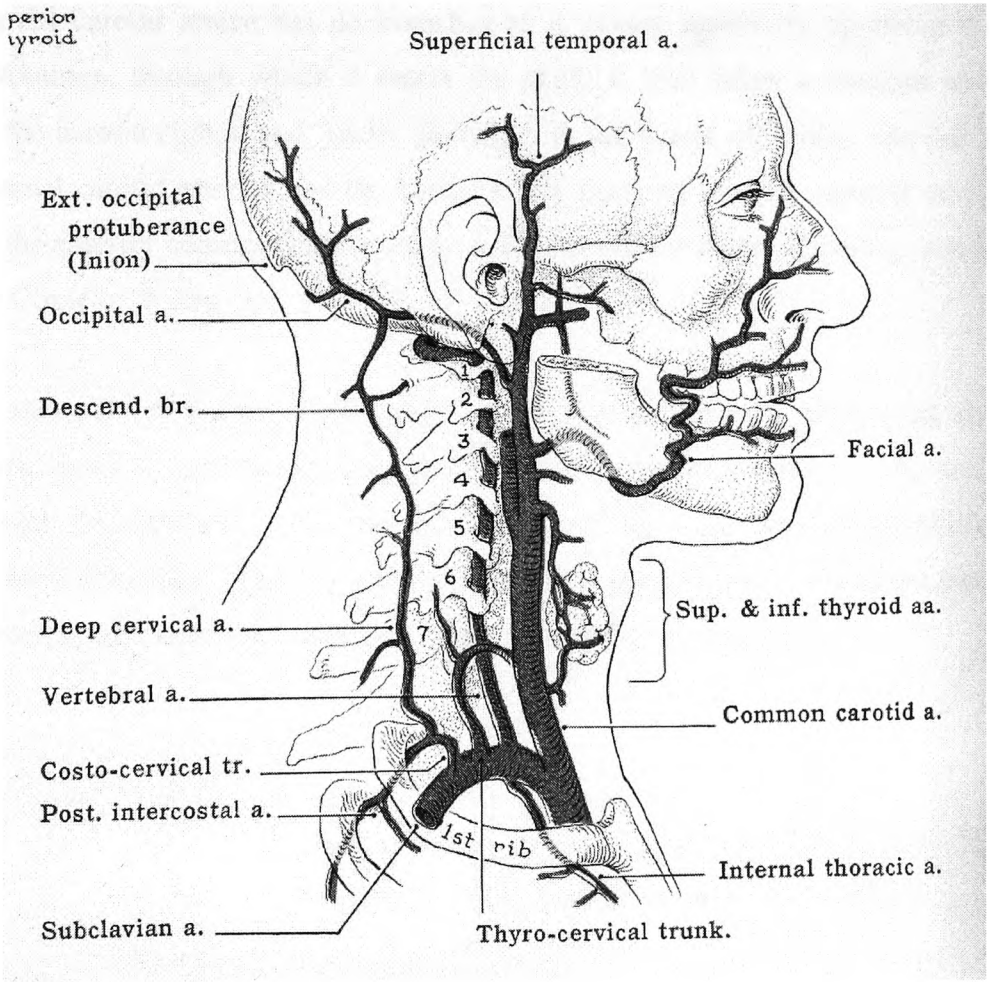
3) Introduction

a) Anatomy

It has been known since ancient time that occlusive pressure on both the carotid arteries will rapidly result in unconsciousness, and the word Καροτιϛ (karotis) reflects this knowledge being the ancient Greek for deep sleep. Although the brain is only about 2% of the total body weight, it receives 15-20% of the body's blood (1). Brain cells are exquisitely sensitive to hypoxia and the autoregulatory system is designed to maintain balance of cerebral oxygen delivery and cerebral oxygen consumption (1). Blood is supplied by two pairs of arteries, the internal carotid arteries and the vertebral arteries. The vertebral arteries join to form the basilar artery. The internal carotid arteries and the basilar artery form a ring of vessels called the Circle of Willis (2).

Figure 1

Extracranial blood supply: *From 'Grants Atlas of Anatomy' 7th Edition.*

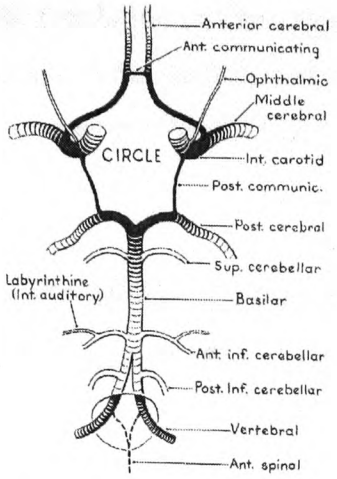


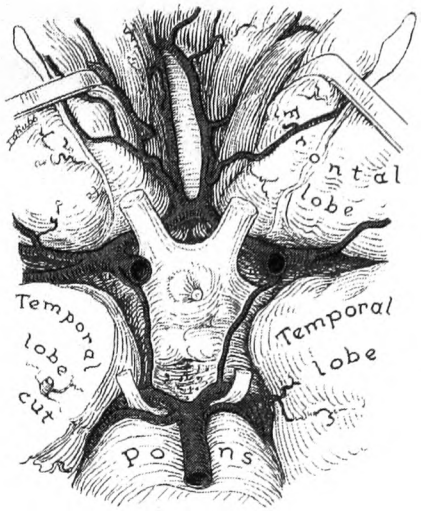
On the right side, the innominate artery (otherwise known as the brachio-cephalic trunk) arises from the arch of the aorta, bifurcates behind the right sterno-clavicular joint into the right common carotid artery and the right subclavian artery. The right vertebral artery arises from the right subclavian artery. The left common carotid artery arises directly from the arch of the aorta, where it lies in front of the left subclavian artery up to the level of the left sterno-clavicular joint, here the two arteries diverge. The left vertebral artery arises from the left subclavian artery. Both common carotid arteries run superiorly within the carotid sheath and adjacent to the internal jugular veins and the vagus nerves. The common carotid arteries bifurcate at the level of the thyroid cartilage into the internal and external carotid arteries. The external carotid artery rapidly divides into a number of branches to supply the face, head and neck. The internal carotid artery at this level is somewhat greater in diameter than the rest of the internal carotid artery and this portion is known as the carotid bulb. The carotid body is a small yellow-grey structure, which lies at the bifurcation of the common carotid lying between the internal and external carotid arteries, and is innervated by the glossopharyngeal nerve, and has a role in the control of blood pressure and pH. The internal carotid artery has no branches as it passes superiorly up towards the carotid foramen, through which it enters the skull; it then takes a tortuous course through the carotid siphon and finally passes on to the Circle of Willis. The left and right internal carotid arteries and the basilar artery merging into the anterior cerebral arteries, the anterior communicating artery and the posterior-communicating artery, to form the Circle of Willis (3).

On both sides, the first part of the vertebral artery arises from the subclavian artery and passes upwards and rapidly disappears into sixth cervical vertebra. The second parts of both the vertebral arteries ascend through the upper six cervical vertebrae in the transverse foramina. The left and right vertebral arteries join to form the basilar artery which in turn enters the posterior part of the Circle of Willis.

Figure 2 a,b

Circle of Willis: *From 'Grants Atlas of Anatomy' 7th Edition.*





b) Control of cerebral blood flow.

Although the human adult brain accounts for only approximately 2% of total body weight, cerebral blood flow (CBF) at 50 ml/min/100g of brain tissue accounts for 15-20% of the resting cardiac output (1). This reflects the high cerebral metabolic rate ($CMRO_2$) and so high demand for oxygen by brain tissue. The brain consumes on average 3.3 ml O_2/min/100g, which again is about 20% of the total body consumption at rest (4). Cerebral blood flow is kept constant over a wide range of conditions in order to maintain cerebral oxygen delivery by a mechanism called autoregulation. Maintaining adequate CBF following injury is particularly important in patients in the intensive care unit setting. We have recently published a review of the various techniques commonly used (5). The five major determinants of cerebral blood flow are blood pressure, arterial carbon dioxide, arterial oxygen, metabolic factors and neural factors.

I) Blood pressure and the auto-regulation of cerebral blood flow

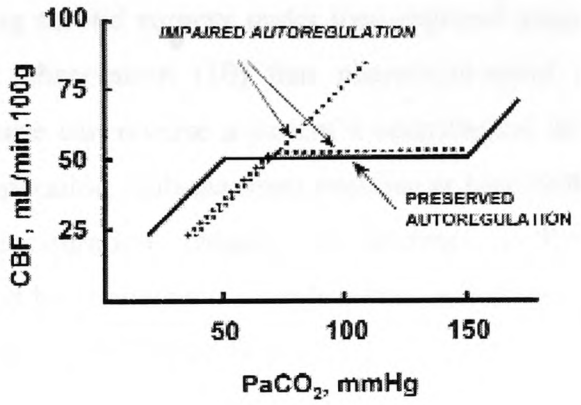
Cerebral blood flow (CBF) autoregulation is the ability of the brain to maintain total and regional CBF constant despite large changes in systemic arterial blood pressure (6). The cerebral perfusion pressure represents the difference between mean systemic arterial pressure and cerebral outflow pressure. The out flow pressure is the higher of

the cerebral venous pressure (jugular venous bulb pressure) and the intracranial pressure. In health, autoregulation is generally expressed as the relationship between CBF and arterial blood pressure since cerebral venous and CSF pressures are low. CBF auto regulation can be impaired or lost following injury or surgery and the monitoring and maintenance of adequate cerebral perfusion is a crucial component of a neuro-intensive care unit (5).

Figure 3

Cerebral blood flow and auto regulation:

Taken from Newfield P & Cottrell JE (Ref 7)



Preserved cerebral pressure auto regulation (solid line) and impaired auto regulation (dashed lines)

The cerebral vascular resistance (CVR) can be expressed by Poiseuille's Law as:

Resistance to flow = $8\ hl / \pi r^4$

Or

$CVR = CPP/CBF = (8 / \pi) \times h \times (l / r^4)$

Where $(8 / \pi)$ is a constant for calculation, h the blood viscosity, l the length and r the radius of the vessel, and CPP is the cerebral perfusion pressure. Importantly the radius enters to the fourth power in the equation, making it the most efficient means of controlling vascular resistance.

In adults under normal conditions, auto regulation of CBF occurs between a cerebral perfusion pressure of roughly 60 mmHg to 150 mmHg (6). Vascular smooth muscle possesses an intrinsic capacity to constrict in response to rises in wall tension and conversely to relax when there are falls in wall tension. Cerebral vasodilatation is maximal at the lower limit of auto regulation, and if the blood pressure falls further the CBF falls passively with cerebral perfusion pressure. At the upper limits of blood pressure controlled auto regulation vasoconstriction is maximal; a further rise in blood pressure may cause the vessels to vasodilate resulting in a rise in CBF and possible disruption of the blood-brain-barrier (5, 6, 8). Metabolic mediators, such as adenosine, can also be involved in the low-pressure range of autoregulation (8).

Our experience during carotid surgery under loco-regional anaesthesia (9) confirmed Stoneham's original observation (10) that pharmacological augmentation of the systemic blood pressure can reverse a patient's neurological deficit during the cross clamp phase of the operation. Sub-maximal exercise at high altitude results in further peripheral arterial desaturation. Despite the decrease in PaO_2, cerebral oxygen delivery is maintained by a number of mechanisms including a rise in arterial blood pressure and increased cerebral blood flow (11).

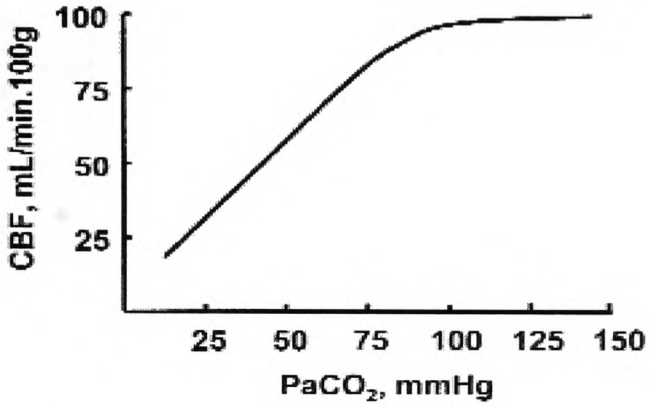
II) Arterial carbon dioxide and the auto-regulation of cerebral blood flow

Arterial carbon dioxide ($PaCO_2$) is a major determinant of CBF, being a powerful cerebral vasodilator (12). A reduction in $PaCO_2$ has strong vasoconstrictor effects on the cerebral blood vessels, reducing cerebral blood flow. In normotensive adults CBF increases almost linearly when arterial PCO_2 ($PaCO_2$) increases from 20 to 80 mmHg. Global CBF varies by about 2 to 4 % for each mmHg change in $PaCO_2$ (13). The effects of $PaCO_2$ on the cerebral circulation are regulated by a complex and interrelated system of mediators. The initial stimulus of CO_2 -induced vasodilatation is a decrease in brain extra cellular pH, further mediated by nitric oxide, prostanoids, cyclic nucleotides, potassium channels, and a decrease in intracellular calcium concentration as a final common mediator (14).

Figure 4

CBF and arterial carbon dioxide:

Taken from Kety SS, Schmidt CF (Ref 12)



Changes in CBF in relationship with P_aCO_2

Systemic blood pressure has an important influence on how $PaCO_2$ affects CBF. Moderate hypotension impairs the response of the cerebral circulation to changes in $PaCO_2$, and severe hypotension abolishes it altogether (15). Similarly, $PaCO_2$ modifies blood pressure determined auto regulation, and from hypercapnia to hypocapnia there is a widening of the auto regulation plateau (16).

We have published extensively on the subject of the effects that changing $PaCO_2$, observed on ascent to altitude has on cerebral perfusion, and this will be discussed further in section 4 of this overview of publications (11, 17, 18, 19).

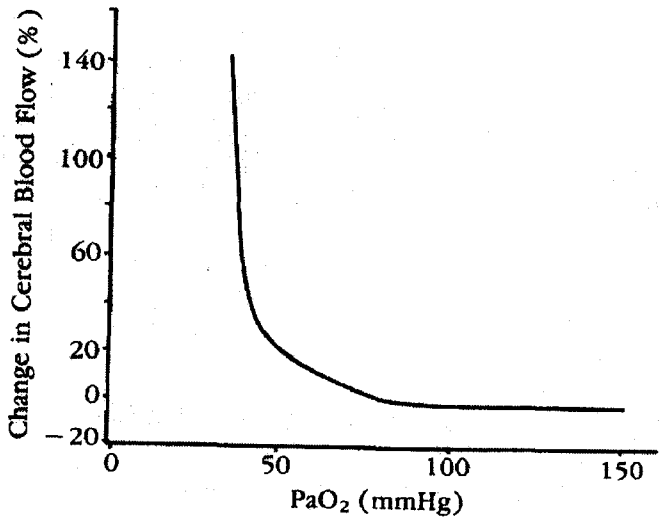
II) Arterial oxygen and the auto-regulation of cerebral blood flow

CBF remains constant above an arterial oxygen (PaO_2) level of 50mmHg, and increases once PaO_2 drops below 50 mmHg maintaining a constant level of cerebral oxygen delivery (12). In normocapneic ventilated rats, a fall in PaO_2 from 130mmHg to 60 mmHg caused little change in cerebral blood flow; however a further reduction in PaO_2 to 25mmHg resulted in a fivefold increase in cerebral blood flow (20).

Figure 5

CBF and Arterial Oxygen:

Taken from Newfield P & Cottrell JE (Ref 7).



Relationship between CBF and PaO_2 showing almost no effect on CBF in the normoxaemic range. CBF is greater if PaO_2 is less than 50 mmHg.

Hypoxia acts directly on cerebral tissue to promote the release of adenosine, and in some cases prostanoids which contribute significantly to cerebral vasodilatation. Hypoxia also acts directly on cerebrovascular smooth muscle to produce hyper polarisation and reduce calcium uptake, both mechanisms enhancing vasodilatation. Hypoxia also appears to promote release of both relaxing and constricting factors from the endothelium, the combined effect of which can either promote or attenuate vasodilatation depending on the artery and species under study.

In addition to chemical stimuli in blood, chemical stimuli present in the CSF such as neurotransmitters that can also affect cerebral haemodynamics. Neurotransmitters can reach vasoactive levels in perivascular CSF as a result of synaptic overflow during neuronal activation or in pathological conditions.

We have published extensively on the subject of the effects that changing PaO_2 observed on ascent to altitude has on cerebral perfusion, and this will be discussed further in section 4 of this overview of (11, 17, 18, 19).

IV) Metabolic auto-regulation of cerebral blood flow

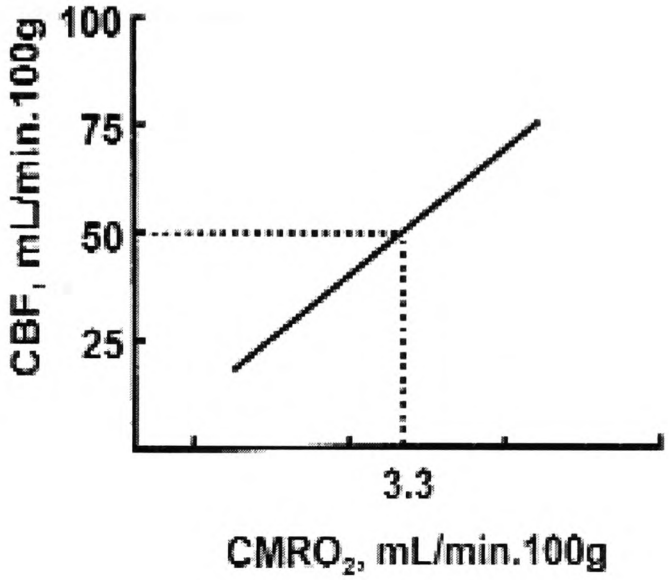
Under most circumstances cerebral blood flow remains remarkably constant (22), and there appears to be a precise matching of cerebral blood flow (and cerebral oxygen delivery) and cerebral oxygen consumption ($CMRO_2$). Cerebral metabolic regulation is the process of adaptation of CBF to the metabolic demands of the brain (23). This matching or coupling occurs regionally, with increases in local blood flow when tissue is metabolically active; for instance there is an increase in blood flow to the visual cortex when it is stimulated (24). The coupling also occurs globally with reductions in blood flow during sleep (25).

CBF is linked to brain function and metabolism so that CBF varies in parallel with $CMRO_2$. This coupling of flow to metabolism is a rapid and precise regulation so that local increases in metabolic demand can be rapidly met by a local increase in CBF and substrate delivery. Several vasoactive metabolic mediators have been proposed for cerebral regulation, including hydrogen ion, potassium, CO_2, adenosine, glycolytic intermediates, phospholipid metabolites (23), and nitric oxide (26). In humans, flow-metabolism coupling is evident during a variety of motor and cognitive tasks that can be mapped using CBF techniques (27).

Figure 6

Metabolic auto-regulation:

Taken from Lou HC et al (Ref 23)



Graph illustrating coupling between CBF and $CMRO_2$. Corresponding normal CBF and $CMRO_2$ values are represented in dashed lines

The global relationship between CBF and $CMRO_2$ can be expressed by the Fick equation where $DajO_2$ is the arterio-jugular venous content difference for oxygen:

$CMRO_2 = DajO_2 \times CBF$ or $DajO_2 = CMRO_2 / CBF$.

We have recently published a review article on techniques to assess cerebral perfusion and metabolism and other articles on similar subjects (6, 9, 11, 17, 18, 19, 21).

V) Neural auto-regulation of cerebral blood flow

Unlike other vascular beds, there is a relative lack of humoral and autonomic control over normal cerebrovascular tone. There is only a small change in CBF with maximal autonomic stimulation (28).

c) Background of methods to determine cerebral perfusion at sea level

I) Nitrous oxide

Cerebral blood flow was first measured using nitrous oxide washout techniques in 1948, and this technique remains the gold standard (29). Kety and Schimdt described the method which involves the introduction of a low proportion (5-10%) of nitrous oxide (NO_2) into the subject's inhalation mixture. The arterial concentration of NO_2 reaches saturation faster than the cerebral venous drainage. The cerebral blood flow (CBF) is obtained by applying Fick's principle to the difference in the arterial and the venous concentrations of NO_2 at fixed time points.

II) ^{133}Xenon

^{133}Xenon is an inert radioactive gas. Following the injection or inhalation of ^{133}Xenon it is possible to measure the rate of arrival of the radioisotope using a scintillation detector over the cranial vault. It is also possible, using multi channel detectors, to assess regional cerebral blood flow (30). This technique has been extensively developed allowing accurate assessments of both global and regional cerebral blood flow both clinically and at altitude (31).

III) Trans-cranial Doppler assessment of the middle cerebral artery velocity

Trans-cranial Doppler is a non-invasive ultrasound-based technique that can be used to measure the velocity of blood within the large arteries of the cerebral arterial circulation. The middle cerebral artery is insonated with a 2MHz pulsed signal transmitted through the temporal bone to a depth between 4.5-6.0cm. The signal is reflected by the solid components of the blood (mostly red blood cells) and distorted by according to the Doppler-shift principle. The reflected waveform gives information about systolic, diastolic and mean arterial velocities (32).

IV) Near infrared cerebral spectroscopy (NIRs)

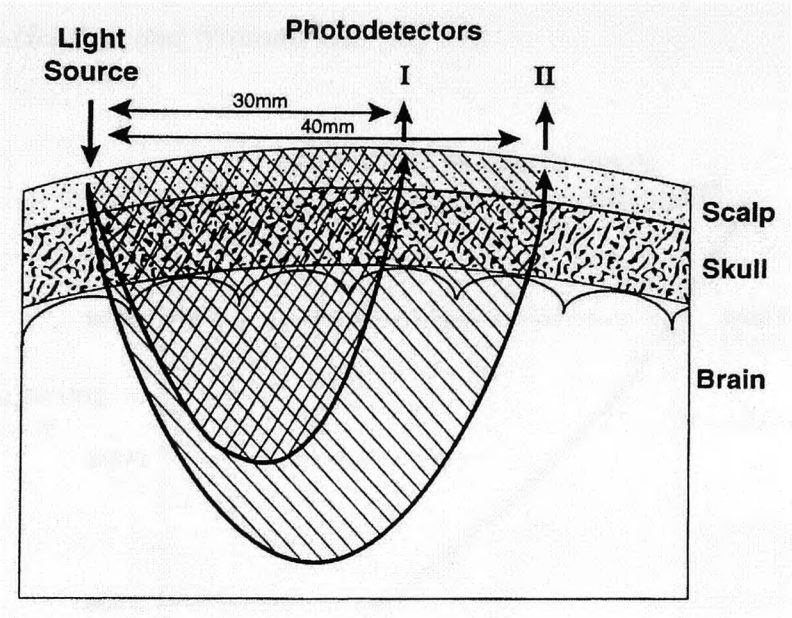
Reflected near infra-red spectroscopy uses light in the NIR spectrum (650-1100nm), and like pulse oximeters and mixed venous oximeters, uses the principles of light transmission and absorption to measure concentrations of oxygenated and deoxygenated haemoglobin in cerebral tissue. The NIRs technique has been described to date in the assessment of cerebral tissue, and many use a two-sensor technique to enable the scalp/skull contribution to be eliminated. By subtracting the readings

obtained from photo detector I from the readings from photo detector II, data regarding tissue oxygenation at a depth of 2.5-5 cms is collected. As such the technique provides information not currently available by any other modality. Reflected near-infrared light spectroscopy allows continuous non-invasive cerebral oxygenation monitoring. The technique was first described in adults in 1991 (33) and has widespread clinical applications.

Figure 7

Near infrared cerebral spectroscopy:

Taken from Williams IM et al (Ref 34)



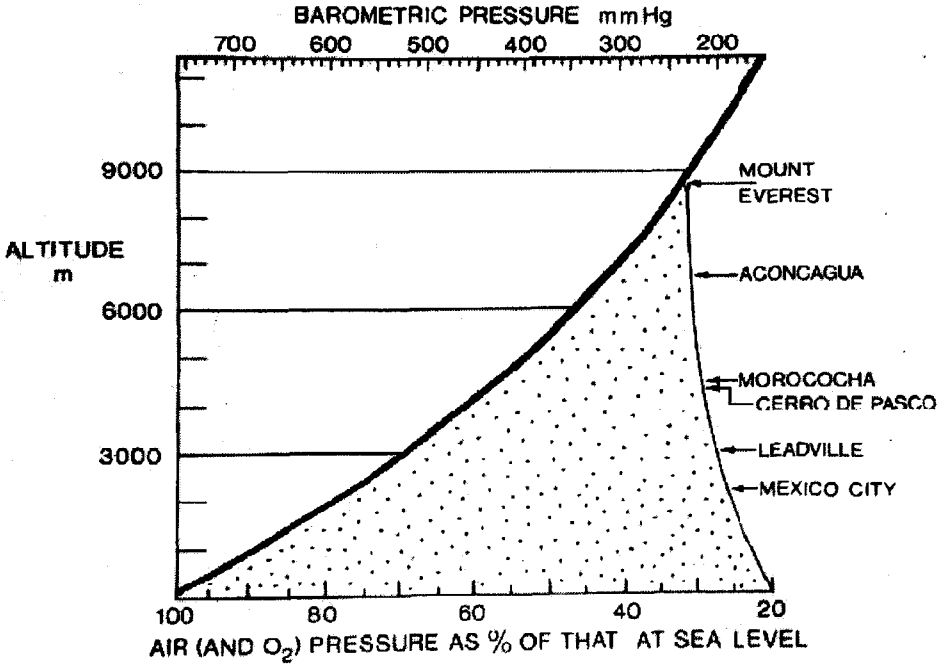
Although NIRs techniques remain mainly a research tool, the technique has been shown to precisely track changes measured in jugular venous bulb saturations in healthy volunteers under conditions of isocapneic hypoxia (24). Assessment of cerebral perfusion under hypoxic circumstances needs to be performed with isocapnea, in order that only one parameter is changed at a time. Isocapnea can be achieved using computerised end tidal forcing techniques (24) where the $FiCO_2$ is varied on a breath by breath basis. The technique has also been validated comparing NIRs with PET scanning, with ^{133}Xenon washout techniques, and with internal carotid artery stump pressures (25). NIRs has been found to be a reliable and reproducible method for evaluation of cerebrovascular reactivity and hypercapnia has been shown to cause a vasodilatation limited to the resistive vessels of the brain (26).

d) Relationship between altitude and barometric pressure

On ascent to altitude there is a fall in ambient barometric pressure (37). Although the percentage of oxygen remains unchanged there is a reduction in the partial pressure of inspired oxygen (PiO_2). In addition to the major changes in PiO_2 there are minor variations, at any given altitude, in barometric pressure observed with both latitude (38) and season (37).

Figure 8

Relationship between altitude and barometric pressure:
Taken from Heath D and Williams DR. (Ref 39).



e) Cerebral perfusion at altitude

In healthy individuals at altitude the factors affecting cerebral perfusion are complex. Whilst there is a hypoxic cerebral vasodilatation, the reduced PaO_2 also results in an increase in the rate and depth of respiration (40). This in turn causes a reduction in $PaCO_2$, which will result in a reduction in the cerebral blood flow (41). It is the interaction between these two opposing effects that will determine the cerebral blood

flow at any particular altitude. There is widespread evidence that ascent to altitude increases cerebral blood flow. In 1966 Severinghaus (42), using the nitrous oxide technique of Seymour Kety (29), demonstrated that cerebral blood flow increased by 24% in the first 6-12 hours at altitude but this fell to 13% above sea level values at 3-5 days (42). These observations were confirmed using trans-cranial Doppler techniques with a 20% rise observed at 18-44 hours returning towards sea level values at 4-12 days. There were no differences between sea level and 4300m TCD cerebral blood flow (CBF) during prolonged exercise. Further evidence of a rise in CBF at altitude is shown in a study that showed a reduction in the mean circulation time of fluorescein through the retina at altitude (43). There appears to be general agreement that there is an initial rise in cerebral blood flow on acute exposure to high altitude, and this gradually returns towards the baseline level with acclimatisation.

I) Cerebral perfusion in acute mountain sickness

Acute mountain sickness (AMS) is a common clinical problem affecting individuals who ascend to high altitude. All travellers to altitudes over 2,500m (8000ft) are potentially susceptible to AMS (44, 45). Symptoms include headache, lethargy, shortness of breath, sleep disturbance, loss of appetite, nausea and vomiting, and the symptoms usually appear within 6-12 hours after arrival at altitude (46, 47). In the Himalayas the prevalence of AMS has been reported to vary from 43 to 63% (46) and in the Alps from 9 to 69% (47). The severity depends upon a number of factors including rate of ascent, the altitude achieved, recent previous acclimatisation, and the susceptibility of the individual to the syndrome (48).

In AMS there is evidence of an increase in CBF, however the pathophysiology of high altitude cerebral oedema (HACE) and AMS in general is uncertain but may in part be a result of a generalised capillary leakage rather than increased cerebral blood flow alone. Conflicting views exist regarding changes in CBF with AMS. Jensen et al demonstrated a rise in ^{133}Xenon cerebral blood flow in all subjects, independent of AMS symptoms (31). However cerebral blood flow is thought by some to rise in acute mountain sickness (49). The observed rise in CBF was postulated to be due to the lower PaO_2 seen in the subjects with AMS. More recently the same group performed a decompression chamber study and demonstrated no link between acute mountain sickness and cerebral blood flow (50). In the first (field study), CBF and

AMS was evaluated after 24 h at 4,559-m altitude. The second (chamber study) assessed alterations in CBF and AMS scores during the first 6 h at the same simulated altitude. The second study differed from the first (field study) in the absence of exercise, cold, and other adjuncts to the mountaineering experience. It has been shown that in subjects with AMS, the cerebral haemodynamic response or the ability of the cerebral vessels to vasoconstrict in response to acute hyperventilation is increased compared to subjects without AMS (51). The trans-cranial Doppler middle cerebral artery velocity (TCD MCA) was also found to be higher in subjects with the lowest SaO_2 (51). There is also evidence of impaired cerebral autoregulation (auto regulation refers to the ability of the brain to maintain CBF at a constant level) on acute exposure to altitude. Subjects were studied on exposure to 4243m by evaluating the increase in mean arterial blood pressure with a phenylephrine infusion (phenylephrine is a sympathomimetic and acts by stimulating alpha-receptors), and by measuring the change in TCD MCA velocity. If there were no change in TCD MCA velocity this would imply perfect autoregulation. However all Sherpas and most of the lowlanders acutely exposed to this altitude showed evidence of impaired cerebral autoregulation. The phenylephedrine infusion resulted in larger increases in blood pressure than occurred at sea level (52). Yang et al (53) published animal work to show 3% CO_2 enriched air improved CBF as assessed by radio-labelled micro spheres. In this model there was no reduction in AMS symptoms with the supplemental CO_2, however CO_2 remained an important determinant of cerebral blood flow at all altitudes.

II) Headache in Acute Mountain Sickness

The headache that occurs at altitude was initially attributed to the increase in cerebral blood flow, however Reeves et al found no correlation between the rise in CBF and headaches in a simulated ascent to 4800m (54). The symptoms of acute mountain sickness and the symptoms of raised intracranial pressure appear similar, with headaches, nausea, photophobia, and ataxia being features of both conditions. The evidence for raised intracranial pressure in subjects with severe AMS is fairly strong. CSF pressure was found to be elevated during AMS compared with that after recovery (55). There are two reports of subjects dying from cerebral AMS have cerebral oedema on autopsy (55, 56) and there was flattening of cerebral convolutions Computerised axial tomography demonstrates diffuse low-density areas consistent with oedema in subjects with HACE (57). However using a non-invasive assessment

(tympanic membrane displacement), alteration in intracranial pressure was found to relate to changes in altitude rather than AMS (58). A further recent study found no evidence of elevated lumbar puncture pressures in twenty two subjects randomly exposed to 12% oxygen for 18 h (59).

Impaired cerebral autoregulation may result in raised capillary hydrostatic pressures and so compound mechanical vascular leaks (59). Disruption of the blood brain barrier may be important in the development of AMS and HACE and is likely to occur in severe cerebral oedema. Animal studies suggest there may be an important further, and to date unidentified factor, required for the blood-brain-barrier to become disrupted (60).

Current evidence suggests a potential role for free radicals in the development of a dysfunctional blood-brain-barrier and this is based upon the susceptibility of the vascular endothelium to damage from redox reactions (61). Normobaric hypoxic stimulus has been shown to activate oxidative stress and this is accentuated by exercise (62) Exercise per se is a risk factor for AMS (63) and we have shown sub-maximal exercise at high altitude results in both arterial desaturation, reduced cerebral oxygenation and alteration in CBF (11). Bailey et al (64, 65) have identified an increase in putative biomarkers of free radical-mediated lipid peroxidation. Preloading subjects with antioxidant prophylaxis resulted in neuroprotection (62). However recent evidence suggests there is no detectable evidence for gross barrier dysfunction in mild to moderate AMS (59).

The blood brain barrier is influenced by the neurotransmitters nitric oxide, histamine, substance P, reactive oxygen species*, 5-hydroxytryptamine, cytokines and endothelial growth factors. Local hypoxia triggers a complex cascade of cellular responses resulting in an increase in lactate, capillary basement membrane disruption and plasma extravasation. Vascular endothelial growth factor (VEGF) may be the most potent identified agent that causes basement membrane disruption and oedema formation. VEGF has been shown to be up regulated by hypoxia in rats (66) and also

*ROS include include oxygen ions, free radicals and peroxides and are small molecules that are highly reactive due to the presence of unpaired valence shell electrons. ROSs form as a natural byproduct of the normal metabolism of oxygen but can damage cell membranes by causing oxidative stress. Cells normally defend themselves against ROS damage through the use of the enzymes superoxide dismutase (SOD) and catalase .

in humans after exercise (67). Relief of high altitude headache with dexamethasone provides indirect evidence of the importance of cerebral oedema and vascular permeability in high altitude headaches since dexamethasone suppresses lipid peroxidation blocks VGEF and reduces endothelial permeability.

To date there has been an assumption that the increase in cerebral blood flow seen at altitude is uniform. However there is increasing evidence, particularly from PET scanning, that there are significant variations in regional blood flow in subjects/patients at sea level (68) and it likely that such variations in regional blood flow will also occur at altitude. PET scanning of subjects inside a hypobaric chamber would give further insights.

Great emphasis has been focused on cerebral blood flow, possibly because this was all that could readily be measured in the field (using nitrous oxide, TCD or ^{133}Xenon). Ascent to altitude results in an increase in cerebral blood flow and yet the subjects are known to be hypoxic. It was recently postulated that cerebral blood flow increases to maintain a constant level of oxygen delivery to the brain (69). Oxygen delivery to the brain is clearly likely to be the critical determinant of health and illness at all altitudes.

III) Supplementary oxygen

Oxygen delivery to tissues is critical in determining performance and illness at all altitudes. Cerebral oxygen delivery (COD) is dependent upon blood flow, arterial oxygenation, the oxyhaemoglobin dissociation curve, the haemoglobin concentration and arterio-venous partioning. Supplementary carbon dioxide will affect the first three to a greater or lesser degree, whilst supplementary oxygen will predominantly affect arterial oxygenation. Paul Bert, in 1878, was the first person to describe deterioration in cerebral function in subjects subjected to acute hypobaria. He noted an impairment of vision, hearing and a mental dullness, which rapidly reversed with oxygen (70). Cerebral function is known to deteriorate at high altitude, and 4000-5000m appears to be the critical altitude at which the effects are first observed (37). Rate of ascent and previous recent exposure as well as the individuals' susceptibility appear to be important. Complex tasks appear to be problematical at an earlier stage as does learning new things. This was first described in a detailed series of experiments undertaken by MacFarland during the 1930s in the Andes. Both simple and complex

psychological functions (arithmetical tests and writing ability) were significantly impaired at altitude (71). Alteration in cerebral function under hypoxic conditions is well recognized. At sea level when the FiO_2 is decreased to 75% of normal, complex task performance is altered, at 65% short term memory is impaired, at 50% judgement is altered and at 30-40% unconsciousness occurs (72).

On the Silver Hut Expedition to Nepal in 1964, Gill et al (73) reported 'falling efficiency' in sorting playing cards in subjects at 5,800m. Acclimatization has been shown in Indian army soldiers stationed at high altitude to result in an improvement in psychomotor efficiency. Psychomotor and numerate memory were impaired in shift workers at Mauna Kea, and improvements were noted with acclimatization (74).

In an attempt to improve neuropsychological function at a simulated altitude of 5000m 6% supplementary oxygen has been used, and this resulted in higher SaO_2 (93.0% vs. 81.6%), quicker reaction times, improved hand-eye co-ordination and a more positive sense of well-being (75). The proposed ALMA radio-telescope at 5000m in Chile will use this novel approach to protecting the workforce (76). Instead of the workforce acclimatising fully to the altitude, supplementary oxygen will be fed through the air conditioning/heating ducts to critical living areas, and oxygen tanks not dissimilar to SCUBA tanks will be used for maintenance purposes. For each 1% of oxygen enrichment, there is an apparent altitude reduction of about 300m. 6% oxygen will therefore have the effect of 'lowering' the telescope from 5000m to an 'apparent' altitude of about 3200m. This altitude is clearly a more reasonable proposition for daily commuting for the astronomers from their base at San Pedro da Atacama (2400m). The safety of the workforce will however be entirely dependent upon the efficacy of the oxygen enrichers and safe transport in the event of the need to evacuate an individual. There are mixed views amongst experts as to whether this is a true advance or a potentially dangerous development.

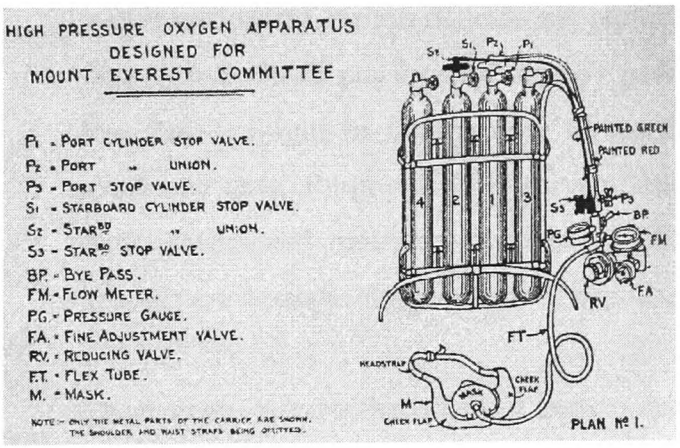
Whether or not exposure to extreme altitudes might result in permanent residual nervous system abnormalities occur remains controversial. A statistically significant decline in digit recall (representing cognitive function) and speed of finger tapping (representing motor function) has been found in individuals following an expedition to the summit of Everest; the abnormalities were less evident at twelve months after

the expedition but still remained significantly different from pre-expedition testing (77). Persistent cognitive impairment was described in climbers who reached summits over 8500m without supplementary oxygen. Magnetic resonance imaging (MRI) in climbers who have been to extreme altitude without oxygen show evidence of permanent cortical atrophy confirming that time at extreme altitude without oxygen can be detrimental (78).

George Finch was the first person to show the practical value of supplementary oxygen for climbing on Mount Everest in 1922.

Figure 9 a,b

Oxygen apparatus for 1924 British Everest Expedition:
Taken from West JB. (Ref 79)



Experimental literature suggests hypoxia alone rarely causes neuronal death. Cats exposed to PaO_2 of 17mmHg for 25 minutes were normal both clinically and neuropathologically unless hypotension supervened. With hypotension infarcts occurred, mainly in the watershed areas. Hypercarbia appears to be cerebro-protective during hypoxic insults, and the high $PaCO_2$ seen in the hypoxic survivors reported by Gray and Horner might be an example of such a phenomenon. In focal ischaemia, hypercarbic ventilation ($Paco_2$ of 65-80 mm Hg) has been shown to attenuate infarct

size (80). On the other hand hypocarbia with respiratory alkalosis might make the brain more vulnerable to hypoxia (81).

IV) Supplementary carbon dioxide

Carbon dioxide induces both direct and indirect circulatory effects. Hypercapnia results in increased cardiac output and an alteration in intrapulmonary shunting with a net increase in PaO_2 (82). As a result of increased cardiac output and increased regional blood flow, including mesenteric flow, there is improved oxygen delivery to tissues. Hypercapnia also shifts the oxyhaemoglobin dissociation curve to the right further improving oxygen delivery to the tissues. In patients with coronary artery disease there is evidence that, acting directly, hypercapnia dilates peripheral arterioles reducing the systemic vascular resistance index, increasing the cardiac index, and augmenting myocardial blood flow (83). Hypocapnia has important detrimental effects at sea level. There is accumulating clinical and basic scientific evidence that points to an active role for carbon dioxide in organ injury, in which raised concentrations of carbon dioxide are protective and low concentrations are injurious (84). A hypothesis put forward recently postulates that hyperventilation resulting in a low $PaCO_2$ might be contributory to the development of adult respiratory distress syndrome (84). Prophylactic hyperventilation of head injury patients is associated with a worsened neurological outcome (85). Experimentally ischaemic strokes in animals are worse in the presence of hypocapnia.

There is no data on the effect of carbon dioxide on peripheral tissue oxygenation at altitude. At sea level, in the peripheral circulation, the indirect effects of vasoconstriction are overcome by the direct vasodilating effect of CO_2 so that the total peripheral resistance decreases. Hypocapnia shifts the oxyhaemoglobin dissociation curve to the left restricting oxygen off-loading at the tissue level and local oxygen delivery may be further reduced by hypocapnic vasoconstriction (84). CO_2 has different effects on different vascular beds. CO_2 is known to be a powerful cerebral vasodilator at sea level. Although CO_2 is known to increase CBF at sea level, there are conflicting reports at altitude (86, 87). Although the peripheral chemoreceptors are sensitive to changes in $PaCO_2$, the main sensor for changes in $PaCO_2$ is the central medullary chemoreceptor, which is located just beneath the surface of the fourth ventricle. The blood brain barrier is readily permeable to dissolved CO_2, less

permeable to H^+ and even less so to HCO_3^-. A rise in $PaCO_2$ is rapidly reflected by a rise in CSF PCO_2, and this causes a rapid increase in CSF $[H^+]$. This is sensed by the chemoreceptors resulting in increased stimulation of the respiratory centre and increased ventilation. Activation of the CNS evokes sympatho-adrenal responses results in increased myocardial contractility, tachycardia and hypertension. Acclimatisation is likely in part to involve the resetting of the central medullary chemoreceptors to new levels of CO_2 (88). Acetazolamide is a carbonic anhydrase inhibitor and may cause a rise in intracellular CO_2 maintaining cerebral blood flow during the hyperventilation of acclimatisation.

Oxygen delivery to tissue in healthy individuals on acute exposure to high altitude is similar in many respects to oxygen deliveries in disease.

f) Pathology of arterial disease

Atherosclerosis is the most common cause of death in the western world (myocardial infarction, cerebral infarction and peripheral vascular disease). The word is derived from the Greek word athero: gruel, paste or porridge and sclerosis: hardness. There is a build up fats, cholesterol, fibrous tissue and calcium within the intimal layer of the artery. The plaques occur mainly in medium and large arteries such as the coronaries, the carotids, the renals and in the arteries to the lower limbs.

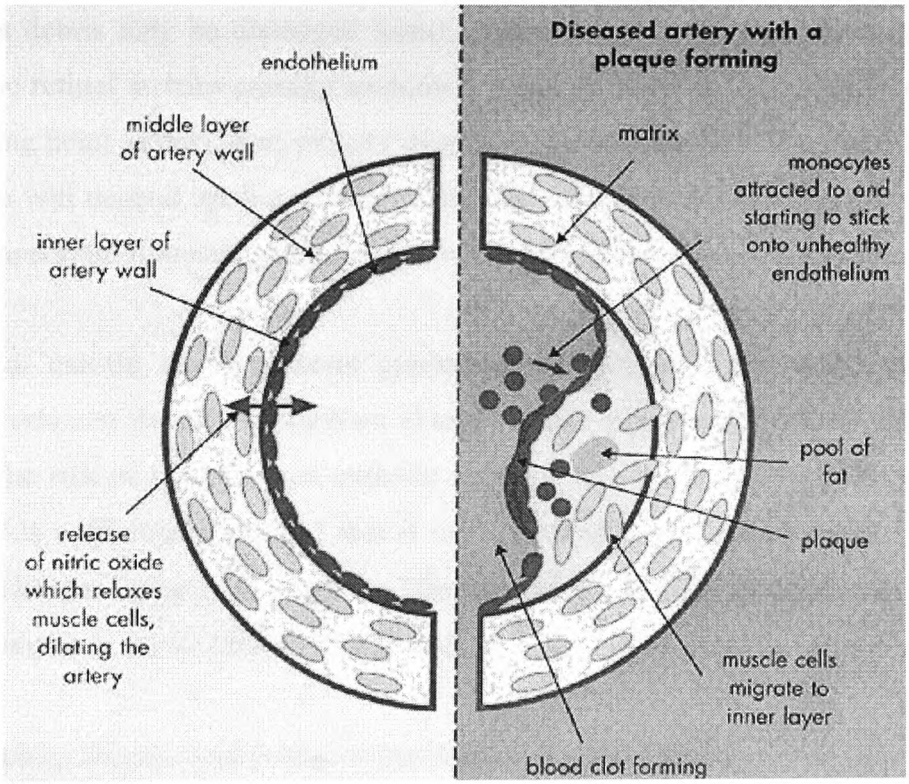
The endothelial lining of an artery has both protective and metabolic functions. Intact the endothelium prevents clots forming on its surface. However damage to the endothelium by trauma, elevated cholesterol levels, high blood pressure, cigarette smoke, and diabetes can all lead to platelet adherence and aggregation on the vessel wall. Following damage to the endothelium, fatty acids, cholesterol, platelets and calcium become incorporated into the vessel wall. Macrophages migrate into the vessel wall and attempt to clear the excessive build up of fats (89). Smooth muscle cells migrate into the intimal layer and are transformed into foam cells as they attempt to deal with the excessive build up of cholesterol and fatty acids (90, 91). They also secrete collagen forming a fibrous cap. The process repeats itself many times until the vessel gradually narrows decreasing distal blood flow. There is evidence that vascular oxidant stress enhances progression and angiogenesis of experimental atheroma (92, 93). One of the potential mechanisms by which statins prevent the development of

atherosclerosis is through their antioxidant properties (94). Ulceration of the plaque will leave a raw highly thrombogenic surface activating the clotting cascade locally and resulting in adherence of platelets. Sudden thrombosis of the vessel is also possible. Depending upon the end organ supplied by the diseased artery and the time scale over which the plaques develop differing clinical scenarios will evolve, a TIA or stroke, angina or myocardial infarction or peripheral rest pain or gangrene. There is evidence that C-reactive protein levels in patients with peripheral arterial disease relate to both the severity of the disease and to future cardiovascular events (95)

Figure 10

Pathogenesis of atheroma

Artwork by CW Chan



Cerebral ischaemia, secondary to extra cranial vascular disease within the internal carotid artery, may be precipitated by thrombosis, embolism or a significant flow limiting reduction of the lumen. The end result of ischaemia is infarction of the brain tissue, which once established is irreversible. However there is a stage when the tissue effects are reversible. A transient ischaemic attack (TIA) is defined as a focal

neurological deficit and in the anterior circulation this commonly results in a contralateral hemi paresis or hemi sensory loss, amaurosis fugax (visual disturbance) or dysphasia, and the deficit fully resolves within 24 hours. Typically it will only last 10-30 minutes. Permanent cerebral damage resulting in a stroke occurs when cerebral tissue is irreversibly damaged. Atherosclerosis of the internal carotid artery results in a localised plaque, which may narrow the artery or ulcerate. Narrowing may continue until the artery occludes by a thrombosis, which extends from the primary site of disease proximally (junction of internal and external carotid artery) and distally to the next major branches where collateral flow will normally restrict its extension. In the internal carotid artery the thrombosis usually extends from the carotid bifurcation to the Circle of Willis (1).

An ulcerated plaque causes local platelet deposition, and where they combine with fibrin thrombus forms. At any point in time the platelet aggregates, thrombus or atheromatous debris may be dislodged forming emboli will be washed downstream lodging in the retinal arteries causing amaurosis fugax or blindness or in the cerebral vessels causing hemi motor, hemi sensory dysphasic TIAs or strokes. The outcome of the embolism will depend upon a number of factors including frequency, size, nature and site of impaction. Repeated embolization will tend to have a cumulative effect.

If the internal carotid artery narrows gradually and without distal embolization, collateral vessels can develop to such an extent that the vessel can occlude with no symptoms. The risk of a subsequent embolic stroke is negligible, but sometimes the blood supply is sufficiently reduced that it cannot respond to fluctuations in blood pressure or changes in arterial oxygen. This can result in a hypo perfusion TIA (deficit <24 hours) or stroke (deficit >24 hours).

d) Carotid artery disease and transient ischaemic attacks (TIAs)

i) Introduction

The risk of stroke after a hemispheric transient ischaemic attack (TIA) is greatest within the first 72 hours, and prevalence as high as 20% within the first month has been reported (96). The Royal College of Physicians 'National Clinical Guidelines for Stroke' (2004) recommend that patients with TIAs or minor stroke should be seen in a

specialist neurovascular clinic within 7 days, and those with more than one TIA (recurrent or crescendo TIAs) should be admitted and investigated immediately (97).

A number of prospective randomised trials have shown a benefit to carotid endarterectomy combined with medical therapy over medical therapy alone in patients with symptomatic critical internal carotid artery stenosis (98, 99, 100). However there is a paucity of data for patients with recurrent or crescendo TIAs, although they are often empirically heparinized prior to urgent surgery. Mentzer et al (101) described 12 patients with crescendo TIAs, 7 underwent emergency carotid endarterectomy and none had major complications, but of the 5 patients treated non-operatively, 3 suffered strokes and 1 died of cerebral infarction. In the Veterans Affairs trialists study, patients with recent TIA or minor stroke were randomised to either surgery or best medical therapy. Of the 98 patients treated medically, 12 developed crescendo TIAs, 4 had minor strokes and 3 had major strokes, and all 12 with crescendo TIAs subsequently underwent uncomplicated urgent carotid endarterectomy (102). In another study (103), 29 patients with repetitive TIAs were treated with heparin until elective carotid surgery was undertaken. There was a mean wait for surgery of 5 days, and whilst on heparin there were 2 carotid occlusions and 13 patients continued to have further TIAs. Post-operatively there was 1 stroke and 1 death due to myocardial infarction. Based upon the reported poor outcome of patients with crescendo TIAs with medical treatment alone, a more aggressive approach with urgent surgical intervention has been advocated (102). However the published results of urgent carotid surgery are variable, with complication rates ranging from no deficits in 12 patients, to operative mortalities as high as 20% and neurological deficits in up to 40% in other series (102, 104-9). A recent systematic review of 13 studies of the risks of carotid endarterectomy in relation to both the clinical indication for and timing of surgery has shown that urgent carotid surgery for evolving symptoms has a much higher risk (19.2%, 95% CI, 10.7 to 27.8) than surgery for stable symptoms (OR, 3.9; 95% CI, 2.7 to 5.7; $P<0.001$) (110). Since both medical and emergency carotid surgery appears to have significant complication rates, is there an alternative approach?

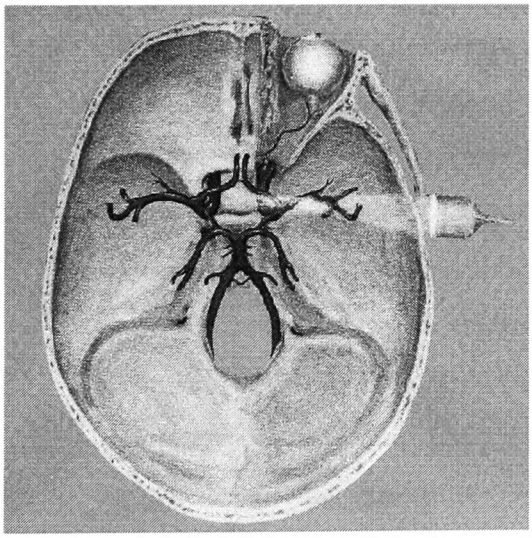
II) Transcranial Doppler, microembolic signals and medical therapy

Transient microembolic signals can be detected in the middle cerebral artery using transcranial Doppler techniques (TCD) and they are frequent phenomena for some

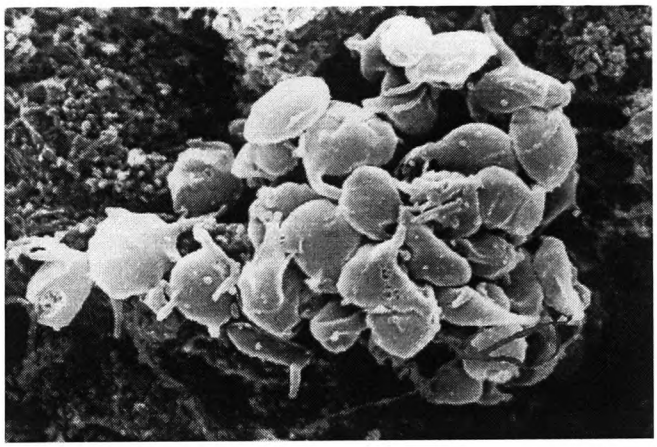
days following an acute stroke (111). Microemboli are a significant independent predictor of early ischaemic recurrence in patients with stroke or TIA of arterial origin (112). In a study of 69 patients with symptomatic carotid stenosis, microemboli were detected more frequently when studied soon after symptoms of cerebral ischaemia (113). In asymptomatic patients with a critical internal carotid artery stenosis, it was demonstrated that when the microembolic signal rate was greater than 2 per hour in the ipsilateral MCA, there was an associated increased risk of developing ischaemia (odds ratio, 31; 95% confidence interval 3-302: p=0.005). A number of further studies have demonstrated a link between persistent cerebral microembolization and the risk of future TIA or stroke (114-116). It appears the presence of microemboli may define a sub-group of patients with critical stenoses that may be at greater risk of having a stroke (117).

Figure 11 a,b

Trans-cranial Doppler:



Platelet micro-embolus:



Taken from CHE Imray & C Tiivas (Ref 32).

Anticoagulation was first shown to influence TCD-detected cerebral microembolism when the efficacy of a heparin infusion was assessed in a forty-five year old woman with a left anterior cerebral infarct without evidence of vascular disease (118). Goertler et al (119) have assessed the efficacy of intravenous acetylsalicylic acid (acetylsalicylic acid inhibits platelet prostaglandin synthesis and the ADP- and

collagen-induced platelet release reaction) in controlling microemboli. Nine patients with recent symptoms arising from critical internal carotid artery stenosis underwent 1-hour of TCD monitoring were given intravenous aspirin 500mg and then the measurements repeated. There was a reduction in the number of microemboli starting within 30 minutes in most patients; however the one patient that showed no fall in the number of microemboli subsequently suffered an ischaemic event. In a further study from the same group (120), 74 patients with symptomatic critical internal carotid artery stenosis underwent 1-hour bilateral TCD monitoring within 1 month of symptoms. 38 patients (51%) had detectable emboli, of those on aspirin (n=48) there was a 40% incidence of microembolic signals, of those not on aspirin (n=26) 70% had detectable microemboli. TCD detected emboli will be controlled in approximately half of patients on maximal medical therapy, whilst in the others persistent embolization is an independent predictor of recurrent TIA or stroke (adjusted odds ratio 37.0; 95% CI 3.5-333; $p<0.003$). If cerebral microemboli persist despite medical therapy, there is an approximately forty-fold increased risk of further neurological events.

Rapid control of microemboli with the glycoprotein IIb/IIIa receptor inhibitor (tirofiban) has been described in twenty-four patients with recent cerebral or retinal embolism of arterial origin (121). With tirofiban, the microembolic signal rate dropped from a median (range) of 38 per hour (9 to 324) to zero in all patients. After cessation of infusion, the inhibitory effect of tirofiban was found to be reversible, with a significant increase in microembolic signals (median 13.5; range 0 to 35; n=16; $P<0.001$). Six patients received overlapping oral anti-platelet agents and remained microemboli-negative. The authors concluded that cerebral microemboli of arterial origin have the properties of solid emboli, with platelet-fibrinogen units as predominant constituent parts and that glycoprotein IIb/IIIa antagonists may have the potential to bridge the ischaemic risk in patients with unstable carotid disease (121). Tirofiban has been also been shown to inhibit extension of microthrombosis, which may occur subsequent to arterial occlusion by emboli.

One concern with monitoring for cerebral microemboli for relatively short periods of time is the potential of missing microemboli. Recently an ambulatory TCD system has been developed which uses an auto-search algorithm to restore vessel insonation

should signal quality fall. Since patients can be monitored continuously for up to five hours, and in view of the likely temporal variability in embolization, the technique is likely to improve the predictive value of recording for microemboli (122).

III) Transcranial Doppler and carotid surgery

1) Intra-operative TCD

During carotid endarterectomy, the common, internal and external carotid arteries all have to be temporarily clamped so the operation can be performed with minimal blood loss. During this cross clamp phase, blood can only reach the ipselateral anterior circulation via the circle of Willis. Historically, TCD was first used during carotid surgery to help to determine the need for shunting during the cross clamp phase (123), and a greater than 90% decrease in the middle cerebral artery velocity is associated with operative stroke (odds ratio 3.6, 95% CI 1.4-9.0) (124). Subsequently, TCD has also been used to measure the intra-operative microembolic load (125, 126). TCD sensitivity to the presence of particulate emboli can help guide surgical dissection of the carotid prior to endarterectomy. Jansen et al. found that a high microembolic load was significantly related to new ischaemic lesions (127). Intra-operatively TCD emboli detection has been used to modify surgical technique or strategy, for example early clamping of the internal carotid artery when there is a high embolic load (128, 128).

2) Post-operative TCD

An early post-operative carotid thrombosis rate of 2-3% is reported (130, 131). It is thought that after carotid endarterectomy, TCD-detected microemboli are platelet aggregates generated by partially denuded and highly thrombogenic vascular endothelium. Unchecked, these aggregates may mature into occlusive thromboemboli, resulting in infarcts in the succeeding hours or days. Microembolic counts greater than 50 per hour in the early post-operative phase after carotid endarterectomy are predictive of the development of ipsilateral focal ischaemia (132, 133). Lennard et al. (134) have eliminated all post-operative strokes with the aid of a three hour TCD monitoring session. They found signs of persistent embolization at >25 microemboli signals/10 min consistently preceded injury. Embolization was completely prevented with incremental infusion of the antiplatelet agent, Dextran-40. The same group have now audited 600 consecutive carotid endarterectomies, following the introduction of

TCD directed Dextran therapy and found that the postoperative thrombotic stroke rate fell from 2.7% to 0% (130, 131). There is evidence that 30 minutes of post-operative monitoring may be adequate (135).

5) Chronological ordered overview publications

The author made major contributions in all scientific steps, including developments of the concepts, grant funding, ethical submission, data collection, and analysis and manuscript preparation and submission for these publications.

a) Altitude related publications

1. Intracranial pressure at high altitude and acute mountain sickness.

Authorship:
AD Wright, **CHE Imray**, MSC Morrisey, RJ Marchbanks and AR Bradwell

Publication:
Clinical Science 1995; **89**: 201-204.

Type of study:
Peer review paper

Background:
Rapid ascent to high altitude is associated with the development of acute mountain sickness. A characteristic clinical feature of AMS is the development of a headache. AMS can progress to high altitude cerebral oedema (HACE), coma and finally death. There is circumstantial and anecdotal evidence that in AMS there is a rise in intracerebral pressure. The development of a non-invasive method of measuring changes in intracranial pressure enabled us to perform a prospective study of AMS in a group of subjects trekking to high altitude. The method was based upon the principle that a patent cochlear aqueduct transmits intracranial pressure to the peri-lymphatic fluid of the cochlea. The resting position of the footplate of the stapes within the oval window depends upon the pressure of peri-lymphatic fluid. Increasing pressure displaces the stapes footplate laterally, allowing a greater degree of freedom for motion of the stapes medially when the stapedius muscle contracts. Movement of

the tympanic membrane can be measured by volume displacement by a transducer probe sealed within the external auditory meatus.

Aims and hypothesis:

This study attempted to measure, using non-invasive techniques the changes in intracerebral pressure on ascent to altitude and with AMS. We believed ascent to altitude would result in raised intracranial pressure

Subject population:

24 healthy individuals on acute ascent to high altitude

Methodology and statistical analysis:

Prospective observational paired study

Student t- Test

Altitude(s):

150m, 3440m, 4120m and 5200m

Interim conclusions:

In this study we measured indirectly changes in intra-cranial pressure indirectly at altitude for the first time. The technique proved to be practical in the field and although no correlation with acute mountain sickness was found it was an important first study in that it became apparent that changes in intra-cerebral physiological parameters could be measured in the field. There was no evidence to support the currently favoured hypothesis that high altitude cerebral oedema is a result of a tight box, that is to say AMS results in brain swelling within a closed space resulting in raised intracranial pressure and reduced cerebral perfusion. We demonstrated a rise in intracranial pressure following a rapid rise in altitude. These findings of a rise in intracranial pressure with an acute hypoxic stimulus have also been found in sheep with peaks occurring at 6 hours (Yang SP, Bergo GW, Krasney E, Krasney JA. Cerebral pressure-flow and metabolic responses to sustained hypoxia: effect of carbon dioxide. Journal of Applied Physiology 1994 76: 303-313).

Figure 12

Sequential changes in tympanic membrane displacement with altitude:

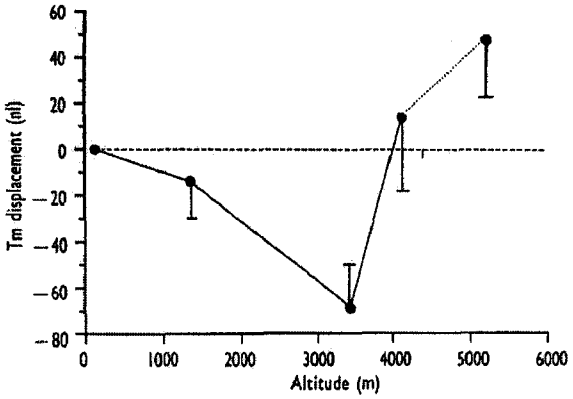


Fig. 1. Sequential changes in tympanic membrane (Tm) displacement from baseline to high altitude. A more negative displacement indicates a rise in intracranial pressure.

Implications:

This study is an important contribution to the study of intracranial pressure at altitude. Mild to moderate AMS does not result in raised ICP. Ascent to altitude does result in measurable rises in ICP. This study did not assess subjects with severe AMS.

2. Near-infrared spectroscopy (NIRs) in the assessment of cerebral oxygenation at high altitude.

Authorship

CHE Imray, NJ Barnett, S Walsh, T Clarke, J Morgan, D Hale, H Hoar, D Mole, I Chesner, AD Wright.

Publication

Wilderness and Environmental Medicine 1998; **9**: 198-203

Publication type:

Peer review paper

Background:

Near-infrared light spectroscopy allows continuous non-invasive cerebral oxygenation monitoring and uses light in the NIR spectrum (650-1100nm). Like pulse oximeters and mixed venous oximeters, the technique uses the principles of light transmission and absorption to measure concentrations of oxygenated and deoxygenated haemoglobin in cerebral tissue. It had been used clinically and appears to give good assessments of trends in cerebral oxygenation.

Aims and hypothesis:

This study aimed to assess cerebral oxygenation on ascent to altitude non-invasively. We hypothesised that there would be a reduction in cerebral oxygenation at altitude.

Subjects population:

20 fit individuals on acute ascent to altitude

Methodology and statistical analysis:

Prospective observational paired study

Student t- Test

Altitude(s):

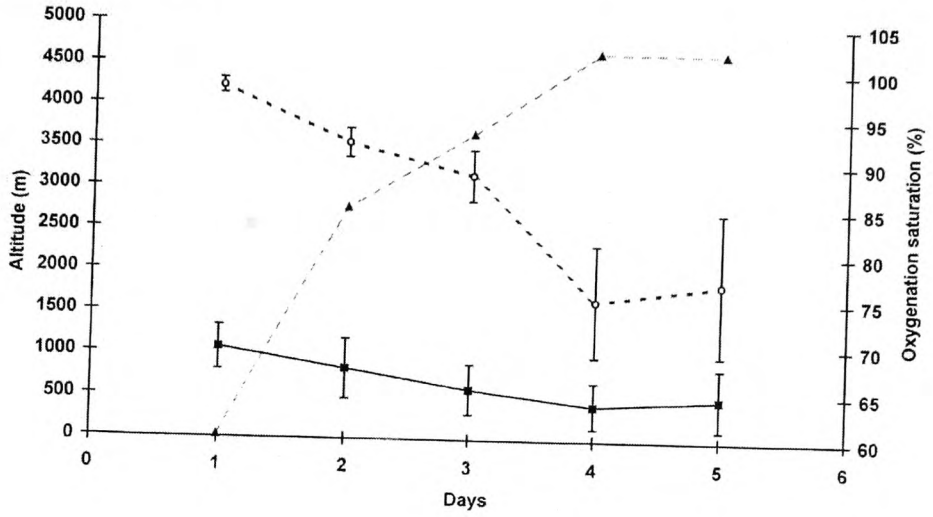
150m (Birmingham,UK), 0m (Arica, Chile), 2770m, 3650m, 4680m

Interim conclusions:

This study is the first to describe the use of cerebral NIRs at altitude and in the field. We knew that with increasing altitude there is a steady decrease in peripheral arterial oxygenation. The fall in PaO_2 results in an increase in cerebral blood flow. The question raised was whether the increase in CBF maintained cerebral oxygen delivery or whether there would be a fall in cerebral oxygenation on ascent to altitude.

Figure 13

Reduction in cerebral NIRs and peripheral arterial saturations with increasing altitude:



Open circle	Peripheral arterial saturations
Solid circle	Cerebral saturations (rSO_2)
Solid triangle	Altitude in metres

Implications:

This important study described for the first time the fall in cerebral oxygenation with ascent to altitude, and the gradual rise in cerebral oxygenation observed as individuals acclimatised with time to 4680m. The NIRs technique proved to be robust and suitable for use in the field.

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

Authorship:

CHE Imray, S Brearey, T Clarke, S Walsh, J Morgan, AD Wright.

Publication:

Clinical Science 2000; **98**:159-164

Publication type:

Peer review paper

Background:

Ascent to altitude results in a reduction partial pressure of inspired oxygen (PiO_2). As a result of this hypoxic stimulation, respiratory rate increases in an attempt to improve PaO_2. Although there is an increase in PaO_2 with hyperventilation there is a fall in $PaCO_2$. The fall in PaO_2 and the fall in $PaCO_2$ have opposing effects on the cerebral circulation, and cerebral NIRs would allow continuous dynamic assessment of cerebral oxygenation. This study was the first study to assess cerebral oxygenation at altitude in response to supplementary oxygen, carbon dioxide and hyperventilation.

Aims and hypothesis:

Having successfully pioneered the use of NIRs in the field, the aim of this study was to assess the dynamic changes in cerebral oxygenation that we hypothesised would occur with various interventions for the first time.

Subjects:

20 fit individuals on acute ascent to altitude

Methodology and statistical analysis:

Prospective observational paired study

Student t- Test

Altitude(s):

150m, 0m, 2770m, 3560m, 4680m

Interim conclusions:

Having successfully shown that cerebral NIRs could be used in the field at altitude, this study began to investigate the factors that were known to affect cerebral blood flow and cerebral oxygen delivery, although in this study no direct measures of cerebral blood flow were undertaken.

Supplementary carbon dioxide increased cerebral oxygenation by increasing the rate and depth of respiration and by probably increased cerebral blood flow.

Supplementary oxygen increased cerebral oxygenation as a result of the large increase in PaO_2 being more important than the likely drop in cerebral blood flow. Somewhat surprisingly hyperventilation decreased cerebral oxygenation at sea level, primarily due to the minor increase in the arterial oxygen and the presumed larger decrease in cerebral blood flow.

Implications:

This was an important study. For the first time dynamic NIRs studies had been successfully undertaken, addressing some of the limitations of field research. At high altitude hyperventilation increased cerebral oxygenation, there was a large rise in arterial oxygen and a probably relatively modest fall in cerebral blood flow. NIRs had been shown to measure dynamic changes in cerebral oxygenation at altitude. More detailed studies using trans-cranial Doppler were indicated.

4. Carbon dioxide contributes to the beneficial effect of pressurisation in a portable hyperbaric chamber.

Authorship:

CHE Imray, S Brearey, T Clarke, S Walsh, J Morgan, AD Wright.

Publication:

Clinical Science 2001; **100**: 151-157.

Publication type:

Peer review paper

Background:

Treatments of AMS include descent or supplementary oxygen. A novel approach introduced in the '90s is the use of the portable hyperbaric chamber. This is an airtight fabric envelope which can be sealed with a subject inside. A foot pump can be used to raise the ambient pressure within the chamber to approximately 200mB (2 psi or 105 mmHg) above the atmospheric pressure. This is equivalent to a simulated descent of

approximately 1000m. This studied assessed for the first time changes in the near infrared cerebral oxygenation of subjects within the chamber at three altitudes.

Aims and hypothesis:

The aim of this study was to assess cerebral NIRs within a portable hyperbaric chamber for the first time, and to assess the effect of the build up of carbon dioxide within the chamber. We hypothesised that there would be an improvement in cerebral rSO_2 which would be further improved by the build up of carbon dioxide.

Subjects:

6, 10, 9 respectively fit individuals on acute ascent to altitude

Methodology and statistical analysis:

Prospective observational paired study

Student t- Test

Altitude(s):

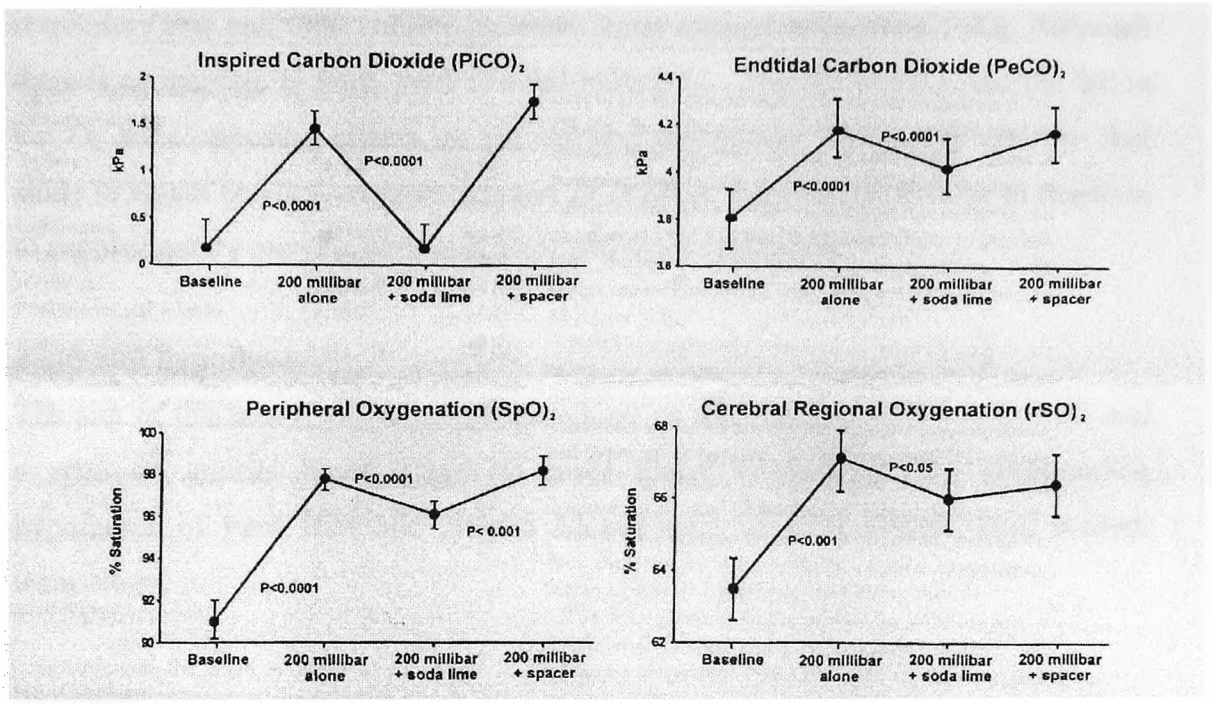
3475m, 4680m, 5005m

Interim conclusions:

This paper demonstrated that portable hyperbaric chambers increased not only the arterial oxygen levels (pulse oximetry), but also increased cerebral oxygenation (NIRs). The effect is short lived, with changes in both arterial oxygen and cerebral oxygenation rapidly returning to pre-pressurisation levels once subjects were removed from the chamber. The second important observation was that the build up of carbon dioxide within the chamber during pressurisation which had previously been felt to be insignificant actually accounted for about one third of the beneficial effect on cerebral oxygenation of the chamber. This observation rekindled the longstanding debate as to the relative merits of oxygen and carbon dioxide which first began in the late eighteenth century between Paul Bert and Angelo Mosso.

Figure 14

Changes in $PiCO_2$, $PeCO_2$, peripheral arterial and cerebral oxygenation in a portable hyperbaric chamber at altitude:



Implications:

For the first time the portable hyperbaric chamber was shown to improve cerebral oxygenation and that the build up of carbon dioxide had clinically measurable beneficial effects.

5. The effect of supplementary carbon dioxide, oxygen, and a mix of carbon dioxide and oxygen on arterial blood gases and on peripheral, muscle and cutaneous oxygenation at 150m and 3459m.

Authorship:

CHE Imray, S Walsh, T Clarke, J Morgan, H Hoar, T Harvey, AR Bradwell, AD Wright.

Publication:

Clinical Science 2003; **104**:1-8.

Publication type:

Peer review paper

Background:

Ascent to altitude results in a reduction PiO_2. As a result of this hypoxic stimulation, respiratory rate and tidal volume increases in an attempt to improve PaO_2. Although there is an increase in PaO_2 there is a fall in $PaCO_2$. The fall in PaO_2 and the fall in $PaCO_2$ have opposing effects on the cerebral circulation. This study was the first study to assess cerebral oxygenation and TCD MCA velocities at altitude in response to supplementary oxygen, carbon dioxide and hyperventilation.

Aims and hypothesis:

The aim of this study was to assess the effects of supplementary carbon dioxide and oxygen on arterial blood gases on acute ascent to altitude. The longstanding hypotheses of Paul Bert and Angelo Mosso were to be assessed using modern technology.

Subjects:

12 fit individuals on acute ascent to altitude

Methodology and statistical analysis:

Prospective observational paired sample study

Student t- Test

Altitude(s): 150m and 3459m.

Interim conclusions:

In this study, a logical development of our paper *'Cerebral oxygenation at high altitude and the response to carbon dioxide, hyperventilation and oxygen'*, we used radial arterial lines to allow measurement of arterial blood gases and transcranial Doppler to measure cerebral blood flow. Having previously shown that cerebral NIRs could be used in the field at altitude, we studied the factors that were known to affect cerebral blood flow and cerebral oxygen delivery.

Figure 15

Changes in arterial saturations and blood gases with supplementary carbon dioxide, oxygen and a mix of carbon dioxide/oxygen at 150m and 3459m:

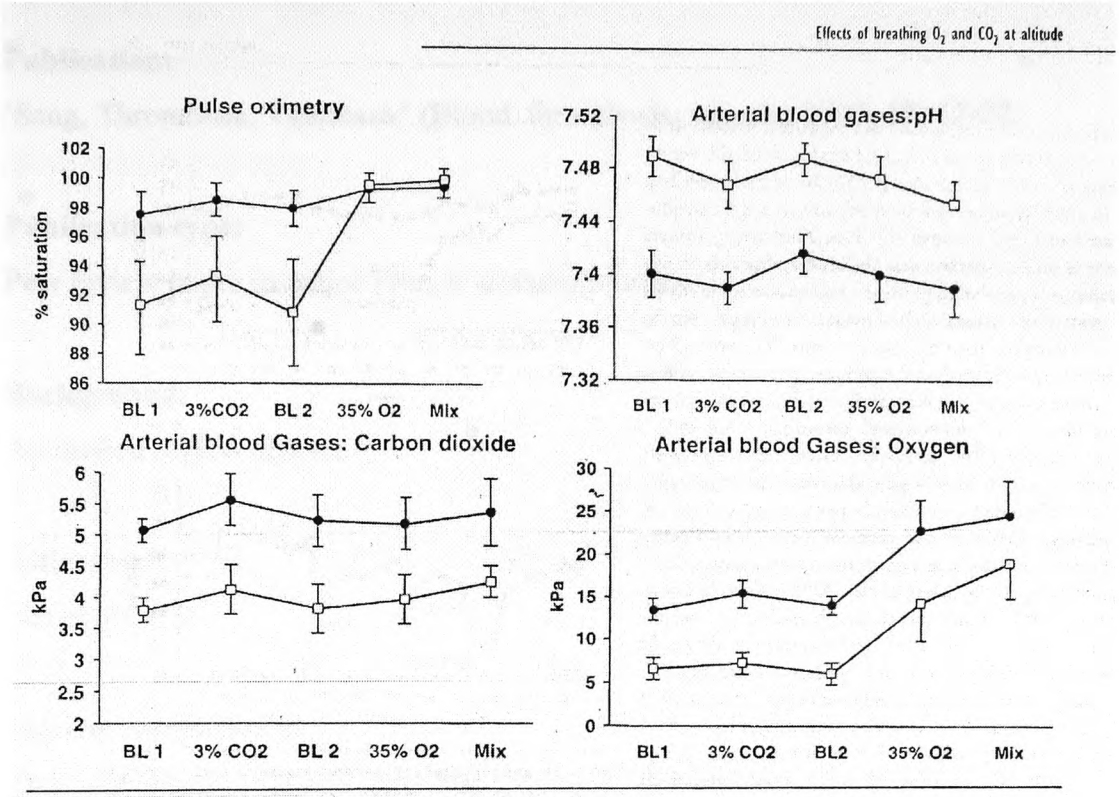


Figure 1 Pulse oximetry and arterial blood gases in 20 subjects at 150 m (●) and at 3459 m (□)

Values are means ± S.D. BL1, first baseline; BL2, second baseline. The results at the end of 5 min of breathing 3% CO_2 in ambient air, at the end of 5 min of breathing 35% O_2 in ambient air and at the end of 5 min of breathing 3% CO_2 + 35% O_2 (mix) in ambient air are shown. Compared with BL1, 3% CO_2 resulted in an increase in pulse oximetry at both altitudes ($P < 0.0001$), a fall in pH at 3459 m ($P < 0.05$), an increase in Pao_2 at both altitudes ($P < 0.01$) and a rise in $Paco_2$ at 150 m ($P < 0.01$). Compared with BL1, 35% O_2 resulted in an increase in pulse oximetry ($P < 0.0001$) and Pao_2 ($P < 0.0001$) at both altitudes. Compared with BL1, the 3% CO_2/35% O_2 mixture resulted in an increase in pulse oximetry at both altitudes ($P < 0.0001$), a decease in pH at 3459 m ($P < 0.0001$), increases in Pao_2 at 150 m ($P < 0.01$) and at 3459 m ($P < 0.001$), and an increase in $Paco_2$ at 150 m ($P < 0.01$).

Implications:

A century old debate involving the great physiologists of the late nineteenth century was resolved. Carbon dioxide increased cerebral oxygenation by increasing the rate and depth of respiration and we demonstrated an increase in cerebral blood flow. Oxygen increased cerebral oxygenation as a result of the large increase in PaO_2 being more important than the drop in cerebral blood flow. The mix of oxygen and carbon dioxide had the most powerful effect.

6. Perfusion cerebrale en haute altitude (High Altitude Cerebral Perfusion).

Authorship: CHE Imray, C Chan, AW Wright.

Publication:

'Sang, Thrombose, Vaisseaux' (Blood, thrombosis, vessels) 2003; **15**: 17-27.

Publication type:

Peer review paper in major French vascular journal.

Background:

An invited review article.

Altitude(s):

Not applicable

Interim conclusions:

This was a historical and scientific review of the literature on cerebral perfusion at high altitude, with an emphasis on the intellectual contributions made by French investigators.

7. Partitioning of arterial and venous volumes in the brain under hypoxic conditions.

Authorship

CB Wolff, **CHE Imray**

Publication

Advances in Experimental Medicine and Biology. 2003; **540:** 19-32.

Publication type: Peer review paper

Background: Near infrared cerebral spectroscopy (NIRS) measures the absorption of light in the NIR spectrum (650-1100nm), and as such measures the concentration of oxygenated and deoxygenated haemoglobin in the interrogated tissue (usually brain). Cerebral NIRs allows continuous non-invasive measurements of cerebral oxygenation.

Aims and hypothesis:

The NIRs technique is based upon the analysis of the near infrared light that has traversed the interrogated tissue. The data is then analysed using an algorithm based upon the Beer-Lambert Law. As such certain mathematical assumptions are made. In this paper we aimed to reassess these assumptions.

Subjects:

8 fit individuals on ascent to altitude

Methodology and statistical analysis:

Prospective observational paired study

Student t -Test

Altitude(s):

Sea level, 2400m, 5005m.

Interim conclusions:

To date cerebral oxygenation was thought to be dependent upon arterial oxygen content, cerebral blood flow and cerebral oxygen consumption. In this paper we put forward an hypothesis based upon mathematical modelling that a fourth factor was involved. This factor was determined by the relative partitioning of the arterial and venous volumes interrogated.

Near-infrared spectroscopy provides a measure of the proportion of blood that is oxygenated. It does not distinguish how much is in the arterial or venous part of the vascular bed. The proportion of total blood in the brain has been estimated to be 28%

arterial and 72% venous. However partitioning of the arterial and venous volumes in the brain under hypoxic conditions has been modeled in this study.

Implications:

Existing cerebral oximeters do not take into account any changes within the arterial and venous compartments of the capillary bed. The proportion of blood in the arterial compartment has been estimated to be 28% (23). In this study we speculated that hypoxia can induce changes in the arterial to venous ratio. This may have important implications on the interpretation of cerebral NIRS data.

8. Medroxyprogesterone at high altitude and in the prevention of acute mountain sickness.

Authorship:

AD Wright, MF Beazley, AR Bradwell, IM Chesner, RN Clayton, PJG Forster, P Hillenbrand, **CHE Imray**.

Publication:

Wilderness and Environmental Medicine 2004; **15(1)** :25-31

Publication type:

Peer review paper

Background:

Progesterone is the most powerful natural respiratory stimulant. It acts via an oestrogen-dependant receptor at hypothalamic sites and influences the respiratory centre via a neural pathway. We examined whether the respiratory stimulant effects of progesterone might reduce the incidence of acute mountain sickness or improve near infrared cerebral oxygenation.

Aims and hypothesis:

The aim was to assess the effect of progesterone on peripheral and cerebral oxygenation. We hypothesised that progesterone's powerful respiratory stimulant effects would have important clinical effects.

Subjects:

20 fit individuals on acute ascent to altitude

Methodology and statistical analysis:

Prospective randomized double blind study

Student t- Test

Altitude(s):

150m, 2660m, 3440m, 4120m, 5200m

Interim conclusions:

Although there was no apparent benefit in reducing the incidence of AMS, the study demonstrated the powerful stimulatory effects of progesterone on respiration. There were improved arterial saturations, decreased end tidal carbon dioxide and but no difference in NIRs. The combination of acetazolamide and medroxyprogesterone resulted in the most marked improvement in PaO_2.

Implications:

The paper demonstrated that progesterone had the expected effect on PaO_2, but is unlikely to be useful clinically.

9. Effect of exercise on cerebral perfusion in humans at high altitude

Authorship:

C.H.E Imray, S. D. Myers, K.T.S. Pattinson, A.R. Bradwell, C. W. Chan, S.Harris, P.Collins, A.D.Wright and the Birmingham Medical Research Expeditionary Society.

Publication:

Journal of Applied Physiology 2005; **99(2)**: 699-706

Publication type:

Peer review paper

Background:

The cardio-pulmonary effects of exercise at altitude have been studied extensively but the effect of exercise on cerebral perfusion has received limited attention. No comparable studies of cerebral oxygenation at VO_{2max}, or any combined measurements of cerebral oxygenation and MCA blood velocity at VO_{2max}, at high altitude have been reported.

Aims and hypothesis:

To assess cerebral perfusion at altitude during exercise and try to determine whether limitations in cerebral perfusion might be a limiting factor to exercise at altitude.

Subjects:

9 fit individuals on acute ascent to altitude.

Methodology and statistical analysis:

Prospective observational paired study

Student t- Test, repeated measures ANOVA

Altitude(s):

150m, 3600m, 4250m, 5250m

Interim conclusions:

Assessments of cerebral blood flow and cerebral oxygenation during exercise and under field conditions have proven challenging. The standard, upright-exercise cycle results in excessive head movement and use of arms, particularly as one approaches maximal exercise. To overcome these difficulties we built a portable, recumbent-exercise ergometer (Alticycle^{TM}) for undertaking cerebral perfusion measurements in the field.

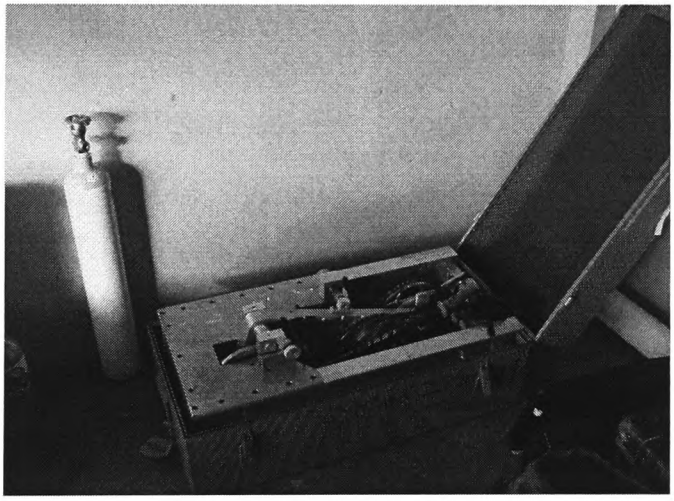
We designed and built a recumbent exercise bike specifically for the experiment. We demonstrated reductions in cerebral oxygenation and oxygen delivery during sub maximal and maximal exercise at altitude. The implications of this work will be discussed in detail in the following section entitled 'Overall Conclusions'.

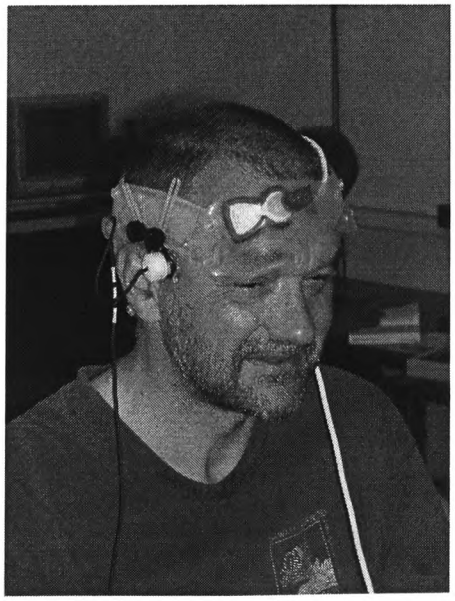
Implications:

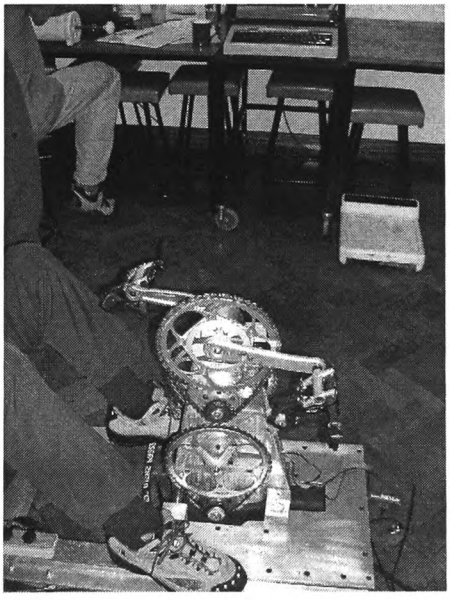
For the first time cerebral perfusion at high and extreme altitude has been assessed during maximal exercise using non-invasive techniques. This paper clearly demonstrates for the first time that cerebral perfusion is limited at maximal exercise at altitude. This limitation of cerebral perfusion may be one of the limiting factors of exercise at altitude. One of the reviewers felt this study was likely to generate or foster numerous further studies.

Figure 16

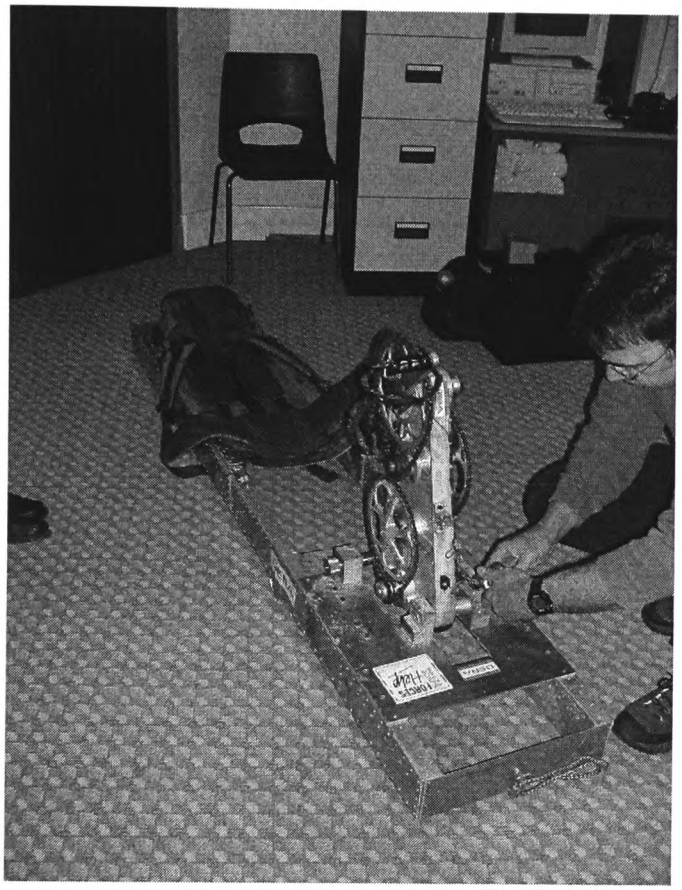
Alticycle™

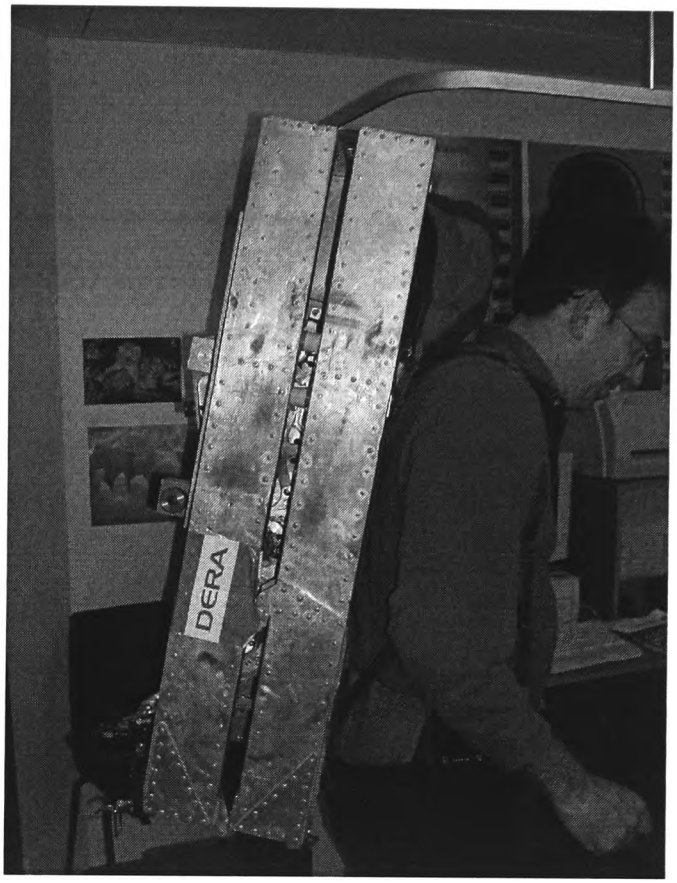






Alticycle™ :





b) Carotid surgery related publications.

10. A comparison of the Invos 3100 and the Critikon 2020 near-infrared spectrophotometers as monitors of cerebral oxygenation

Authorship:

CHE Imray and C Knickenberg.

Publication:

Anaesthesia 1997: **52(8)**; 805.

Publication type:

Peer review letter

Background:

In order to operate on the carotid artery, as part of a strategy for stroke prevention, it is necessary to temporarily clamp the common, external and internal carotid arteries. This results in hypoperfusion of the ipselateral anterior cerebral circulation. Depending upon the adequacy of the collateral cerebral circulation there may be a resulting compromise to local cerebral perfusion. In a patient undergoing carotid surgery under general anaesthesia a number different techniques have been used to assess the situation. Internal carotid artery stump pressure, EEG and transcranial Doppler assessments have been used. During the cross clamp phase of carotid surgery it is possible to measure the arterial pressure in the internal carotid artery or 'stump pressure', and this has been used as a measure of adequacy of the cerebral collateral circulation. In the late 1990s a new non-invasive technique of near-infrared spectrophotometry (NIRs) as a monitor of cerebral oxygenation was introduced.

Interim conclusions:

In this letter we described our experiences in the use of cerebral near infrared cerebral spectroscopy both in the operating theatre and also at altitude. Our response was to other authors who felt the Critikon 2020 unreliable in theatre. We countered their criticism by recounting our experience, in particular emphasising the importance of careful experimental or clinical techniques. It was also my first publication on the subject of cerebral NIRs.

Implications:

NIRs cerebral spectroscopy is an important research tool, which is robust and functions satisfactorily in both the hospital and field setting if due care and attention is applied to technical details and methodology.

11. Near-infrared cerebral spectroscopic (NIRs) monitoring of patients undergoing carotid endarterectomy under loco-regional anaesthesia.

Authorship:

D Williams, P Laws, **CHE Imray**, S Lambert, P Horrocks.

Publication:

Annals of the Royal College of Surgeons of England 1999:**81**; 431-432.

Publication type:

Peer review paper

Background:

The new technique of non-invasive cerebral NIRS was used in this study to attempt to assess the adequacy of the collateral cerebral circulation during the cross clamp phase of carotid endarterectomy.

Aims and hypothesis

The aim of this study was to assess cerebral oxygenation during carotid surgery. The hypothesis was that NIRs might offer a simple non-invasive technique that might reduce the inherent risks of surgery.

Subjects:

45 patients undergoing carotid endarterectomy under loco-regional anaesthesia

Interim conclusions:

This paper was one of the first to describe the use of cerebral NIRs during loco-regional anaesthetic carotid surgery. The technique proved to be simple and reliable to use, but the range of changes observed during the cross clamp phase was large. Consequently, the determination of a drop in cerebral NIRs consistent with an absolute threshold where a shunt has to be used could not be satisfactorily determined.

Implications:

The range of changes of cerebral NIRs observed during the cross-clamp phase was too large to confidently predict preservation of adequacy of cerebral perfusion. In my opinion NIRs remains a research tool.

12. Blood pressure manipulation during loco-regional anaesthetic carotid surgery.

Authorship:

CHE Imray, M Mead, A Thacker and W Dimitri.

Publication:

British Journal of Anaesthesia, 2002; **88(2):** 303-304.

Publication type:

Peer review letter

Background:

During a carotid surgery (endarterectomy) it is necessary to temporarily clamp the common, internal and external carotid arteries. If there is an inadequate collateral cerebral circulation a temporary indwelling carotid shunt needs to be inserted to prevent a neurological deficit. Stoneham et al describe two cases where pharmacologically augmenting the systemic blood pressure reversed the neurological deficits.

Interim conclusions:

In this letter we responded to the observation that a small rise in blood pressure could reverse a neurological deficit during the cross-clamp phase of local anaesthetic carotid surgery. We had observed a rise in cerebral oxygenation (NIRs) when the patients' blood pressure was augmented. There appeared to be an increase in cerebral oxygen delivery associated with a rise in blood pressure. Up until this time it was felt that cerebral blood flow was constant across a wide range of systemic blood pressures.

13. Crescendo TIAs: The use of pre-operative TCD directed I.V. Dextran therapy to control symptoms and emboli prior to elective carotid endarterectomy.

Authorship:

N Lennard, C Vijayasekar, C Tiivas, D Higman and CHE Imray.

Publication:

British Journal of Surgery 2003; **90**: 166-170.

Publication type:

Peer review paper

Background:

There is little evidence as to how to best manage patients with recurrent or crescendo TIAs. Based upon the reported poor outcome of patients with crescendo TIAs with medical treatment alone, a more aggressive approach with urgent surgical intervention has been advocated. However the published results of urgent carotid surgery are variable and some reports describe high morbidity and mortality figures. A recent systematic review of the risks of carotid endarterectomy in relation to both the clinical indication for and timing of surgery has shown that urgent carotid surgery for evolving symptoms has a much higher risk than surgery for stable symptoms. Since both medical and emergency carotid surgery appear to have significant complication rates, this paper describes a new and an alternative approach.

Aims and hypothesis:

We aimed to reduce the risk of surgery to patients in the very high risk category of recurrent and crescendo TIAs. Our hypothesis being that these patients embolised from their internal carotid plaque and that contrary to wide belief the emboli were predominantly platelet emboli rather than cholesterol emboli.

Subjects:

19 patients with crescendo or recurrent TIAs

Methodology and statistical analysis:

Prospective observational study

Interim conclusions:

In this study, it was shown that it was possible to influence the timing of carotid surgery in patients with recurrent or crescendo TIAs. Nineteen patients were treated with a combination of aggressive TCD-directed medical therapy and elective surgery.

Following a TIA, patients were assessed as outpatients in the vascular laboratory, and each was questioned about any focal neurological symptoms within the previous four weeks (hemi sensory, hemi motor, dysphasia or amaurosis fugax). All patients then underwent a routine carotid Duplex, and those with more than one focal event and an appropriate sided critical internal carotid stenosis underwent one-hour of TCD monitoring of the symptomatic middle cerebral artery. Patients with more than one focal event and microembolic signal(s) were admitted to hospital. Maximal oral medical therapy was started, and a TCD-directed intravenous infusion of Dextran 40 was commenced. The infusion was incrementally increased until there were no cerebral microembolic signals. Since no patient had symptoms once the microemboli ceased, it would appear that sustained embolization is associated with symptoms.

We hypothesised that the delay between admission and the next elective list allows a period of plaque stabilisation to occur, reducing the operative risk compared to emergency surgery with an unstable plaque. The delay has the additional advantage of moving high-risk surgery out of the emergency arena and into elective hours with the independently demonstrated lower complication rates, and could be used to allow safe inter-hospital transfer.

Implications:

This paper, originally presented in oral format in November 2001, is of profound clinical importance, fundamentally altering our perceptions of how to deal with patients who continue to embolise after a carotid artery TIA or stroke. Converging lines of evidence from other groups confirms the approach, and I have a review article on the subject Lancet Neurology, September 2005 (32).

14. Timing of surgery in symptomatic carotid disease.

Authorship:

CHE Imray, DJ Higman, C Tiivas.

Publication:

Lancet 2004; **363(9420)**:1553-4.

Publication type:

Peer review letter

Background:

The risk of stroke after a hemispheric transient ischaemic attack (TIA) is greatest within the first 72 hours, and prevalence as high as 20% within the first month has been reported. A case for all carotid surgery to be performed within two weeks of the index focal event was put forward.

Interim conclusions:

If the optimal timing of surgery is two weeks after the patient's last symptoms, then the implications for health care provision are enormous. In order to be able to offer the highest risk patients early surgery, an attempt to stratify the risk of waiting needs to be made. Transcranial Doppler can be used to assess both middle cerebral artery velocity and also platelet microemboli. Immediately after a carotid territory TIA or stroke there is a rise in microemboli in the middle cerebral artery, and those patients who continue to embolize are at a greater risk of a further neurological event. A high micro-embolic load after carotid endarterectomy is also associated with early carotid thrombosis. Control of the high embolic load using intravenous TCD directed antiplatelet agents reduces the risk of early postoperative stroke. It is possible to influence the timing of carotid surgery in patients with recurrent or crescendo TIAs. Control of both emboli and symptoms using TCD directed Dextran allowed these high-risk patients to undergo carotid surgery safely on the next elective list.

Implications:

Microemboli appear to be a surrogate marker for future embolic events (TIAs or strokes) and the pharmacological efficacy of any therapeutic intervention can now rapidly and non-invasively be assessed. TCD emboli detection may offer an approach as to how to manage patients both medically and surgically.

15. Validity of near-infrared cerebral spectroscopy.

Authorship: K Pattinson, Clutton-Brock, **CHE Imray**

Publication:

British Journal of Anaesthesia. 2004; **59(5)**: 507-8

Publication type:

Peer review letter

Background:

A response to a letter describing the use of cerebral NIRs in paediatric cardiac surgery.

Interim conclusions:

This letter discusses the limitations of near infrared spectroscopy. In particular raising concerns about making important clinical decisions based upon cerebral NIRs in children undergoing cardio-pulmonary bypass procedures without controlling for temperature.

Implications:

NIRs remains in my opinion an interesting research tool offering important insights into the observed trends in cerebral oxygenation. Failing to realise the limitations in the technique has potentially serious consequences.

16. Screening for carotid disease and 'stroke prevention units'

Authorship:

CHE Imray and K Pattinson.

Publication:

British Medical Journal. 2004; **329(7478)**: 1344.

Publication type:

Peer review letter

Background:

The risk of stroke after a hemispheric transient ischaemic attack (TIA) is greatest within the first 72 hours, and prevalence as high as 20% within the first month has been reported. The Royal College of Physicians 'National Clinical Guidelines for Stroke' (2004) recommend that patients with TIAs or minor stroke should be seen in a specialist neurovascular clinic within 7 days, and those with more than one TIA (recurrent or crescendo TIAs) should be admitted and investigated immediately.

Interim conclusions:

Transcranial Doppler ultrasound can detect microemboli. This allows the efficacy of therapeutic interventions to be rapidly and non-invasively assessed. Controlling the rate of embolization reduces the risk of an early postoperative stroke. Controlling emboli and symptoms in patients with recurrent or crescendo transient ischaemic attacks using Doppler-directed drug therapy allows these high-risk patients to undergo elective carotid surgery safely. In our opinion, patients with focal neurological events need assessment within 24-48 hours. Those with critical carotid stenoses, symptoms and emboli should be admitted to a 'Stroke Prevention Unit' (similar to a coronary care unit). The unit would be jointly managed by vascular surgeons and stroke physicians, with high staff to patient ratio. Rapid control of microemboli could be achieved, and since microemboli appear to be surrogate markers for future embolic events, some strokes will be prevented.

Implications:

Some strokes are preventable, particularly if a more aggressive treatment approach is adopted, this approach is clearly described in this publication.

17. Are some strokes preventable? A potential role for transcranial Doppler in TIAs of carotid origin.

Authorship:
CHE Imray and C Tiivas.

Publication:
Lancet Neurology 2005; **4(9)**: 580-6.

Publication type:
Peer review article.

Methodology and statistical analysis:

Medline and Pubmed search from 1980 to June 2005.

Interim conclusions:

Immediately after a TIA or stroke there is a rise in TCD-detected cerebral microembolic signals (MES). Those patients who continue to embolize are at greater risk of a further neurological event (112). A recent systematic review of 13 studies of the risks of carotid endarterectomy in relation to both the clinical indication for and timing of surgery has shown that urgent carotid surgery carries a much higher risk (19.2%, 95% CI, 10.7 to 27.8) than elective surgery (OR, 3.9; 95% CI, 2.7 to 5.7; P<0.001)(110).

Recurrent or crescendo TIA patients represent a particularly high-risk group. It is possible to stop both emboli and further symptoms in these patients with TCD-directed intravenous antiplatelet agents. The dose being incrementally increased until the MES cease. Consequently it is possible to influence the timing of surgical intervention, allowing patients to undergo carotid endarterectomy safely on the next elective list (167), avoiding the risks associated with urgent or emergency surgery (110) or the risks associated with delay in patients whose MES persist despite oral antiplatelet therapy (120).

Implications:

In this review we argue the case for greater use of TCD in stroke prevention. We believe the closer integration of medical and surgical approaches can prevent some strokes.

In North America the approach in high risk patients with recurrent symptoms is to advocate urgent surgery with the high associated risks (110). In the UK, patients tend to be treated medically for a longer period of time exposing the patient to risks associated with delay (120). We argue the case for an evidence based integrated multidisciplinary approach.

MES are surrogate markers for the risk of future embolic events. The pharmacological efficacy of therapeutic interventions can now be assessed rapidly, non-invasively and inexpensively. TCD emboli detection appears to offer an important advance enabling the optimal integration of both medical therapy and the timing of surgery.

6) Overall conclusions

In this final section, I will concentrate on my two most recently published major papers. Both papers give important new insights into our existing knowledge and understanding and they draw upon the previous publications techniques and methodologies.

Cerebral perfusion at high altitude

Paul Bert (1833-1886), the French physiologist, has been described as the father of modern high altitude physiology. The publication of *La Pression Barometrique* in 1878 put forward the views that the harmful effects of high altitude are caused by the low PaO_2 (70). One of his critical observations was that various animals including sparrows, guinea pigs and frogs became ill or died at the same partial pressure of oxygen independent of whether it had been produced as a result of a reduced total atmospheric pressure or a reduction in the oxygen fraction. He found that unconscious animals could be revived if the oxygen concentration was increased. He was also the first person to describe deterioration in cerebral function in subjects subjected to acute hypobaria. He noted an impairment of vision, hearing and a mental dullness, which rapidly reversed with oxygen.

Angelo Mosso (1846-1910) was Professor of Physiology in Turin. He had a wide range of interests but was particularly interested in the cerebral blood flow and its possible involvement in the development of acute mountain sickness. Mosso set up a remarkable experiment directly challenging Bert's hypothesis that the effects of altitude were primarily due to lack of oxygen (136). He persuaded his technician Giorgio Mondo to be exposed to 6500m in a chamber. He alleviated symptoms of mountain sickness with 0.9% carbon dioxide. He felt carbon dioxide had a protective role in preventing the deleterious effects of sudden ascent to altitude.

Non-invasive cerebral perfusion techniques at altitude

NIRS techniques have been shown to be robust and reliable at altitude, and as a result the technique has provided important insights into cerebral oxygen delivery and the mechanisms by which adequate oxygenation is sustained under most circumstances.

There is a steady fall in NIRs cerebral regional oxygenation (rSO_2) with increasing altitude in subjects on exposures to high altitude from 70.2(2.4) % at 150m to 63.6(2.3) % at 4680m (it should be noted that the rSO_2 represents mixed venous and arterial saturations). There was an associated fall in SaO_2 from 98.1(0.9) % at 150m to 75.1(5.9) % at 4680m. End tidal carbon dioxide fell from 5.9(0.6) kPa to 3.4(0.3) kPa. (137).

Dynamic NIRS studies assessing various physiological manipulations such as hyperventilation, oxygen therapy and CO_2 supplementation have been studied. 3% CO_2 enriched air markedly improved cerebral oxygenation at both sea level and 4680m and oxygen at 6l/min improved cerebral oxygenation at 4680m. Voluntary hyperventilation reduced cerebral oxygenation at sea level and 2270m, had no effect at 3650m but improved cerebral oxygenation at 4680m. At sea level the hyperventilation reduced the $PaCO_2$ resulting in cerebrovasoconstriction and a reduction in cerebral oxygenation, whilst at 4680m, hyperventilation improved the PaO_2 so markedly that this effect appeared to override the cerebovasoconstrictive effect (17).

The cardio-pulmonary effects of exercise at altitude have been studied extensively but the effect of exercise on cerebral perfusion has received limited attention. No comparable studies of cerebral oxygenation at maximal exercise (VO_{2max}), or any combined measurements of cerebral oxygenation and MCA blood velocity at VO_{2max}, at high altitude have been reported. The results from our Journal of Applied Physiology paper (11) showed reductions in cerebral oxygenation and oxygen delivery during sub maximal and maximal exercise at altitude.

The major determinants of cerebral blood flow are PaO_2, $PaCO_2$ (138) and blood pressure, and each of these is altered by both exercise and altitude. Reductions in both PaO_2 and $PaCO_2$ on acute exposure to altitude, and during exercise at altitude, will have opposing effects on cerebral blood flow. Furthermore the effects of these stimuli will be modified with acclimatization. An important part of the respiratory acclimatization to altitude is the change in the hypercapnic ventilatory response, resulting in increased ventilatory sensitivity to carbon dioxide (88). It has been shown

that both cerebral blood flow and cerebral oxidative metabolism returns toward baseline by 3 weeks at 5260 m (139).

Our finding that acute exposure to the three altitudes had no effect on resting mean systemic arterial blood pressure is consistent with other reported studies (140). The rise in mean blood pressure in response to sub maximal exercise at each high altitude was similar to that found at 150 m, but was only significantly increased at the two highest altitudes. The fall in blood pressure at VO_{2max} is consistent with other reports (140, 141). The changes in blood pressure we observed with exercise at altitude are well above the range at which autoregulation has been shown to occur. Auto regulation maintains a constant cerebral blood flow of 50 to 60 ml $100g^{-1}$ tissue min^{-1} over arterial pressures ranging from 60 to 140 mmHg (142). Experience during carotid endarterectomy under loco-regional anesthesia suggests that cerebral blood flow during the cross-clamp phase can be increased with a fairly modest rise in blood pressure, avoiding the need for shunting. A rise in systolic blood pressure of 35 to 45 mmHg can reverse neurological deficits (9), and is also associated with improved regional cerebral oxygenation (10). The rise in blood pressure may maintain cerebral perfusion during sub maximal exercise at altitude but the fall in blood pressure at VO_{2max} could be a critical factor limiting exercise.

Figure 17

Changes in MCAV with exercise at SL, 3,610m, 4,750m and 5,260m

Taken from CHE Imray et al (Ref 11)

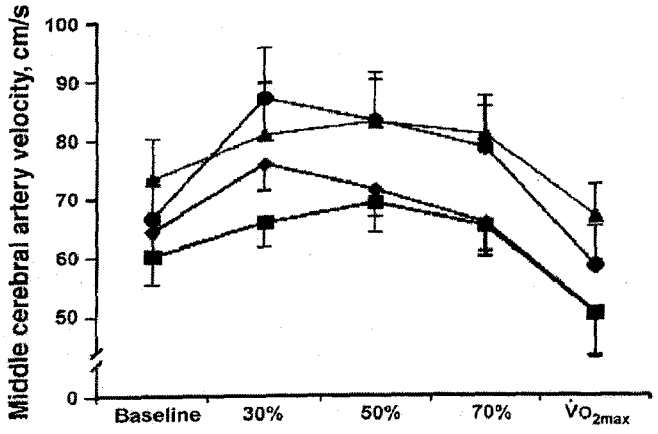


Fig. 2. Changes in middle cerebral artery blood velocity during exercise at different altitudes (■, 150 m; ◆, 3,610 m; ●, 4,750 m; ▲, 5,260 m). Values are means and SE. Velocity at rest increased with increasing altitude ($P < 0.05$). At all altitudes, velocity increased during submaximal exercise ($P < 0.05$–0.0001) but fell at maximal oxygen uptake ($\dot{V}O_{2\,max}$; $P < 0.01$–0.0001).

NIRs measures changes in cerebral tissue oxygenation which is dependant upon blood flow, arterial oxygenation, cerebral metabolism and arterial/venous partitioning (the relative proportion in either the arterial or venous vascular beds). The fall in arterial oxygen saturation at rest with increasing altitude was the most likely cause of the decrease in resting cerebral oxygenation and the increase in resting MCA blood velocity. Similar rises in MCA blood velocity have previously been reported, and appear to be most marked on acute ascent, gradually returning towards normal over the following days to weeks (139, 143, 144).

Figure 18

Change in $rSO_2$with exercise at SL, 3,610m, 4,750m and 5,260m

Taken from CHE Imray et al (Ref 11)

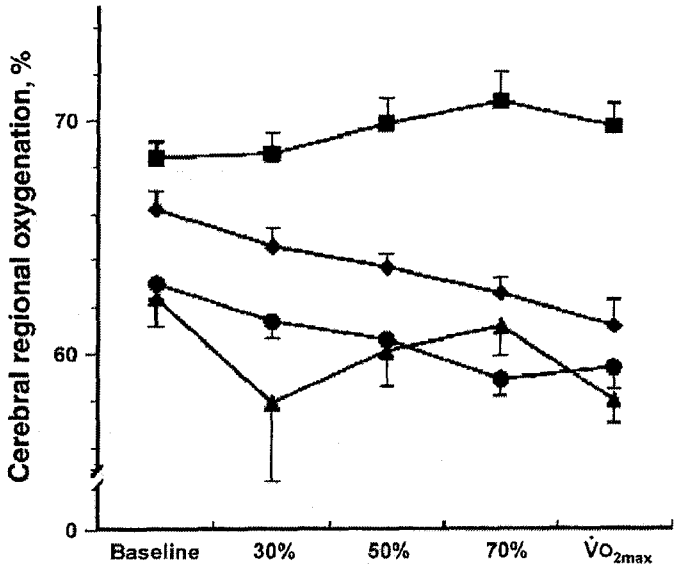


Fig. 3. Changes in cerebral oxygenation at different altitudes (■, 150 m; ◆, 3,610 m; ●, 4,750 m; ▲, 5,260 m). Values are means and SE. Resting oxygenation decreased with increasing altitude ($P < 0.0001$). At 150 m, oxygenation increased during submaximal exercise ($P < 0.0001$) and at $\dot{V}O_{2\,max}$ ($P < 0.05$). At higher altitudes, oxygenation was reduced during submaximal exercise and at $\dot{V}O_{2\,max}$ ($P < 0.01$–0.0001).

The small rise in cerebral oxygenation during sub maximal exercise at 150 m could have occurred as a result of an increase in oxygen delivery induced by a gradual fall of cerebral vascular resistance and a matching increase in MCA velocity; but an alternative explanation for the observed rise in cerebral oxygenation could be decreased cerebral oxygen consumption. Similar changes in MCA blood velocity and cerebral oxygenation during sub maximal exercise have been reported (145, 146,

147). At VO_{2max} at 150 m there was a rise in cerebrovascular resistance and an associated fall in MCA velocity. Cerebrovascular resistance was calculated using the formula: CVR_{est} = (mean arterial blood pressure / MCA blood velocity) Despite this, near infrared cerebral oxygenation remained higher than the resting levels. This may be attributable to decreased oxygen uptake which has been described previously during exhaustive exercise at sea level (148).

In contrast, at the high altitudes studied, cerebral oxygenation (rSO_2) fell progressively during sub maximal exercise, with a further fall at maximal exercise. There was an increase in cerebral deoxygenated hemoglobin (HDO_2) with both altitude and exercise. Saito and colleagues (149) showed similar changes in cerebral oxygenation at sea level and a fall at 2,700 m and 3,700 m during sub maximal exercise, which was equivalent to our level of 50% of VO_{2max}. However we found that although cerebral oxygen delivery was sustained to 70% VO_{2max} at sea level, at the high altitudes studied, oxygen delivery peaked at 30% VO_{2max} and thereafter fell. With partial acclimatization there appeared to be a trend towards improved cerebral oxygen delivery as seen at 5,260 m. The increase in MCA blood velocity during sub maximal exercise may have been due to several factors, the most important of which would appear to be increases in mean blood pressure, because there were only small changes in end-tidal CO_2. Our finding of a gradual fall of cerebral oxygenation during sub maximal exercise and VO_{2max} at altitude may be attributed to the gradual fall in oxygen delivery. At sea level there was a rise in cerebral oxygenation at VO_{2max} despite a fall in MCAV and an explanation could be that at VO_{2max} there is a decrease in cerebral oxygen consumption. We believe the slight differences in cerebral oxygenation during sub maximal exercise at the two highest altitudes were due to the relatively small change in altitude, and to some acclimatization between the two tests.

It has been shown that during maximal exercise on a rowing machine in elite athletes (150), arterial oxygen saturation and regional cerebral oxygenation decrease, but are maintained at resting levels with moderate hyperoxia (inspired O_2 fraction 0.3). Exercise performance was also elevated without a change in muscle oxygenation, indicating that the cerebral hypoxia rather than muscle hypoxia appears to be a contributing factor for the limitation of exercise capacity. There was an observed reduction in arterial CO_2 at maximal exercise. In a second sea level study by the same

group, cerebral perfusion was shown to increase in excess of the increases in the global cerebral metabolic activity during the brain activation associated with exercise and that lactate supplements glucose as energy fuel for the brain when the plasma lactate level is elevated. Furthermore, as evidenced by $MCAV_{mean}$ determined by transcranial Doppler, cerebral perfusion was enhanced and cerebral oxygenation determined by near-infrared spectroscopy suggested flow increased to a larger extent than the corresponding metabolic oxygen demand (145).

Figure 19

Change in cerebrovascular resistance with exercise at SL, 3,610m, 4,750m and 5,260m

Taken from CHE Imray et al (Ref 11)

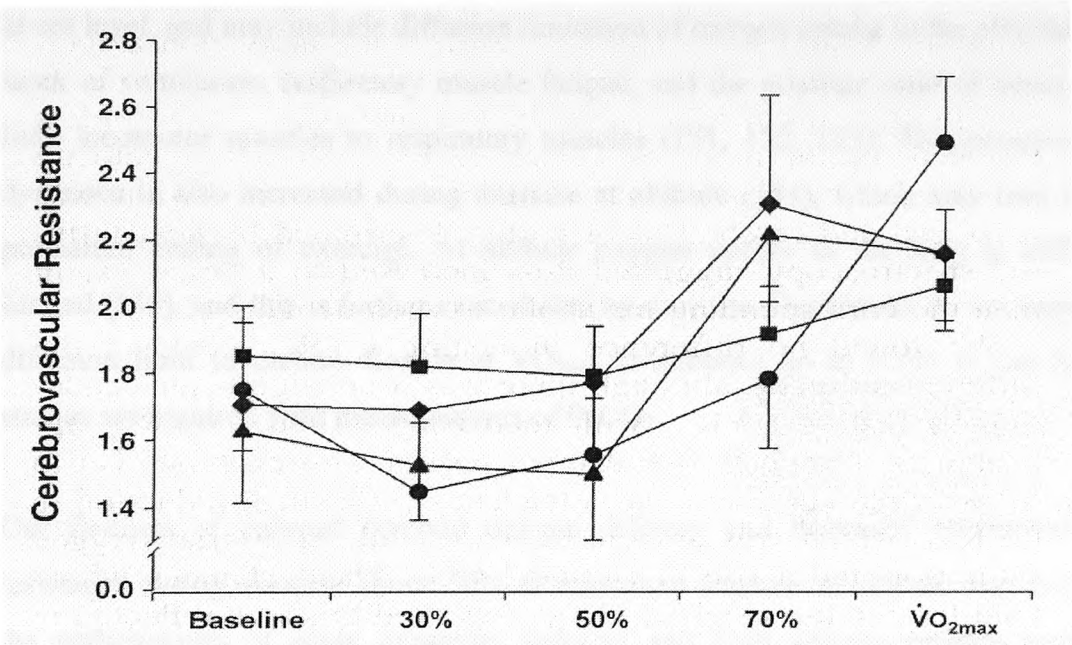


Fig. 4. Changes in cerebrovascular resistance at different altitudes (■, 150 m; ◆, 3,610 m; ●, 4,750 m; ▲, 5,260 m). Values are means and SE. Resting values did not change with increasing altitude. Resting and $\dot{V}O_{2\,max}$ values were not significantly different at 150 m but rose at 3,610 m ($P < 0.05$), 4,750 m (not significant), and 5,260 m ($P < 0.0001$).

CVR_{est} appeared to change in two distinct phases with exercise. Up to 50% of VO_{2max} there was a tendency for a small reduction in CVR_{est}, which was associated with a fall in arterial oxygen saturation and a rise in end-tidal CO_2. These changes would tend to

increase cerebral blood flow and this was reflected in the rise in cerebral oxygen delivery observed at all altitudes at 30% sub maximal exercise. There appeared to be a second phase between 70% and VO_{2max}. In this phase there was a marked rise in CVR_{est} at all altitudes and this is associated with falls in end-tidal CO_2 and small rises in arterial oxygen saturation. Both of these changes would tend to decrease cerebral perfusion, and again this was reflected by the reduction of cerebral oxygen delivery observed at all altitudes at VO_{2max}. Somewhat surprisingly we found no direct correlation between end-tidal CO_2 and CVR_{est}. However the CVR_{est} is a product of the complex dynamic inter-relationship between all the variables mentioned above as well as changes in hypoxic and hypercapnic ventilatory responses and cerebrovascular responsiveness to CO_2.

The factors limiting exercise at altitude may be different from those that limit exercise at sea level, and may include diffusion limitation of oxygen uptake in the alveolus, the work of ventilation, respiratory muscle fatigue, and the possible steal of blood from limb locomotor muscles to respiratory muscles (151, 152, 153). The perception of dyspnoea is also increased during exercise at altitude (154), which may lead to the premature ending of exercise. At altitude oxygen uptake in the lung is diffusion limited (155), and this is further exacerbated by exercise. Our results do not support a diffusion limit of carbon dioxide at VO_{2max} at altitudes up to 5,260 m but further studies are required with measurements of $PaCO_2$.

Our findings of reduced cerebral oxygen delivery and increased cerebrovascular resistance during exercise above 50% of maximum exercise at altitude may relate to the pathogenesis of acute mountain sickness and high altitude cerebral oedema. Exercise is likely to exacerbate acute mountain sickness through increased hypoxia and our results confirm that the brain is subjected to increasing hypoxia during exercise. Our results may explain the deterioration seen in the accuracy of marksmanship caused by acute exposure to altitude and independent of exercise (156) as well as transient and focal neurological deficits occurring at altitude (157, 158). The large rises in blood pressure observed on exercising close to or at VO_{2max} could explain some of the focal and global transient and permanent neurological events observed at high altitude. Clinical examination at a later time point might miss the period of profound hypertension. It is also of interest that the standard formula of 220-

age (years) used to predict maximal heart rate provided a good estimate at 150 m but increasingly underestimated maximal heart rate at each of the high altitudes (11). This finding has implications for studies using this formula for predicting energy expenditure or work rate during exercise at altitude.

Figure 20

Change in cerebral oxygen delivery with exercise at SL, 3,610m, 4,750m and 5,260m

Taken from CHE Imray et al (Ref 11)

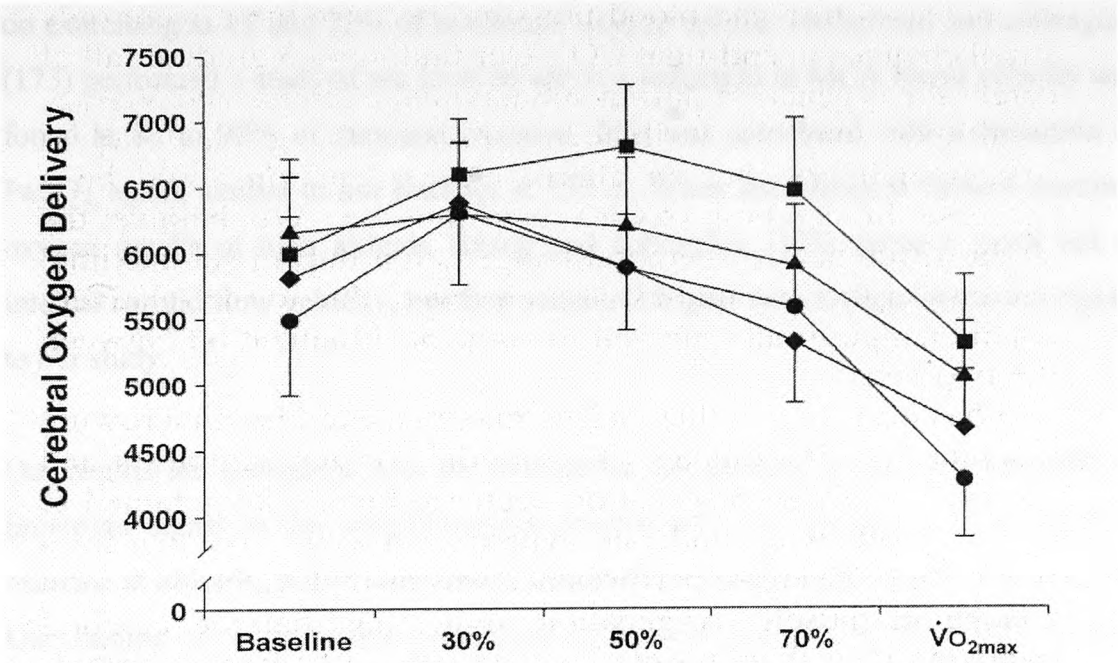


Fig. 5. Changes in cerebral oxygen delivery at different altitudes (■, 150 m; ◆, 3,610 m; ●, 4,750 m; ▲, 5,260 m). Values are means and SE. Resting values did not change with increasing altitude. Resting and $\dot{V}O_{2\,max}$ values were not significantly different at 150 m but fell at 3,610 m ($P < 0.01$), 4,750 m ($P < 0.01$), and 5,260 m ($P < 0.01$).

The reduction in cerebral oxygenation we demonstrated at sub maximal exercise is relevant for normal climbing at oxygen uptakes of 50 to 75% maximum oxygen uptake (159). The finding that mountaineers with a more vigorous ventilatory response to hypoxia have more residual neurobehavioral impairment maybe a result of reduced cerebral oxygen delivery (160). The hypercapneic vasoconstriction and subsequent reduced cerebral oxygenation might be due to a hypocapnic driven reduction in cerebral blood flow (160). Schoene and colleagues (161) showed that the fall in SaO_2 on exercise at altitude was actually greater in subjects with a low hypoxic

could arise as an artifact from the increase in amplitude and frequency of the arterial pressure waveform used in Doppler ultrasound studies (171). Nevertheless cerebral blood flow measured by 133-xenon clearance increased by 31% during sub maximal exercise at sea level (172). Our finding of a 15% increase in MCA blood velocity was similar to the 14% reported by Hellstroem and colleagues (173), who combined duplex ultrasonography and transcranial Doppler ultrasonography. Our results are also comparable to those reported by Huang and colleagues (174) who on acute exposure to 4300 m, recorded increases in internal carotid flow velocity of 15 to 33% on exercising at 45 and 72% of maximum oxygen uptake. Hellstroem and colleagues (173) performed a study at sea level in which a reduction in MCA blood velocity was found at 80 to 90% of maximal exercise. This was associated with a reduction of $PaCO_2$, again, similar to our findings at 150 m. When exercising at 96% of maximal oxygen uptake at high altitude Huang and colleagues (174) noted a small fall in internal carotid flow velocity, but flow remained higher than resting levels, in contrast to our study.

Our results are consistent with the hypothesis that cerebral blood flow provides an important signal to the central nervous system and may become a factor limiting exercise at altitude, rather than cardio-respiratory capacity and muscle fatigue (175). Our finding of considerable reductions in cerebral oxygen delivery and cerebral oxygenation during exercise at altitude suggest that these may provide the critical signals. The reduction of cerebral oxygenation during exercise, if it persists during altitude acclimatization, may explain why VO_{2max} is reduced despite normalization of arterial oxygen content (176). Reduction in cerebral oxygenation during exercise may exacerbate the neurological features of AMS and contribute to the development of high-altitude cerebral edema and other neurological deficits. Our results lend credence to the time-honored advice to avoid strenuous exercise on arrival at high altitude.

b) Cerebral perfusion under ischaemic conditions and the role of trans-cranial Doppler microemboli detection in crescendo transient ischaemic attacks

I) Arterial plaque stabilisation

Plaque rupture with the subsequent formation of an intraluminal, platelet-rich thrombus is the central mechanism leading to critical reduction of coronary perfusion

in the acute coronary syndrome (177). Current therapeutic strategies for acute coronary syndrome aim at the inhibition of activation of platelets and the coagulation cascade and the suppression of platelet aggregation and fibrin formation.

Figure 21

Composite schematic of symptomatic carotid artery stenosis

Taken from CHE Imray & CAS Tiivas (Ref 32)

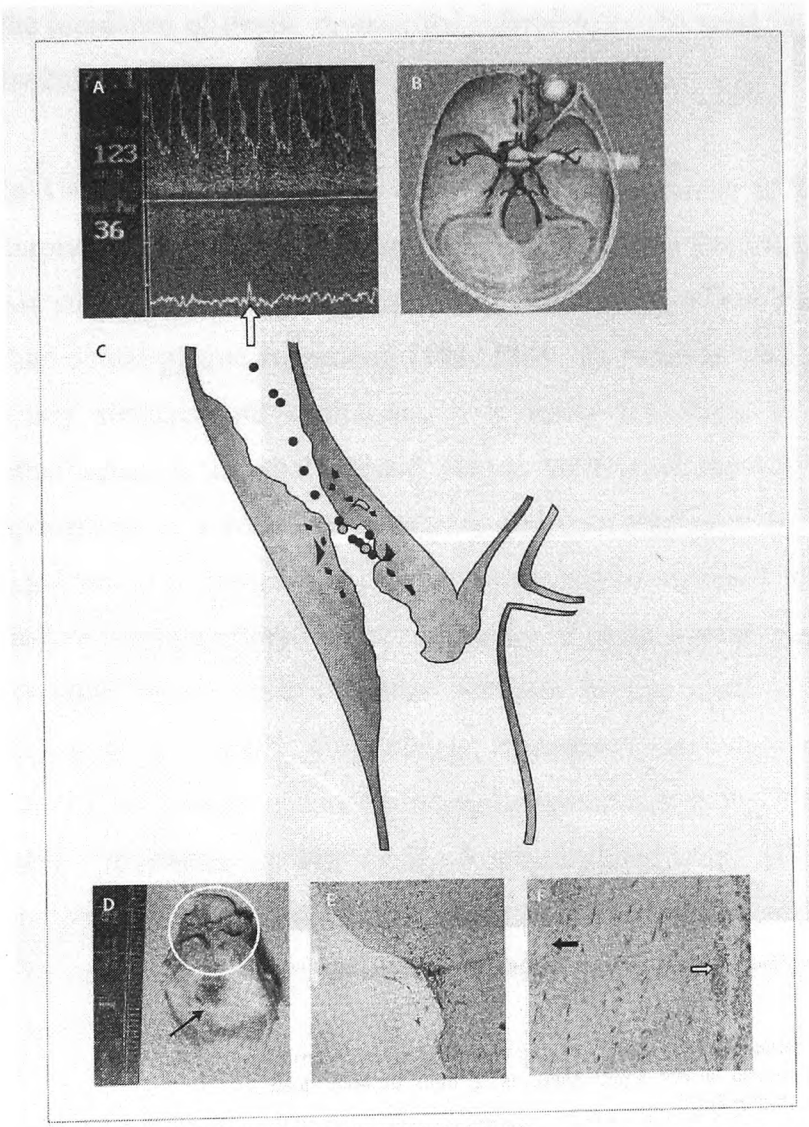


Figure 3: **Composite schematic of symptomatic carotid-artery stenosis**
High intensity transient signal (A, arrow) detected on transcranial doppler insonation of the middle cerebral artery via a temporal window using a 2 MHz probe (B). Carotid bifurcation with artherosclerotic plaque (C) causing >70% stenosis. Emboli originating from surface ulcer or plaque rupture shower the cerebral circulation. Carotid plaque showing surface ulceration (C, right; D, arrow) and disruption of media with intraplaque haemorrhage (D, circle). Microscopy of unstable plaque with subendothelial macrophage accumulation (E; CD68 stain light microscopy, ×100); and intraplaque haemorrhage (F, black arrow) and ulcerated surface with overlying erythrocytes (F, white arrow; haematoxylin and eosin light microscopy, ×200).

The use of acetylsalicylic acid and glycoprotein IIb/IIIa receptor inhibitors is established therapy for the acute coronary syndrome, and efficacy is documented in

several large clinical studies (178, 179, 180). A strategy involving medical stabilisation with a glycoprotein IIb/IIIa receptor inhibitor before coronary interventions was assessed in the CAPTURE study. Patients admitted with unstable angina and who continued to have refractory ischaemia, underwent cardiac catheterization. Patients who were deemed good candidates for coronary interventions were randomized into abciximab therapy for 18-24 hours before angioplasty and one hour afterwards or placebo treatment with coronary angioplasty. Abciximab decreased the incidence of death, myocardial infarction or the need for urgent revascularization by 29% at 30 days (181).

In 1963, Julian et al (182) described the importance of ulcerative plaques at the carotid bifurcation and concluded that embolization from these plaques could occur. It has subsequently been suggested that stabilisation of the plaque was more important than actual plaque regression (183, 184). In patients with a critical internal carotid artery stenosis and symptoms, it is likely that there is an acute rupture of an atherosclerotic internal carotid plaque with superimposed thrombosis. There then appears to be a period of instability and increased activity within the carotid plaque heralded by an increase in cerebral microemboli signals detectable downstream in the middle cerebral artery. In our experience of patients with crescendo or recurrent TIAs, abolition of microembolization prevents further focal events (185). Microemboli appear to be primarily solid platelet aggregates, since they have been controlled with various antiplatelet agents including intravenous aspirin (186, 187), Dextran 40 (188-193), tirofibran (194), and S-nitrosoglutathione (195). Clopidogrel 75mg preoperatively resulted 10-fold reduction in the relative risk of those patients having >20 emboli in the postoperative period (odds ratio, 10.23; 95% CI, 1.3 to 83.3; P=0.01) (196).

Although crescendo or recurrent TIAs appear to at particularly high risk for development of subsequent stroke, recent data from a large, multicentre, nonselected, observational study underscores the "not so benign" prognosis for all TIA patients (197). The high prevalence of stroke following the index TIA ranges from 20% in the first month, to 5% within two days and 10.5% within ninety days (198).

ventilatory drive. The observed reduction of cerebral oxygen delivery during exercise may be more important than absolute altitude in determining the development of acute mountain sickness. At any give altitude arterial and cerebral oxygenations are a dynamic variable dependent upon absolute altitude, oxygen delivery and oxygen consumption. A resting individual at a higher altitude may have the same cerebral oxygenation as an exercising individual at a lower altitude. Both subjects are at the same 'virtual' altitude. Assessing cumulative hypoxic insult (time at a 'virtual altitude') over a 24-hour period might more accurately predict the hypoxic stress an individual has experienced.

The limitations of the NIRs methodology have been reviewed (162, 163). The 2-sensor technique eliminates the contribution from the scalp and skull, thereby giving a measurement of tissue oxygenation at a depth of 2.5 to 5.0 cm. Concerns over contamination of the intracerebral readings with scalp blood flow have been raised in the past. Providing the spacing between the scalp detectors is adequate, scalp flow makes no significant contribution. This was demonstrated using laser Doppler velocimetry and occlusion of scalp flow using a pneumatic tourniquet (164). Near-infrared spectroscopy provides a measure of the proportion of blood that is oxygenated. It does not distinguish how much is in the arterial or venous part of the vascular bed. The proportion of total blood in the brain has been estimated to be 28% arterial and 72% venous (165). In this study we assumed that neither hypoxia nor exercise affects the arterio-venous partitioning. However partitioning of the arterial and venous volumes in the brain under hypoxic conditions at rest has been modeled (166), and it is possible that further changes could occur with exercise.

The trans-cranial Doppler technique is operator dependent and requires careful focusing of the ultrasound probe on the MCA. We standardized this as far as possible by using one experienced operator (167). We cannot be certain whether arterial diameter remained constant during the exercise tests at altitude but other studies at sea level found no changes with either decreases or increases in $PaCO_2$ (168) or during hypocapnia alone (169). Jorgensen and colleagues (170) showed that the increase in regional cerebral perfusion during exercise at sea level occurred in the MCA territory, with increases in mean MCA blood velocities of 19 to 32%. However it has been suggested that much of the increase in MCA blood velocity in response to exercise

II) Timing of surgery

More recently, it has been shown that it is possible to influence the timing of carotid surgery in patients with recurrent or crescendo TIAs (185); nineteen patients were treated with a combination of aggressive TCD-directed medical therapy and elective surgery. Following a TIA, patients were assessed as outpatients in the vascular laboratory, and each was questioned about any focal neurological symptoms within the previous four weeks (hemi sensory, hemi motor, dysphasia or amaurosis fugax). All patients then underwent a routine carotid Duplex, and those with more than one focal event and an appropriate sided critical internal carotid stenosis underwent one-hour of TCD monitoring of the symptomatic middle cerebral artery. Patients with more than one focal event and microembolic signal(s) were admitted to hospital. Maximal oral medical therapy was started, and a TCD-directed intravenous infusion of Dextran 40 was commenced. The infusion was incrementally increased until there were no microembolic signals. Since no patient had symptoms once the microemboli ceased, it would appear that sustained embolization is associated with symptoms. Just as in the post-operative phase, in the pre-operative phase a single embolus does not cause a TIA, but a high embolic load indicates the individual is at greater risk of further neurological events. Patients underwent carotid endarterectomy safely on the next elective operating list up to ten days later. Forty-eight patients with recurrent or crescendo TIAs and associated microembolic signals have now been treated with TCD-directed medical therapy followed by elective surgery with similar results. In five patients who continued to embolize despite maximal oral medical therapy and Dextran 40 at 60mls/hour, microembolic signals were rapidly controlled with a glycoprotein IIb/IIIa receptor inhibitor infusion (unpublished data). We suspect that the delay between admission and the next elective list allows a period of plaque stabilisation to occur, reducing the risk compared to emergency surgery with an unstable plaque. The delay has the additional advantage of moving high-risk surgery out of the emergency arena and into office hours with the known lower associated complication rates (110).

Having controlled symptoms and emboli, there may be a group of patients in whom a subsequent surgical procedure may not be appropriate and the efficacy of subsequent medical therapy can be further assessed.

III) Implications

There are important implications in how all TIAs should be managed. In our opinion all patients presenting with TIA or minor stroke require rapid clinical assessment and Duplex examination to determine the state of the internal carotid arteries (ideally within 24-48 hours). The presence of a critical internal carotid stenosis and more than one TIA requires a TCD study to interrogate the appropriate MCA for microemboli. Those with a critical internal carotid stenosis, symptoms and emboli should be admitted to 'Stroke Prevention and Care Units', similar to coronary care units and should be jointly managed by stroke physicians, neurologists and vascular surgeons. With a high staff to patient ratio, frequent corrections of cardiovascular, metabolic and haematological factors could be achieved, with the aim of preventing strokes from occurring (199, 200). Elective surgery is likely to have better outcomes than the conventional treatments of either medical therapy alone or urgent surgery. Failure to control either microemboli or symptoms with a symptomatic critical internal carotid stenosis remains an indication for urgent surgery.

Figure 22

Surgical technique and carotid plaque appearance

Taken from CHE Imray & CAS Tiivas (Ref 32)

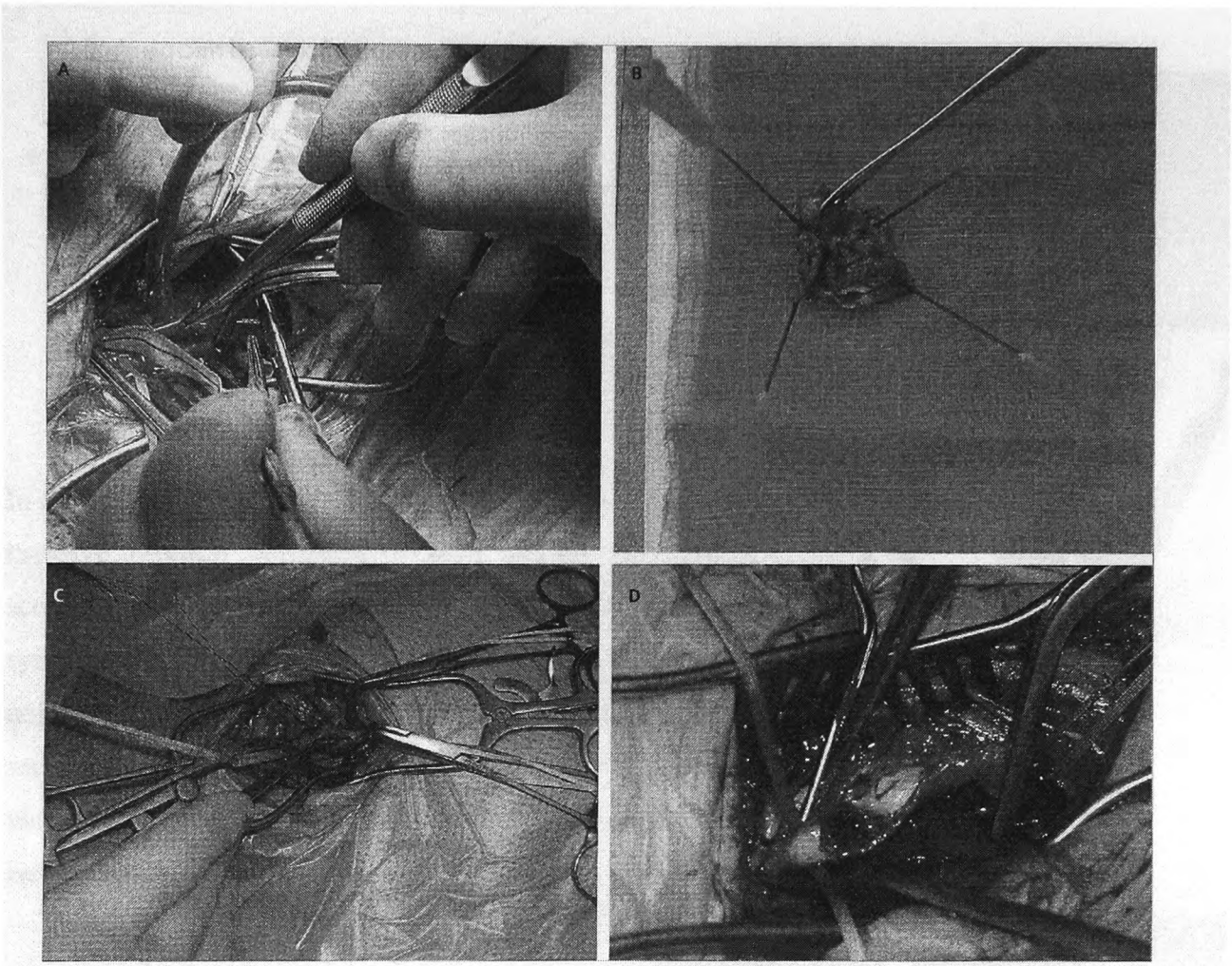


Figure 2: Surgical technique and carotid plaque appearance
A: right carotid endarterectomy with shunt in situ. B: carotid plaque with platelet frond from a symptomatic patient. C and D: intraoperative photographs of a symptomatic carotid plaque.

In 1951, Fisher postulated 'the final thrombus rebuilds itself several times before finally holding' prior to carotid occlusion (201). Platelet microemboli appear to be generated by the thrombogenic surface of the internal carotid artery plaque and have a remote downstream effect, sometimes with devastating clinical outcomes. Emboli are surrogate markers for future ischaemic events, and their control with TCD-directed therapies may offer new insights into how to optimize the management of these high-risk patients, since the pharmacological efficacy of any therapeutic intervention can now be rapidly and non-invasively assessed. We believe that until further studies are

performed, TCD directed anti-platelet therapy in these high-risk patients offer a logical, inexpensive and evidence-based multidisciplinary approach which also allows for the individualization of treatment.

In this overview the author has developed two broad themes, firstly aspects of non-invasive cerebral perfusion at high altitude (in particular NIRs and TCD) and secondly in the use of TCD to control cerebral microemboli in patients with symptomatic carotid artery disease. The two themes are interrelated, firstly by the non-invasive cerebral perfusion monitoring techniques that have been used, and secondly by the insights that the altitude studies give into the clinical situations and vice versa. The hypoxic healthy brain at altitude is in some ways a model for the ischaemic brain.

He has demonstrated original and significant contributions to the existing knowledge by:

I) Critically appraising previous work.

II) Demonstrating the ability to design and develop new methodologies for the investigations.

III) Conducting the research, often in extremely harsh environmental conditions.

IV) Analysing the data obtained.

V) Developing theoretical interpretations to explain the data obtained.

VI) The work has been extensively presented at local, national and international conferences (See Appendix 1)

6) References

1. RJ Last. C.S. Sinnatamby (Editor) Anatomy: Regional and Applied. Churchill Livingstone. ISBN: 0443056110
2. Thomas Willis: 1621-1675, Physician to James II
3. Grants Atlas of Anatomy 7th Edition
4. Young WL, Ornstein E. Cerebral and spinal cord blood flow. In: Cottrell JE, Smith DS, eds. *Anesthesia and Neurosurgery.* St. Louis, MO: Mosby, 1994: 17-58
5. K Pattinson, Wynne Jones, **CHE Imray.** Monitoring of intracranial pressure, cerebral perfusion and metabolism. *Continuing Education in Anaesthesia, Critical Care and Pain.* 2005; **5(4):** 130-133).
6. Paulson OB, Strandgaard S, Edvinsson L. Cerebral auto regulation. *Cerebrovasc. Brain. Metab.* Rev. 1990;**2:** 161-192.
7. Newfield P, Cottrell JE. Neuroanaesthesia: Handbook of Clinical and Physiologic essentials. Second Edition. Little Brown and Company. ISBN 0-316-60471
8. Bouma GJ, Muizelaar JP. Cerebral blood flow, cerebral blood volume, and cerebrovascular reactivity after severe head injury. *J.Neurotrauma.* 1992; 9 Suppl 1:S333-S348
9. **CHE Imray**, M Mead, A Thacker and W Dimitri. Blood pressure manipulation during loco-regional anaesthetic carotid surgery. *British Journal of Anaesthesia,* 2002; **88(2)**: 303-304
10. Stoneham MD, Warner O. Blood pressure manipulation during awake carotid surgery to reverse neurological deficit after carotid cross-clamping *Br J Anaesth.* 2001 Oct; **87(4)**:641-4)
11. **C.H.E Imray**, S. D. Myers, K.T.S. Pattinson, A.R. Bradwell, C. W. Chan, S.Harris, P.Collins, A.D.Wright and the Birmingham Medical Research Expeditionary Society Effect of exercise on cerebral perfusion in humans at high altitude. *Journal of Applied Physiology* 2005; **99(2)**: 699-706
12. Kety SS, Schmidt CF. The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. *J.Clin.Invest.* 1948; **27**: 484-492
13. Reivich M. Arterial PCO2 and cerebral hemodynamics. *Am.J.Physiol.* 1964; **206:** 25-35

14. Brian JE, Jr. Carbon dioxide and the cerebral circulation. *Anesthesiology.* 1998; **88**: 1365-1386

15. Harper AM. Auto regulation of cerebral blood flow: influence of the arterial blood pressure on the blood flow through the cerebral cortex. *J.Neurol.Neurosurg.Psychiatry.* 1966; **29**: 398-403

16. Paulson OB, Strandgaard S, Edvinsson L. Cerebral auto regulation. *Cerebrovasc.Brain.Metab.Rev.* 1990; **2**: 161-192

17. **CHE Imray**, S Brearey, T Clarke, S Walsh, J Morgan, AD Wright. Cerebral oxygen at high altitude and the response to carbon dioxide, hyperventilation and oxygen. *Clinical Science* 2000; **98**: 159-164.

18. **CHE Imray**, S Brearey, T Clarke, S Walsh, J Morgan, AD Wright. Carbon dioxide contributes to the beneficial effect of pressurisation in a portable hyperbaric chamber. *Clinical Science* 2001; **100**: 151-157.

19. **CHE Imray**, S Walsh, T Clarke, J Morgan, H Hoar, T Harvey, AR Bradwell, AD Wright. The effect of supplementary carbon dioxide, oxygen, and a mix of carbon dioxide and oxygen on arterial blood gases and on peripheral, muscle and cutaneous oxygenation at 150m and 3459m. *Clinical Science* 2003; **104**: 1-8

20. Borgstrom L, Johannsson H, and BK Siesko. The relationship between arterial PO2 and cerebral blood flow in hypoxic hypoxia. *Acta Physiol. Scand.* 1975; **93**: 423-32

21. **CHE Imray**, A Thacker, M Mead. Oxygen administration can reverse neurological deficit following carotid cross-clamp. *British Journal of Anaesthesia* 2005; **95(2)**: 274-5

22. Lassen NA Control of cerebral circulation in health and disease *Circ. Res.* 1974; **34**: 749-760

23. Lou HC, Edvinsson L, MacKenzie ET. The concept of coupling blood flow to brain function: revision required? *Ann.Neurol.* 1987; **22**: 289-297

24. Hoge RD, Atkinson J, Gill B, Crelier GR, Marrett S, Pike GB. Linear coupling between cerebral blood flow and oxygen consumption in activated human cortex. *Proc Natl Acad Sci U S A.* 1999; **96(16)**: 9403-8

25. Tyrrell P. Tomographic measurement of cerebral blood flow and metabolism with positron emitting isotopes in man. In : Cerebral Blood Flow and Metabolism. AM Harper and SC Jennett, eds. Manchester University Press, Manchester 1990 ; pp 90-107

26. Buchanan JE, Phillis JW. The role of nitric oxide in the regulation of cerebral blood flow. *Brain.Res.* 1993; **610**: 248-255

27. Petersen SE, Fox PT, Snyder AZ, Raichle ME. Activation of extrastriate and frontal cortical areas by visual words and word-like stimuli. *Science.* 1990; **249:**1041-1044

28. Thiel A, Zickmann B, Stertmann WA, Wyderka T, Hempelmann G. Cerebrovascular carbon dioxide reactivity in carotid artery disease. Relation to intraoperative cerebral monitoring results in 100 carotid endarterectomies. *Anesthesiology.* 1995; **82**: 655-661

29. Kety SS and Schmidt CF. The nitrous oxide method for the quantitative determination of cerebral blood flow in man: theory, procedure and normal values. *J. Clin. Invest.* 1948; **27**: 476-483

30. (Hoedt-Rasmussen K, Sveinsdottir E, Lassen NA. Regional cerebral blood flow in man determined by intra-arterial injection of radioactive inert gas. *Circulation Research* 1966; **18**: 237-247).

31. Jensen JB, Wright AD, Lassen NA, Harvey TC, Winterborn MH, Raichle ME, Bradwell AR. Cerebral blood flow in acute mountain sickness. *J Appl. Physiol.* 1990; **69** : 430-3

32. **CHE Imray**, C Tiivas. Are some strokes preventable? A potential role for transcranial Doppler in TIAs of carotid origin. *Lancet Neurology* 2005; **4(9)**: 580-6

33. McCormick PW, Stewart M, Goetting MG, Balakrishnan G. Regional cerebrovascular oxygen saturation measured by optical spectroscopy in humans. *Stroke* 1991; **22**: 596-602

34. Williams IM, Vohra R, Farrel A, Picton AJ, Mortimer AJ, McCollum CN. Cerebral oxygen saturation, transcranial Doppler ultrasonography and stump pressure in carotid surgery. *British Journal of Surgery.* 1994; **81(7)**: 960-64

35. Henson LC, Calalang C, Temp JA, Ward DS. Accuracy of cerebral oximeter in healthy volunteers under conditions of isocapnic hypoxia. *Anesthesiology* 1998; **88(1)**: 58-65.

36. Totaro R, Barattelli G, Quaresima V, Carolei A, Ferrari M. Evaluation of potential factors affecting the measurement of cerebrovascular reactivity by near-infrared spectroscopy. *Clinical Science* 1998; **95**: 497-504

37. Ward MP, Milledge JS, West JB High Altitude Medicine and Biology 3rd Edition

38. Brunt D, Physical and Dynamical Meteorology, 2nd Edition. Cambridge University Press, p379, 1952

39. Heath D and Williams DR. High altitude medicine and pathology. 4th Edition. Oxford University Press, Oxford. 1995

40. Cunningham DJC, Patrick JM, Lloyd BB. The respiratory response of man to hypoxia in *Oxygen in the animal organism* (eds. F Dickens and E Neil), Pergamon, Oxford. 1964 pp 227-93

41. Harper AM, Glass HI. Effect of alterations in the arterial carbon dioxide tension on the blood flow through the cerebral cortex at normal and low arterial pressures. *J. Neurol. Neurosurg. Psychiatry* 1965; **28**; 449-52

42. Severinghaus JW, Chiodi H, Eger EI, Brandstater B, Hornbein TF. Cerebral blood flow in man at high altitude. Role of cerebrospinal fluid pH in normalization of flow in chronic hypocapnia. *Circ. Res.* 1966; **19**:274-82

43. Milledge J.S. Chapter 2.3. High Altitude in Harries M, Williams C et al. (editors). Oxford textbook of Sports Medicine. Oxford University Press 1994; pages 217-230.

44. Ward MP, Milledge, J.S.West. High Altitude Medicine and Physiology. London: Chapman and Hall Medical; 1995

45. Hackett, P.M., Rennie, D., Levine, H.F. The incidence, importance, and the prophylaxis of acute mountain sickness. *Lancet.* 1976; **2 (7996)**: 1149-1154.

46. Lionel Dumont, Chahe Mardirosoff, Martin R Tramer. Efficacy and harm of pharmacological prevention of acute mountain sickness: quantitative systematic review. *Br Med J.* 2000; **321(7256)**:267-72

47. Maggiorini, K., Buhler, B., Walter, K., Oelz, O. Prevalence of acute mountain sickness in the Swiss Alps. *Br Med J.* 1990; **301**: 853-855.

48. Schneider M, Bernasch D, Weymann J, Holle R, Bartsch P. Acute mountain sickness: influence of susceptibility, pre-exposure, and ascent rate. *Med Sci Sports Exerc.* 2002; **34(12):** 1886-91)

49. Baumgartner RW, Bartsch P, Maggiorini M, Waber U and O Oelz. Enhanced cerebral blood flow in acute mountain sickness. *Aviat. Space Environ. Med.* 1994 **65**:726-9

50. Baumgartner RW, Spyridopoulos S, Bartsch P, Maggiorini M, and O Oelz. Acute mountain sickness is not related to cerebral blood flow: a decompression chamber study. *J Appl Physiol* 1999; **86**: 1578-1582

51. Jansen GF, Krins A, Basnyat B Cerebral vasomotor reactivity at high altitude in humans *J Appl Physiol.* 1999; **86(2)**: 681-6

52. Jansen GFA, Krins A, Basnyat B, Bosch A, and Odoom JA. Cerebral autoregulation in subjects adapted and not adapted to high altitude. *Stroke* 1999; **31**; 2314-2318

53. Yang S-P, Bergo GW, Krasney E, Krasney JA. Cerebral pressure-flow and metabolic responses to sustained hypoxia: effect of CO2. *J. Appl. Physiol.* 1994; **76(1):** 303-13

54. Reeves JT, Moore LG, McCullough RE et al. Headache at high altitude is not related to the internal carotid arterial blood velocity. *J Appl Physiol* 1985; **59**: 905-15

55. Singh I, Khanna PK, Srivastra MC, Lal M, Roy SB, Subramanyam CSV Acute Mountain Sickness *N. Eng. J. Med.* 1969; **280**: 175-84

56. Dickinson J, Heath D, Gosney J, Williams D. Altitude related deaths in seven trekkers in the Himalayas. *Thorax* 1983; **38**: 646-56

57. Fukushima M, Yasaki K, Shibamoto T et al Findings of brain computed tomography in patients with high altitude pulmonary edema. In Hypoxia, Exercise and Altitude. Eds: JR Sutton, CS Houston, and NL Jones. Liss, New York, 1983; pp 456-7

58. AD Wright, **CHE Imray**, MSC Morrisey, RJ Marchbanks and AR Bradwell. Intracranial pressure at high altitude and acute mountain sickness. *Clinical Science* 1995; **89**: 201-204

59. Bailey DM, Roukens R, Knauth M, Kallenberg K, Christ S, Mohr A, Genius J, Storch-Hagenlocher B, Meisel F, McEneny J, Young IS, Steiner T Hess K, Bartsch. Free radical-mediated damage to barrier function is not associated with altered brain morphology in high-altitude headache. *Journal of Cerebral Blood Flow and Metabolism.* June 2005 Epub advance online publication

60. Krasney J. Cerebral hemodynamics and high altitude cerebral edema. In: *Hypoxia: women at altitude* (Houston CS, Coates G, Editors), Burlington, Vermont: Queen City Press, 1997; 254-68

61. Bailey DM, Davies B, Young IS, Jackson MJ, Davison GW, Isaacson R, Richardson RS. EPR spectroscopic detection of free radical outflow from an isolated muscle bed in exercising humans. *Journal of Applied Physiology.* 2003; **94**: 1714-4

62. Bailey DM, Davies B, Young IS. Acute mountain sickness; prophylactic benefits of antioxidant vitamin supplementation at high altitude. *High Altitude Medicine and Biology*. 2001; **2**: 21-9

63. Roach RC, Icenogle M, Hingofer-Szalkay H, Maes D, Sandoval D, Robergs R, Lium D, Loeppky JA. Exercise exacerbates acute mountain sickness at simulated high altitude. *Journal of Applied Physiology*. 2000; **88** : 581-5

64. Bailey DM, Davies B, Young, Hullin DA, Sneddon PS. A potential role for free radical-mediated skeletal muscle soreness in the pathophysiology of acute mountain sickness. *Aviation Space and Environmental Medicine*. 2001; **72**: 513-21

65. Bailey DM, Kleger G-R, Holzgraefe M, Ballmer P, Bartsch P. Pathophysiological significance of peroxidative stress, neuronal damage and membrane permeability in acute mountain sickness. *Journal of Applied Physiology*. 2004; **96**: 1459-63

66. Xu, F., Sevringhaus, JW Rat brain VEGF expression in alveolar hypoxia: possible role in high-altitude cerebral edema. *J. Appl. Physiol*. 1998; **85** : 53-57

67. Prior BM, Yang HT, Terjung RL. What makes vessels grow with exercise training? *J Appl Physiol* 2004; **97**: 1119-1128.

68. Richardson RS, Wagner H, Mudaliar SR, Saucedo E, Henry R, Wagner PD. Exercise adaptation attenuates VEGF gene expression in human skeletal muscle. *Am J Physiol Heart Circ Physiol*. 2000 Aug; 279(2): H772-8

69. Wolff CB. Cerebral blood flow and oxygen delivery at high altitude. *High Altitude Medicine and Biology*. 2000; **1**: 33-38

70. Paul Bert. La pression barometrique. Paris: Masson, 1878.

71. MacFarland RA. Psycho-physiological studies at high altitude in the Andes I. The effect of rapid ascents by aeroplane and train. *Comp. Psychol*. 1937; **23(1)**: 191-225

72. Blass, JP, Gibson, GE. The consequences of mild grade hypoxia. *Advances in Neurology*. 1979; **2**: 229

73. Gill MB, Poulton EC, Carpenter A, et al. Falling efficiency in sorting cards during acclimatization at 19,000ft. *Nature* 1964; **203**: 436

74. Forster PJG. Telescopes in high places, in Aspects of Hypoxia, (Ed D Heath) Liverpool University Press, Liverpool 1986; pp 217-33

75. Gerard AB, McElroy MK, Taylor MJ, Grant I, Powell FL, Holverda S, Sentse N, and J West. Six percent oxygen enrichment of room air at simulated 5000m

altitude improves neuropsychological function. *High Altitude Medicine and Biology.* 2000; **1:** 51-61

76. Gerard AB, McElroy MD, Taylor MJ et al. Six percent oxygen enrichment of room air at simulated 5000m altitude improves neuropsychological function. *High Altitude Medicine Biology* 2000; **1**: 51-61

77. West JB. Do climbs to extreme altitude cause brain damage? *Lancet* 1986 **2(8503):** 387-388

78. Garrido E, Castello A, Ventura AL, et al . Cortical atrophy and other brain magnetic resonance imaging (MRI) changes after extremely high altitude climbs without oxygen. *Int J Sports Med* 1993; **14**: 232-4

79. West JB. 'High Life' p184, 185 ISBN 0-19 512194-5

80. Simon RP, Niiro M, Gwinn R. Brain acidosis induced by hypercarbic ventilation attenuating focal ischemic injury. *J Pharm Exp Ther* 1993; **267**: 1428-1431.

81. Tombaugh GC and Sapolsky RM. Short review. Evolving concepts about the role of acidosis in ischemic neuropathology. *J Neurochem.*1993; **61**: 793-803.

82. Hickling KG, Joyce C. Permissive hypercapnia in ARDS and its effects on tissue oxygenation. *Acta Anaesthesiol Scand* 1995; **107**: 201-08

83. Kazmaier S, Weyland A, Buhre W, Stephan H, Rieke H, Filoda K and Sontag H. Effects of respiratory alkolosis and acidosis on myocardial blood flow and metabolism in patients with coronary artery disease. *Anesthesiology.* 1998; **89**: 831-7

84. Laffey JG, Kavanagh BP. Carbon dioxide and the critically ill –too little of a good thing? *Lancet* 1999; **354**: 183-86

85. Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized trial. *J. Neurosurg.* 1991; **75**: 731-39

86. Bartsch P, Baumgartener RW, Waber U, Marggorini M, Oelz O. Comparison of carbon-dioxide-enriched, oxygen-enriched and normal air in the treatment of acute mountain sickness. *Lancet* 1990; **336**:772-75

87. Harvey TC, Winterborn MH, Lassen NA, Raichle ME, Jensen J, Richardson NV, Bradwell AR and the Birmingham Medical Research and Expeditionary Society. Effect of carbon dioxide in acute mountain sickness: a rediscovery. *Lancet* 1988; **2(8612)**: 639-641

88. Kellogg RH. The role of carbon dioxide in altitude acclimatization. In 'The Regulation of Human Respiration'. Editors DJC Cunningham and BB Lloyd. Blackwell Scientific Publications, Oxford, 1963; pp 379-94

89. Miller FJ Jr, Gutterman DD, Rios CD, et al. Superoxide production in vascular smooth muscle contributes to oxidative stress and impaired relaxation in atherosclerosis. *Circ Res.* 1998; **82**: 1298–1305.

90. Galis ZS, Johnson C, Godin D, et al. Targeted disruption of the matrix metalloproteinase-9 gene impairs smooth muscle cell migration and geometrical arterial remodeling. *Circ Res.* 2002; **91**: 852–859

91. Rosenson RS. Statins in atherosclerosis: lipid lowering agents with antioxidant properties. *Atherosclerosis.* 2004; **173(1)**: 1-12

92. Lefer DJ, Grainger DN. Monocyte rolling in early atherogenesis. *Circulation.* 1999; **84**: 1353-1355.

93. Vainas T, Stassen FR, de Graaf R, Twiss EL, Herngreen SB, Welten RJ, van den Akker LH, van Dieijen-Visser MP, Bruggeman CA, Kitslaar PJ. C-reactive protein in peripheral arterial disease: relation to severity of the disease and to future cardiovascular events. *J Vasc Surg.* 2005; **42(2)**: 243-51.

94. JJ Khatri, C Johnson, R Magid, SM Lessner, KM Laude, SI Dikalov, DG Harrison, H-J Sung, Y Rong, ZS Galis. Vascular Oxidant Stress Enhances Progression and Angiogenesis of Experimental Atheroma. *Circulation.* 2004; **109**: 520-525

95. Griendling KK, Alexander RW. Oxidative stress and cardiovascular disease. *Circulation.* 1997; **96**: 3264–3265

96. Coull A, Lovett J, Rothwell P on behalf of the Oxford Vascular Study. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public organization of services. *BMJ* 2004; **328**: 326-8

97. The Royal College of Physicians 'National Clinical Guidelines for Stroke'. 2nd Edition June 2004. P31. Laverham Press Ltd, Sudbury Suffolk.
ISBN 1 86016 208 8

98. North American Symptomatic Carotid Endarterectomy Trial Collaborators: Beneficial effect of carotid endarterectomy in patients with high grade carotid stenosis. *N Eng J Med* 1991; **325**: 445-453

99. European Carotid Surgery Trialists' Collaborative Group: MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or mild (0-29%) carotid artery stenosis. *Lancet* 1991: **337**: 1235-1243

100. Mayberg MR, Wilson, SE, Yatsu F, Weiss DG, Messina L, Hershey LA, Colling C, Eskridge J, Deykin D, Winn HR. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Co-operative Studies Program 309 Trialist Group. *JAMA* 1991 **266**: 3332-3

101. Mentzer RM, Finkelmeier BA, Crosby IK, Wellons HA. Emergency carotid endarterectomy for fluctuating neurologic deficits. *Surgery* 1981; **89**: 60-6

102. Wilson SE, Mayberg MR, Yatsu F, Weiss DG. Crescendo transient ischemic attacks: a surgical imperative. Veterans Trialists. *J Vasc Surg* 1993; **17**: 249-55

103. Nehler MR, Moneta GL, McConnell DB, Edwards JM, Taylor LM, YeagerRA, Porter JM. Anticoagulation followed by elective carotid surgery in patients with repetitive transient ischemic attacks and high-grade stenosis. *Arch Surg* 1993; **128**:1117-21

104. J Goldstone, WS Moore. Emergency carotid artery surgery in neurologically unstable patients. *Arch Surg* 1976; **111**: 1284-129

105. Schneider C, Johansen K, Konigstein R, Metzner C, Oettinger W. Emergency carotid thromboendarterectomy: safe and effective. *World J Surg* 1999; 23:1163-7

106. Brandl R, Brauer RB, Maurer PC. Urgent carotid endarterectomy for stroke in evolution. *Vasa* 2001; **30**: 115-21

107. Greenhalgh RM, Cuming R, Perkin GD, McCollum CN. Urgent carotid surgery for high-risk patients. *Eur J Vasc Surg* 1993 Suppl A:25-32

108. Eckstein HH, Schumacher H, Klemm K, Laubach H, Kraus T, Ringle P, Dorfler A, Weigand M, Bardenheuer, H, Allenberg JR. Emergency carotid endarterectomy. *Cerebrovascular Dis* 1999; **9**:270-81

109. Gertler JP, Blankenstein JD, Brewster DC, Moncure AC, Cambria RP, LaMuraglia GM, Darling RC, Abbott WM. Carotid endarterectomy for unstable and compelling neurologic conditions: do the results justify an aggressive approach? *J Vasc Surg* 1994; **19**: 42-40

110. Bond R, Rerkasem K, Rothwell PM. Systematic review of the risks of carotid endarterectomy in relation to the clinical indication for and timing of surgery. *Stroke* 2003; **34:** 2302-3

111. U Sliwka, A Lingnau, WD Stohlmann, P Schmidt, M Mull, R R Diehl, J Noth. Prevalence and time course of microembolic signals in patients with acute stroke. *Stroke* 1997; **28** :358-363

112. L. Valton, V Larrue, A Pavy le Traon, P Massabuau, G Geraud. Microembolic signals and risk of early recurrence inpatients with stroke or transient ischemic attack. *Stroke* 1998; **29**: 2125-2128

113. AM Forteza, VL Babikian, C Hyde, M Winter, V Pochay. Effect of time and cerebrovascular symptoms on the prevalence of microembolic signals in patients with cervical carotid stenosis. *Stroke* 1996; **27**: 687-690

114. VL Babikian, C Hyde, MR Winter. Cerebral microembolism and early recurrent cerebral or retinal ischemic events. *Stroke* 1997; **28**: 1314-1318

115. J Molloy, HS Markus. Asymptomatic embolization predicts stroke and TIA risk in patients with carotid artery stenosis. *Stroke* 1999; **30**: 1440-1443

116. S Gao, KS Wong, T Hansberg, WW Lam, DW Droste, EB Ringelstein. Microembolic signal predicts recurrent cerebral ischaemic events in acute stroke patients with middle cerebral artery stenosis. *Stroke* 2004; **35**: 2832-6

117. M Siebler, A Nachtmann, M Sitzer, G Rose, A Kleinschmidt, J Rademacher, H Steinmetz. Cerebral microembolism and the risk of ischemia in asymptomatic high-grade internal artery stenosis. *Stroke* 1995; **26**: 2184-2186

118. M Siebler, A Nachtmann, M Sitzer, H Steinmetz. Anticoagulation monitoring and cerebral microemboli detection. *Lancet* 1994; **344**: 555

119. Goertler M, Baeumer M, Kross R, Blaser T, Lutze G, Jost S, Wallesch CW. Rapid decline of cerebral microemboli of arterial origin after intravenous acetylsalicylic acid. *Stroke* 1999; **30**: 66-9

120. Goertler M, Blaser T, Krueger S, Hofmann K, Baeumer M, C-W Wallesch. Cessation of embolic signals after antithrombotic prevention is related to reduced risk of recurrent arterioembolic transient ischaemic attack and stroke. *J Neurol Neurosurg Psychiatry* 2002; **72**: 338-342

121. Junghans U, Siebler M. Cerebral microembolism is blocked by tirofibran, a selective nonpeptide platelet glycoprotein IIb/IIIa receptor antagonist. *Circulation* 2003; **107**: 2717-2721

122. Mackinnon AD, Aaslid R, Markus HS. Long-term ambulatory monitoring for cerebral emboli using transcranial Doppler ultrasound. *Stroke* 2004; **35**: 73-8

123. Jansen C, Vriens EM, Eikelboom BC, Vermeulen FEE, van Ginj J, Ackerstaff RGA. Carotid endarterectomy with transcranial Doppler and electroencephalographic monitoring: a prospective study in 130 operations. *Stroke* 1993; **24:** 665-669

124. Ackerstaff RGA, Moons KGM, van de Vlasakker, Moll FL, Vermeulen FEE, Algra A, Spencer MP. Asscociation of intraoperative transcranial Doppler monitoring variables with stroke from carotid endarterectomy. *Stroke* 2000; **31:**1817-1823

125. Smith JL, Evans DH, Fan L, Gaunt ME, London NJ, Bell PR, Naylor AR. Interpretation of embolic phenomena during carotid endarterectomy. *Stroke* 1995; **26**: 2281-4

126. Gaunt ME, Martin PL, Smith JL, Rimmer T, Cherryman G, Ratcliff DA, Bell PR, Naylor AR. Clinical relevance of intraoperative embolization detection by transcranial Doppler ultrasonography during carotid endarterectomy: a prospective study of 100 patients. *Br J Surg* 1994; **81**: 1435-9

127. Jansen C, Ramos LMP, van Heeswijk JPM et al. Impact of microembolism and hemodynamic changes in the brain during carotid endarterectomy. *Stroke* 1994; **25** :992-7

128. Jansen C, Moll FL, Vermulen FEE, et al: Continuous transcranial Doppler ultrasonography and electroencephalography during carotid endarterectomy: a multimodal monitoring system to detect intraoperative ischemia. *Ann Vasc Surg* 1993; **7**: 95-101

129. Jansen C, Vriens EM, Eikelboom BC, et al: Carotid endarterectomy with transcranial Doppler and electroecephalographic monitoring. A prospective study in 130 operations. *Stroke* 1993; **24**: 665-669

130. Hayes PD, Lloyd AJ, Lennard N, Wolstenholme JL, London NJ, Bell PR, Naylor AR. Transcranial Doppler-directed Dextran-40 therapy is a cost-effective method of preventing carotid thrombosis after carotid endarterectomy. *Eur J Vasc Endovasc Surg* 2000; **19**: 56-61

131. Naylor AR, Hayes PD, Allroggen H, Lennard N, Gaunt ME, Thompson MM, London NJ, Bell PR. Reducing the risk of carotid surgery: a 7-year audit of the role of monitoring and quality control assessment. *J Vasc Surg* 2000; **32**:750-9

132. CR Levi, AK Roberts, G Fell, MC Hoare, JP Royale, A Chan , BC Beiles, GC Last, CF Bladin, GA Donnan. Transcranial Doppler microembolus detection in

the identification of patients at high risk of perioperative stroke. *Eur J Endovasc Surg* 1997; **14**:170-176

133. CR Levi, H O'Malley, G Fell, AK Roberts, MC Hoare, JP Royale, A Chan , BC Beiles, BR Chambers, CF Bladin, GA Donnan. Transcranial Doppler detected cerebral microembolism following carotid endarterectomy. High microembolic signal loads predict postoperative cerebral ischaemia. *Brain* 1997; **120**: 621-629

134. Lennard N, Smith J, Dumville J et al. Prevention of postoperative thrombotic stroke after carotid endarterectomy: the role of transcranial Doppler ultrasound. *J Vasc Surg* 1997; **26**:579-84

135. CWM Chan, C Tiivas, G Pritchard, DJ Higman, CHE Imray. Post operative trans cranial Doppler monitoring- an early warning device? *International Angiology* 2000; **19** (Suppl): 128.

136. Mosso A. Life of man on the High Alps. London: T Fisher Unwin,1898.

137. **CHE Imray**, NJ Barnett, S Walsh, T Clarke, J Morgan, D Hale, H Hoar, D Mole, I Chesner, AD Wright. Near-infrared spectroscopy in the assessment of cerebral oxygen at high altitude. *Wilderness and Environmental Medicine* 1998; **9**: 198-203

138. Ainslie PN, and Poulin MJ. Ventilatory, cerebrovascular, and cardiovascular interactions in acute hypoxia: regulation by carbon dioxide. *J Appl Physiol* 2004; **97**: 149-159.

139. Moller K, Paulson OB, Hornbein TF, Colier WN, Paulson AS, Roach RC, Holm S, and Knudsen GM. Unchanged cerebral blood flow and oxidative metabolism after acclimatization to high altitude. *J Cereb Blood Flow Metab* 2002; **22**: 118-126.

140. Vogel JA and Harris CW. Cardiopulmonary responses of resting man during early exposure to high altitude. *J Appl Physiol* 1967; **22**: 1124-1128.

141. Vogel JA, Hansen JE and Harris CW. Cardiovascular responses in man during exhaustive work at sea level and high altitude. *J Appl Physiol* 1967; **23**: 531-539.

142. Humphey PRD. Clinical relevance of measurements of cerebral blood flow. *Brit J Hosp Med* 1981; **26**: 233-241.

143. Huang SY, Moore LG, McCullough RE, McCullough RG, Micco AJ, Fulco C, Cymerman A, Manco-Johnson M, Weil JV, and Reeves JT. Internal carotid and vertebral arterial flow velocity in men at high altitude. *J Appl Physiol* 1987; **63**: 395-400.

144. Jensen JB, Wright AD, Lassen NA, Harvey TC, Winterborn MH, Raichle ME, and Bradwell AR. Cerebral blood flow in acute mountain sickness. *J Appl Physiol* 1990; **69**: 430-433.

145. Ide K, Horn A and Secher NH. Cerebral metabolic response to submaximal exercise. *J Appl Physiol* 1999; **87**: 1604-1608.

146. Ide K, and Secher NH. Cerebral blood flow and metabolism during exercise. *Prog Neurobiol* 2000; **61**: 397-414.

147. Nielsen HB, Boesen M, and Secher NH. Near-infrared spectroscopy determined brain and muscle oxygenation during exercise with normal and resistive breathing. *Acta Physiol Scand* 2001; **171:** 63-70.

148. Dalsgaard MK, Ogoh S, Dawson EA, Yoshiga CC, Quistorff B, and Secher NH. Cerebral carbohydrate cost of physical exertion in humans. *Amer J Physiol Regul Integr Comp Physiol* Epub 2004; **287**: R534-540.

149. Saito S, Nishihara F, Takazawa T, Kanai M, Aso C, Shiga T and Shimada H. Exercise-induced cerebral deoxygenation among untrained trekkers at moderate altitudes. *Arch Environ Health* 1999; **54**: 271-276

150. Nielsen HB, Boushel R, Madsen P, and Secher NH. Cerebral desaturation during exercise reversed by O_2 supplementation. *Am J Physiol Heart Circ Physiol* 1999; **277**: H1045-1052.

151. Cibella F, Cuttita G, Romano S, Grassi B, Bonsignore G and Milic-Emili J. Respiratory energetics during exercise at high altitude. *J Appl Physiol* 1999; **86**: 1785-1792.

152. Gudjonsdottir M, Appendini L, Baderna P, Purro A, Patessio A, Villanis G, Pastorelli M, Sigurdsson SB and Donner CF. Diaphragm fatigue during exercise at high altitude: the role of hypoxia and workload. *Eur Respir J* 2001; **17**: 674-680.

153. Mognini P, Saibene F and Veicsteinas A. Ventilatory work during exercise at high altitude. *Int J Sports Med* 1982; **3**: 33-36

154. Burki NK, McConnell JW, Ayub M and Liles RM. Effects of acute prolonged exposure to high-altitude hypoxia on exercise-induced breathlessness. *Clin Sci* 1999; **96**:327-333

155. West JB, Boyer SJ, Graber DJ, Hackett PH, Maret KH, Milledge JS, Peters RM, Pizzo CJ, Samaja M, Sarnquist FH, Schoene RB and Winslow RM. Maximal exercise at extreme altitudes on Mount Everest. *J Appl Physiol* 1983; **55**: 688-698

156. Tharion WJ, Hoyt RW, Marlowe BE, and Cymerman A. Effects of high altitude and exercise on marksmanship. *Aviat Space Environ Med.* 1992; **63**:114-117.

157. Basnyat B, Wu T, and Gertsch JH. Neurological conditions at altitude that fall outside the usual definition of altitude sickness. *High Alt Med Biol* 2004; **5**: 171-179.

158. Murdoch DR. Focal neurological deficits associated with high altitude. *Wilderness Environ Med* 1996; **7**: 79-80.

159. Pugh LGCE. Muscular exercise on Mt Everest. *J Physiol (Lond)* 1958; **141**: 233-261.

160. Hornbein TF, Townes BD, Schoene RB, Sutton JR and Houston CS. The cost to the central nervous system of climbing to extremely high altitude. *N Engl J Med* 1989; **321**: 1714-1719.

161. Schoene RB, Lahiri S, Hackett PH, Peters RM, Milledge JS, Pizzo CJ, Sarnquist FH, Boyer SJ, Graber DJ, Maret KH and West JB. Relationship of hypoxic ventilatory response to exercise performance on Mount Everest. *J Appl Physiol* 1984; **56**: 1478-1483.

162. Schindler E, Zickmann B, Muller M, Boldt J, Knoll J and Hernpelmann G. Cerebral oximetry by infrared spectroscopy in comparison with continuous measurement of oxygen saturation of the jugular vein bulb in intervention of the internal carotid artery. *Vasa* 1995; **24**: 168-175.

163. Pattinson K, Clutton-Brock T, and **Imray C**. Validity of near-infrared cerebral spectroscopy. *Anaesthesia* 2004; **59**: 507-508.

164. Owen-Reece H, Elwell CE, Wyatt JS, and Delpy DT. The effect of scalp ischaemia on measurement of cerebral blood volume by near-infrared spectroscopy. *Physiol Meas* 1996; **17**: 279-286.

165. McCormick PW, Stewart M, Goetting MG, and Balakrishnan G. Regional cerebrovascular oxygen saturation measured by optical spectroscopy in humans. *Stroke* 1991; **22**: 596-602.

166. CB Wolff, **CHE Imray**. Partitioning of arterial and venous volumes in the brain under hypoxic conditions. *Advances in Experimental Medicine and Biology.* 2003; **540**: 19-32.

167. Lennard NS, Vijayasekar C, Tiivas C, Chan CWM, Higman, DJ, and **Imray CHE**. Control of emboli in patients with recurrent or crescendo transient ischaemic attacks using preoperative transcranial Doppler-directed Dextran therapy. *Br J Surg* 2003; **90**: 166-170.

168. Serrador JM, Picot PA, Rutt BK, Shoemaker JK, and Bondar RL. MRI measures of middle cerebral artery diameter in conscious humans during simulated orthostasis. *Stroke* 2000; **31**: 1672-1678,.

169. Valdueza JM, Balzer JO, Villringer A, Vogl TJ, Kutter R, and Einhaupl KM. Changes in blood flow velocity and diameter of the middle cerebral artery during hyperventilation: assessment with MR and transcranial Doppler sonography. *Am J Neuroradiol* 1997; **18:** 1929-1934.

170. Jorgensen LG, Perko G and Secher NH. Regional cerebral artery mean flow velocity and blood flow during dynamic exercise in humans. *J Appl Physiol* 1992; 73: 1825-1830.

171. Poulin MJ, Syed RJ and Robbins PA. Assessments of flow by transcranial Doppler ultrasound in the middle cerebral artery during exercise in humans. *J Appl Physiol* 1999 ; **86:** 1632-1637

172. Thomas SN, Schroeder T, Secher NH and Mitchell JH. Cerebral blood flow during submaximal and maximal dynamic exercise in humans. *J Appl Physiol* 1989; **67**: 744-748.

173. Hellstroem G, Fischer-Colbrie W, Wahlgren NG and Jogestrand T. Carotid artery blood flow and middle cerebral artery blood flow velocity during physical exercise. *J Appl Physiol* 1996; **81:** 413-418.

174. Huang SY, Tawney KW, Bender PR, Groves BM, McCullough RE, McCullough RG, Micco AJ, Manco-Johnson M, Cymerman A, Greene ER and Reeves JT. Internal carotid flow velocity with exercise before and after acclimatisation to 4300m. *J Appl Physiol* 1991; **71**: 1469-1476.

175. Kayser B. Exercise starts and ends in the brain. *Eur J Appl Physiol* 2003; **90**: 411-419.

176. Calbet JAL, Boushel R, Radegran G, Sondergaard H, Wagner PD and Saltin B. Why is VO_2max after altitude acclimatization still reduced despite normalization of arterial O2 content? *Am J Physiol Regul Integr Comp Physiol* 2003; **284**: R304-R316.

177. E Falk, PK Shah, V Fuster. Coronary Plaque Disruption. *Circulation* 1995; **92**: 657-671

178. The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998; **338:** 1498-505

179. The PURSUIT Trial Investigators. Inhibition of Platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med* 1998; **339**:436-43

180. The PARAGON Investigators: International, randomized, controlled trial of Lamifiban (a glycoprotein IIb/IIIa inhibitor), heparin , or both in unstable angina. *Circulation* 1998; **97**:2386-95

181. The CAPTURE Investigators. Randomized placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina; The CAPTURE Study. *Lancet* 1997; **349**;429-35

182. Julian OC, Dye WS, Javid H et al: Ulcerative lesions of the internal carotid artery bifurcation. *Arch Surg* 1963; **86**: 803-809

183. Barth JD: Lipoproteins and the progression/regression of atherosclerosis. *Baillieres Clin Endocrinol Metab* 1995; **9**: 849-866

184. Stark RM: Review of the major intervention trials of lowering coronary artery disease risk through cholesterol reduction. *Am J Cardiol* 1996; **78**: 13-19

185. Lennard NS, Vijayasekar C, Tiivas C, Chan CWM, Higman DJ, **Imray CHE.** Control of emboli in patients with recurrent or crescendo transient ischaemic attacks using preoperative transcranial Doppler-directed Dextran therapy. *British Journal Surgery* 2003; **90** : 166-170

186. Goertler M, Baeumer M, Kross R, Blaser T, Lutze G, Jost S, Wallesch CW. Rapid decline of cerebral microemboli of arterial origin after intravenous acetylsalicylic acid. *Stroke* 1999; **30**: 66-9

187. Goertler M, Blaser T, Krueger S, Hofmann K, Baeumer M, C-W Wallesch. Cessation of embolic signals after antithrombotic prevention is related to reduced risk of recurrent arterioembolic transient ischaemic attack and stroke. *J Neurol Neurosurg Psychiatry* 2002; **72**: 338-342

188. Hayes PD, Lloyd AJ, Lennard N, Wolstenholme JL, London NJ, Bell PR, Naylor AR. Transcranial Doppler-directed Dextran-40 therapy is a cost-effective method of preventing carotid thrombosis after carotid endarterectomy. *Eur J Vasc Endovasc Surg* 2000;**19**:56-61

189. Naylor AR, Hayes PD, Allroggen H, Lennard N, Gaunt ME, Thompson MM, London NJ, Bell PR. Reducing the risk of carotid surgery: a 7-year audit of the role of monitoring and quality control assessment. *J Vasc Surg* 2000; **32**:750-9

190. CR Levi, AK Roberts, G Fell, MC Hoare, JP Royale, A Chan , BC Beiles, GC Last, CF Bladin, GA Donnan. Transcranial Doppler microembolus detection in the identification of patients at high risk of perioperative stroke. *Eur J Endovasc Surg* 1997; **14**:170-176

191. CR Levi, H O'Malley, G Fell, AK Roberts, MC Hoare, JP Royale, A Chan , BC Beiles, BR Chambers, CF Bladin, GA Donnan. Transcranial Doppler detected cerebral microembolism following carotid endarterectomy. High microembolic signal loads predict postoperative cerebral ischaemia. *Brain* 1997; **120**: 621-629

192. Lennard N, Smith J, Dumville J et al. Prevention of postoperative thrombotic stroke after carotid endarterectomy: the role of transcranial Doppler ultrasound. *J Vasc Surg* 1997; **26**:579-84

193. CWM Chan, C Tiivas, G Pritchard, DJ Higman, **CHE Imray**. Post operative trans cranial Doppler monitoring - an early warning device? *International Angiology* 2000; **19 (Suppl)**: 128

194. Junghans U, Siebler M. Cerebral microembolism is blocked by tirofibran, a selective nonpeptide platelet glycoprotein IIb/IIIa receptor antagonist. *Circulation* 2003; **107**: 2717-2721

195. Kapostza Z, Martin J, Markus HS. Switching off embolization from symptomatic carotid plaque using S-Nitrosoglutathione. *Circulation* 2002; **105**; 1480-1484

196. Payne DA, Jones CI, Hayes PD, Thompson MM, London NJ, Bell PR, Goodall AH, Naylor AR. Beneficial effects of clopidogrel combined with aspirin in reducing cerebral emboli in patients undergoing carotid endarterectomy. *Circulation* 2004 ; **109**:1476-81

197. M Daffertshofer, O Mielke, A Pullwitt, M Felsenstein, M Hennerici. Transient Ischemic Attacks are more than "Ministrokes". *Stroke*. 2004; **35**: 2453-58

198. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA*. 2000; 284:2901-6.

199. **Imray C**, Higman D, Tiivas C. Timing of surgery in symptomatic carotid disease. *Lancet* 2004; **363**: 1553-4

200. **Imray CHE**, Pattinson K. Surgery for carotid artery stenosis: Patients with critical stenoses should be admitted to stroke prevention units. *British Medical Journal* 2004; **329**: 1344

201. Fisher M. Occlusion of the internal carotid arteries. *Arch Neurol Psychiatry* 1951; **65:** 346-377

7) Appendix 1

Cerebral Perfusion under hypoxic conditions and at high altitude

PRESENTATIONS TO LEARNED SOCIETIES

Non invasive intracranial pressure monitoring.
Presented to the **Birmingham Hypoxia Symposium, November 1993.**

Methyl progesterone acetate Vs Acetazolamide as a respiratory stimulant at altitude.
Presented to the **Birmingham Hypoxia Symposium, November 1993.**

Non invasive intracranial pressure monitoring.
Presented to the **Medical Research Society, London, 1994.**

Non invasive intracranial pressure monitoring in acute mountain sickness.
Presented to the **World Hypoxia Symposium, Banff, Canada. February 1995.**

Near-infra red cerebral spectroscopic monitoring of patients undergoing carotid endarterectomy under loco-regional anaesthesia.
Presented at the **Norman Tanner Prize Session of the Royal Society of Medicine. September 1998**.

Near-infra red cerebral spectroscopic monitoring of patients undergoing carotid endarterectomy under loco-regional anaesthesia.
Presented at the **Vascular Society of Great Britain and Ireland. Hull, November 1998.**

Carbon dioxide or oxygen at altitude? The effect on arterial blood gases at sea level and on acute exposure to altitude.
Presented to the **1999 International Hypoxia Symposium, Jasper, Canada. March 1999.**

Carbon dioxide and cerebral blood flow at sea level and on acute exposure to altitude.
Presented to the **1999 International Hypoxia Symposium, Jasper, Canada. March 1999.**

Carbon dioxide or oxygen at altitude? Cutaneous, muscle and cerebral oxygenation.
Presented to the **1999 International Hypoxia Symposium, Jasper, Canada. March 1999.**

Carbon dioxide contributes to the beneficial effect of pressurisation in a portable hyperbaric chamber.
Presented to the **1999 International Hypoxia Symposium, Jasper, Canada. March 1999.**

Near-infra red cerebral spectroscopy to assess cerebral oxygenation at altitude.
Presented to the **1999 International Hypoxia Symposium, Jasper, Canada. March 1999.**

Acute mountain sickness may be induced by exercise.
Presented to the **1999 International Hypoxia Symposium, Jasper, Canada. March 1999.**

Recommended changes in the Lake Louise Acute Mountain Sickness (AMS) scoring system.
Presented to the **1999 International Hypoxia Symposium, Jasper, Canada. March 1999.**

Cerebral oxygenation at high altitude and the response to carbon dioxide, hyperventilation and oxygen.
Presented to the **1999 International Hypoxia Symposium, Jasper, Canada. March 1999.**

Reduction in cerebrovascular reserve capacity in normal individuals at altitude.
Presented to the **1999 International Hypoxia Symposium, Jasper, Canada. March 1999.**

Cerebral oxygenation at high altitude and the response to carbon dioxide, hyperventilation and oxygen.
Presented to the **South East Anaesthetic Society, La Plagne, France, March 1999.**

A randomised controlled trial of progesterone in preventing acute mountain sickness.
Presented to the **1999 International Hypoxia Symposium, Jasper, Canada. March 1999.**

Carbon dioxide or oxygen at altitude? The effect on arterial blood gases at sea level and on acute exposure to altitude. Presented at the **Walsgrave Poster Competition January 2000**

Carbon dioxide and cerebral blood flow at sea level and on acute exposure to altitude.
Presented at the **Walsgrave Poster Competition January 2000.**

Carbon dioxide or oxygen at altitude? Cutaneous, muscle and cerebral oxygenation.
Presented at the **Walsgrave Poster Competition January 2000.**

Carbon dioxide contributes to the beneficial effect of pressurisation in a portable hyperbaric chamber.
Presented at the **Walsgrave Poster Competition January 2000.**

Near-infra red cerebral spectroscopy to assess cerebral oxygenation at altitude.
Presented at the **Walsgrave Poster Competition January 2000.**

Acute mountain sickness may be induced by exercise.
Presented at the **Walsgrave Poster Competition January 2000.**

Recommended changes in the Lake Louise Acute Mountain Sickness (AMS) scoring system.
Presented at the **Walsgrave Poster Competition January 2000**.

Cerebral oxygenation at high altitude and the response to carbon dioxide, hyperventilation and oxygen.
Presented at the **Walsgrave Poster Competition January 2000.**

Reduction in cerebrovascular reserve capacity in normal individuals at altitude.
Presented at the **Walsgrave Poster Competition January 2000.**

High Altitude Cerebral Perfusion
European Young Vascular Surgeons, Courcheval, France, March 2000.

Carbon dioxide or oxygen at altitude? Cutaneous, muscle and cerebral oxygenation
West Midlands Physicians, May 2000

Near-infrared spectroscopy at high altitude: New insights into high altitude physiology.
Presented to the **IV World Congress on Mountain Medicine and High Altitude Physiology, XV Annual Meeting of the Chilean Society of Physiological Sciences, VIII Chilean Congress on Sciences of Physical Exercise and the X Congress of the Northern Chile Medical Society, University of Tarapaca, Arica, Chile 1st-6th October 2000.**

The effect of Acetazolamide on peripheral pulse oximetry in partially acclimatised individuals.
Presented to the **IV World Congress on Mountain Medicine and High Altitude Physiology, XV Annual Meeting of the Chilean Society of Physiological Sciences, VIII Chilean Congress on Sciences of Physical Exercise and the X Congress of the Northern Chile Medical Society, University of Tarapaca, Arica, Chile 1st-6th October 2000.**

Carbon dioxide contributes to the beneficial effect of pressurisation in a portable hyperbaric chamber at high altitude.
Presented to the **IV World Congress on Mountain Medicine and High Altitude Physiology, XV Annual Meeting of the Chilean Society of Physiological Sciences, VIII Chilean Congress on Sciences of Physical Exercise and the X Congress of the Northern Chile Medical Society, University of Tarapaca, Arica, Chile 1st-6th October 2000.**

Modifications of the Lake Louise Acute Mountain Sickness Scoring System.
Presented to the **IV World Congress on Mountain Medicine and High Altitude Physiology, XV Annual Meeting of the Chilean Society of Physiological Sciences, VIII Chilean Congress on Sciences of Physical Exercise and the X Congress of the Northern Chile Medical Society, University of Tarapaca, Arica, Chile 1st-6th October 2000.**

The use of the nepholometer at high altitude
Presented to the **IV World Congress on Mountain Medicine and High Altitude Physiology, XV Annual Meeting of the Chilean Society of Physiological Sciences, VIII Chilean Congress on Sciences of Physical Exercise and the X Congress of**

the Northern Chile Medical Society, University of Tarapaca, Arica, Chile 1st-6th October 2000.

Carbon dioxide at high altitude: A century of investigation and speculation
Presented to the **IV World Congress on Mountain Medicine and High Altitude Physiology, XV Annual Meeting of the Chilean Society of Physiological Sciences, VIII Chilean Congress on Sciences of Physical Exercise and the X Congress of the Northern Chile Medical Society, University of Tarapaca, Arica, Chile 1st-6th October 2000.**

Operating Telescopes at high altitude- the experience on Mauna Kea
Presented to the **IV World Congress on Mountain Medicine and High Altitude Physiology, XV Annual Meeting of the Chilean Society of Physiological Sciences, VIII Chilean Congress on Sciences of Physical Exercise and the X Congress of the Northern Chile Medical Society, University of Tarapaca, Arica, Chile 1st-6th October 2000.**

Carbon dioxide contributes to the beneficial effect of pressurisation in a portable hyperbaric chamber at high altitude.
Presented to the **Medical Research Society, 2000.**

Near-infra red cerebral spectroscopy to assess cerebral oxygenation at altitude.
Presented to the **Medical Research Society, 2000.**

Near infrared cerebral spectroscopy and the carbon dioxide cerebrovascular reserve capacity at altitude
Presented to the **World Hypoxia Symposium 2001, Jasper, and Canada.**

Hypoxic ventilatory response and acute mountain sickness
Presented to the **World Hypoxia Symposium 2001, Jasper, Canada.**

Trans cranial doppler and near infrared cerebral spectroscopy: Acetazolamide cerebrovascular reserve capacity at 150m and 4600m.
Presented to the **World Hypoxia Symposium 2001, Jasper, Canada.**

The effect of 12% oxygen gas mix on peripheral and cerebral oxygenation and the response to supplementary carbon dioxide
Presented to the **World Hypoxia Symposium 2001, Jasper, Canada.**

The effect of Acetazolamide on peripheral pulse oximetry and cerebral perfusion in partially acclimatised individuals.
Presented to the **World Hypoxia Symposium 2001, Jasper, Canada.**

'Cerebral' hypoxic ventilatory response and acute mountain sickness
Presented to the **World Hypoxia Symposium 2001, Jasper, Canada.**

Cerebral perfusion in sea level commuters at 5050m elevation
Presented to the **World Hypoxia Symposium 2001, Jasper, Canada.**

Cerebral, hepatic, renal, skeletal muscle and peripheral oxygenation at 0m, 2400m and 5050m
Presented to the **World Hypoxia Symposium 2001, Jasper, Canada.**

Cerebral perfusion at 0m, 2400m and 5050m and the response to voluntary forced hyperventilation
Presented to the **World Hypoxia Symposium 2001, Jasper, Canada.**

Field technique for the assessment of the 'reverse' cerebro-vascular reserve capacity
Presented to the **World Hypoxia Symposium 2001, Jasper, Canada.**

Near infra-red cerebral spectroscopy and the assessment of cerebral blood volume at sea level and
correlation with susceptibility to the development of acute mountain sickness.
Presented to the **World Hypoxia Symposium 2001, Jasper, Canada.**

Near infrared cerebral spectroscopy and the assessment of cerebral blood flow at altitude.
Presented to the **World Hypoxia Symposium 2001, Jasper, Canada.**

Clinical observations on Acetazolamide prophylaxis in Nepalese porters.
Presented to the **World Hypoxia Symposium 2001, Jasper, Canada**

Does transcranial Doppler have a role in the preoperative management of carotid stenosis? Paper presented at the **14th Congress of the European Chapter of the International Union of Angiology; Cologne,May 23-26 2001**
A simple but aggressive transcranial Doppler directed dextran-40 therapy regime reduces postoperative carotid thrombosis. Paper presented for **the IUA 2001 Prize at the 14th Congress of the European Chapter of the International Union of Angiology; Cologne, May 23-26 2001.**

TIAs: The use of pre-operative TCD directed I.V. dextran therapy to control symptoms and emboli prior to elective carotid endarterectomy.
Founder's Prize, Vascular Surgical Society of Great Britain & Ireland, Brighton, November 2001. Presented by NS Lennard

Cerebral oxygen delivery falls with voluntary forced hyperventilation at altitude.
Presented to the **World Congress on High Altitude Medicine April 2002 Barcelona.**

3% carbon dioxide increases cerebral oxygen delivery when breathing hypoxic gas mixtures
Presented to the **World Congress on High Altitude Medicine April 2002 Barcelona.**

3% carbon dioxide increases cerebral oxygen delivery at 150m and 3540m
Presented to the **World Congress on High Altitude Medicine April 2002 Barcelona**

Cerebral oxygen delivery falls with voluntary forced hyperventilation at altitude.
World Congress on High Altitude Medicine April 2002 Barcelona.

3% carbon dioxide increases cerebral oxygen delivery when breathing hypoxic gas mixtures
World Congress on High Altitude Medicine April 2002 Barcelona.

3% carbon dioxide increases cerebral oxygen delivery at 150m and 3540m

World Congress on High Altitude Medicine April 2002 Barcelona

Are 'stable' carotid plaques less prone to post endarterectomy micoembolization?
73rd European Atherosclerosis Society Salzburg. July 7-10th 2002.

The antipoptotic effect of exogenous VEGF on serum starved endothelial cells is mediated via VEGFR-1 & VEGFR-2.
73rd European Atherosclerosis Society Salzburg. July 7-10th 2002.

Are 'stable' carotid plaques less prone to post endarterectomy micoembolization?
73rd European Atherosclerosis Society Salzburg July 7-10 2002.

Effect of hard exercise on proteinuria at high altitude
13th International Hypoxia Symposium, Banff, Alberta. February 2003

Oxygen consumption whilst climbing mountains- is a slow plod strategy better than rush and rest?
13th International Hypoxia Symposium, Banff, Alberta. February 2003.

Cerebral desaturation at VO2Max at high altitude
13th International Hypoxia Symposium, Banff, Alberta. February 2003

Increased PO2 gradient not cerebral blood flow improves brain oxygenation
13th International Hypoxia Symposium, Banff, Alberta. February 2003

The effect of oxygen bolus on cerebral oxygenation and blood flow at altitude
13th International Hypoxia Symposium, Banff, Alberta. February 2003

Supine exercise cycle ergometer for cerebral studies.
13th International Hypoxia Symposium, Banff, Alberta. February 2003

Improved cerebral oxygenation during acute hyperventilation at altitude is not due to improved cerebral blood flow
13th International Hypoxia Symposium, Banff, Alberta. February 2003

Non-invasive beat to beat blood pressure measurement at high altitude
13th International Hypoxia Symposium, Banff, Alberta. February 2003

The effect of sildenafil (Viagra) on cerebral haemodynamics at altitude
13th International Hypoxia Symposium, Banff, Alberta. February 2003

Acute mountain sickness in adolescents

13th International Hypoxia Symposium, Banff, Alberta. February 2003

Wobble board , acute mountain sickness and cerebral regional oxygenation
13th International Hypoxia Symposium, Banff, Alberta. February 2003

Field testing of a new high-altitude O2 delivery system in the Bolivian Andes.
13th International Hypoxia Symposium, Banff, Alberta. February 2003.

Post operative monitoring of carotid patients.
Mercian Vascular Meeting May 2003

TCD directed Tirofibran for Dextran resistant microembolization.
Mercian Vascular Meeting May 2004

Virtual altitude: An Hypothesis which may explain why exercise exacerbates AMS.
13th International Hypoxia Symposium, Lake Louise, Alberta. February 2005

Advances in Mountain Medicine Education in the United Kingdom
13th International Hypoxia Symposium, Lake Louise, Alberta. February 2005

Blood pressure changes during exercise at altitude
13th International Hypoxia Symposium, Lake Louise, Alberta. February 2005

Sildenafil at altitiude and acclimatisation
13th International Hypoxia Symposium, Lake Louise, Alberta. February 2005

Crescendo and recurrent transient ischaemic attacks- a clinical imperative.
West Midland Surgeons 2005

8) Appendix 2

Clinical Science (1995) 89, 201–204 (Printed in Great Britain)

Intracranial pressure at high altitude and acute mountain sickness

A. D. WRIGHT*, C. H. E. IMRAY*, M. S. C. MORRISSEY*, R. J. MARCHBANKS†‡ and A. R. BRADWELL*

*Birmingham Medical Research Expeditionary Society, Department of Immunology, The Medical School, Edgbaston, Birmingham, U.K., and †Audiology Centre, Royal National Throat, Nose and Ear Hospital, London, U.K.

(Received 11 October 1994/3 March 1995; accepted 17 March 1995)

1. Raised intracranial pressure has been noted in severe forms of acute mountain sickness and high-altitude cerebral oedema, but the role of intracranial pressure in the pathogenesis of mild to moderate acute mountain sickness is unknown.

2. Serial measurements of intracranial pressure were made indirectly by assessing changes in tympanic membrane displacement in 24 healthy subjects on rapid ascent to 5200 m.

3. Acute hypoxia at 3440 m was associated with a rise in intracranial pressure, but no difference was found in pressure changes at 4120 or 5200 m in subjects with or without symptoms of acute mountain sickness.

4. Raised intracranial pressure, though temporarily associated with acute hypoxia, is not a feature of acute mountain sickness with mild or moderate symptoms.

INTRODUCTION

The clinical features of mild to moderate acute mountain sickness (AMS) include headache, nausea and vomiting which may progress to the more serious malignant form with ataxia, confusion and death. Raised intracranial pressure and cerebral oedema secondary to hypoxia are central themes in the suggested mechanisms of AMS [1]. Evidence for raised intracranial pressure in AMS has been obtained in uncontrolled studies. Papilloedema was noted in 23 of 44 severe cases of AMS reported by Dickinson in [2], and increases of 60–210 mmH_2O in cerebrospinal fluid (CSF) pressure were found at lumbar puncture in 34 cases [3]. Attempts to measure intracranial pressure changes in the mild to moderately severe AMS are limited to short-term CSF pressure measurements in hypobaric chamber studies. In three subjects taken to a simulated altitude of 5000 m until symptoms of AMS appeared, there was no change in the direct measure of CSF pressure at lumbar puncture, though acute hypoxic gas inhalation resulted in a rise in pressure [4]. Studies in sheep exposed to normobaric hypoxia for 72 h showed no change in intracranial pressure despite increases in brain water content [5].

The development of a non-invasive method of measuring changes in intracranial pressure [6, 7] has enabled us to undertake a prospective study of AMS in a group of subjects trekking to high altitude to ascertain if raised intracranial pressure is an early feature of the AMS syndrome.

SUBJECTS AND METHODS

Twenty-four healthy subjects (22 males, two females) aged 22–65 years were studied before and during ascent to high altitude (Table 1). Subjects were randomly allocated to one of four treatments with six subjects in each of the following groups: placebo, acetazolamide, medroxyprogesterone and acetazolamide with medroxyprogesterone. Drug treatment was started after baseline studies and 1 week before departure to the Himalayas.

Symptoms of AMS were recorded using a self-assessment questionnaire each morning (21 symptoms) and evening (20 symptoms), scoring each symptom as 0 (absent), 1 (slight), 2 (moderate), 3 (quite a lot) and 4 (maximum), giving a maximum score of 84 morning and 80 evening. Blood gases were measured on arterialized capillary blood using a Corning blood gas analyser (Ciba Corning model 238) at 3440, 4120 and 5200 m at the same time as the intracranial pressure studies. Intracranial pressure was measured indirectly by recording the displacement of the tympanic membrane (Tm) in one ear during stapedial reflex contraction elicited by a 1000-Hz stimulus at sound pressures 100–115 dB administered on 10 occasions for 500 ms every 7 s with the subject lying comfortably for at least 5 min before starting the test (MMS-10 tympanic displace-

Key words: acute mountain sickness, high altitude, intracranial pressure.

Abbreviations: AMS, acute mountain sickness; CSF, cerebrospinal fluid; Tm, Tympanic membrane.

‡Present address: Non-invasive Intracranial Pressure Assessment Unit, Wessex Regional Centre for Paediatric Surgery, Southampton General Hospital, Southampton, U.K.

Correspondence: Dr A. D. Wright, Department of Medicine, Queen Elizabeth Hospital, Birmingham B15 2TT, U.K.

Table 1. Experimental protocol.

Day	Drugs	Altitude (m)	Transport	Time of study
0	Nil	150		Morning
1	Trial started	150		
14	Trial	150 to 1348	Flight	
15	Trial	1348		Morning
16	Trial	1348 to 2600	Flight	
17	Trial	2600 to 3440	Trek	Evening
18	Trial	3440 to 4120	Trek	
19	Trial	4120		Morning
20	Trial	4120 to 5200	Trek	
21	Trial stopped	5200		Morning

ment analyser) [6]. The method is based on the principle that a patent cochlear aqueduct transmits intracranial pressure to the perilymphatic fluid of the cochlea. The resting position of the footplate of the stapes within the oval window depends on the pressure of the perilymphatic fluid. Increasing pressure displaces the stapes footplate laterally, allowing a greater degree of freedom for motion of the stapes medially when the stapedius muscle contracts. This movement is transmitted to the tympanic membrane to produce a more inward-going displacement. Conversely, a reduction in cochlear pressure draws the footplate medially and results in a more outward-going displacement of the tympanic membrane on stapedial contraction. Movement of the tympanic membrane can be measured by volume displacement by a transducer probe sealed within the external auditory meatus. The technique is sensitive enough to detect changes in cochlear pressure with cardiac pulse and respiration, hence the need to average 10 consecutive readings. The technique has been validated by comparison with direct intracranial and CSF pressure measurements [7] but is best used for detecting changes in intracranial pressure rather than for obtaining absolute pressures. However, calculation of an approximate change in intracranial pressure can be made by assuming that the change in Tm displacement occurring between readings in the sitting and lying positions corresponds to a rise of 150 mmH_2O CSF pressure.

For valid results, the technique depends on normal middle ear pressure and an intact, free-moving tympanic membrane. A hand-held tympanometer was used to assess these features in each subject before any measurement of Tm displacement in baseline studies and at 1348 m. At higher altitudes tympanic membrane mobility was assessed by pneumatic otoscopy. The equipment was adapted for field use and before the expedition was tested satisfactorily at −23°C and at 0.5 atmospheres pressure.

Tm replacement results were excluded in three subjects: in two subjects no measurable reflex was obtained and in one subject the data were incomplete because of descent [8]. Two subjects were not available for baseline studies at 150 m and one

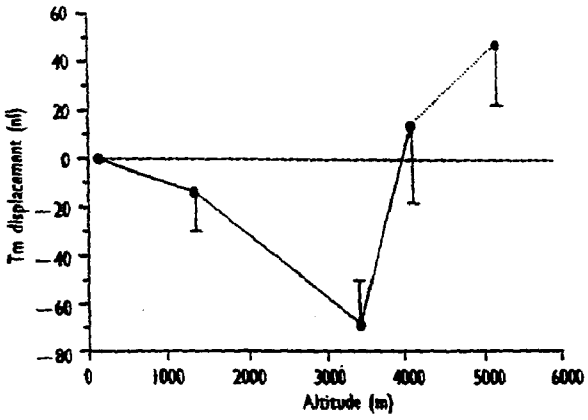


Fig. 1. Sequential changes in tympanic membrane (Tm) displacement from baseline to high altitude. A more negative displacement indicates a rise in intracranial pressure.

subject was omitted inadvertently when measurements were being made at 3440 m. At 5220 m 12 subjects were chosen for study by the medical officer on the basis of definite AMS symptoms ($n=6$) or trivial or no AMS symptoms ($n=6$). Blood gas data were not obtained in one subject in the no symptoms group at this altitude, and his results have been excluded.

Statistical significance was assessed by paired t-testing and regression analysis. Approval for the studies was given by the Research Ethics Committee of the South Birmingham Health Authority, and subjects gave their informed consent.

RESULTS

The change in mean Tm displacement was not significantly different comparing baseline with results at 1348 m, with a mean change of −13.9 nl (SE 17.5), but there was an additional significant mean fall of −54.9 nl (18.7) in displacement at 3400 m ($P<0.01$) and subsequent mean rise of +82.8 nl (34.7) at 4120 m ($P<0.05$) (Fig. 1). No difference was found in the change in mean Tm displacement on ascending from 4120 m to 5220 m in subjects with moderate AMS (questionnaire score 43.8, SD 17.8) or minimal AMS (score 10.2, SD 10.7) (Fig. 2). The AMS scores were taken from the two questionnaires completed at 5220 m. Similarly, there was no overall correlation of Tm displacement changes from 1348 to 5200 m with AMS scores in the whole group.

The change in mean Tm displacement on ascending from 1348 to 3440 m correlated with the PaO_2 measured at 3440 m ($r=0.43$, $P<0.02$) (Fig. 3), but not with pH, $PaCO_2$ or plasma bicarbonate measurements measured at 3440 m, and was not different in the six subjects with mild headache compared with 14 subjects without symptoms. The change in mean Tm displacement on ascending from 1348 to 4120 m or from 1348 to 5220 m did not correlate with PaO_2 measured at 4120 m

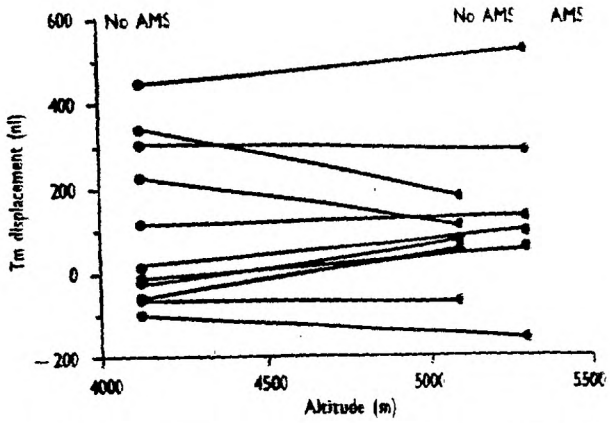


Fig. 2. Change in tympanic (Tm) displacement on ascent from 4120 to 5200 m in five subjects free of acute mountain sickness (AMS) compared with six subjects with AMS. Mean change Tm displacement no AMS −19 ml (not significant), AMS +26.6 ml (not significant).

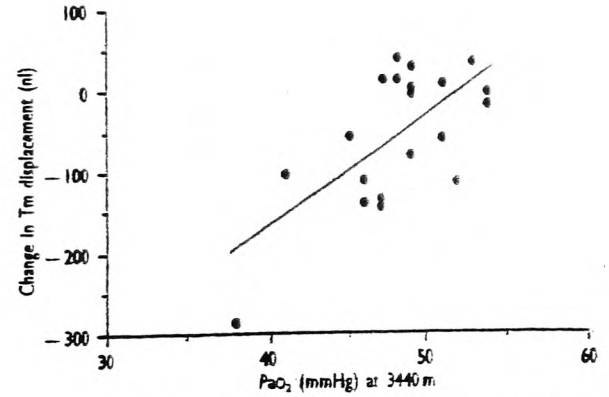


Fig. 3. Change in tympanic membrane (Tm) displacement measured at 1348 and 3440 m compared with PaO_2 measured at 3440 m. $r = 0.43$, $P < 0.01$.

($r = 0.26$) or 5220 m ($r = 0.02$) respectively. The change in Tm displacement on ascending from 1348 to 3440 m was equivalent to a mean rise in intracranial pressure of 91.3 mmH_2O (SD 157).

DISCUSSION

Our results show that raised intracranial pressure is not a feature of the early stages of AMS, confirming results in hypobaric chamber studies [4]. We suggest that the headache, nausea and vomiting of mild to moderate AMS may be due to other intracranial changes, such as cerebral oedema. Reported raised intracranial pressure in AMS is obviously associated with more serious illness, as suggested by the finding of papilloedema in some subjects with high-altitude cerebral oedema [2]. Such severe illness did not occur in our studies.

Acetazolamide is known to reduce CSF production, but it is doubtful whether it affects CSF [illegible] when given intravenously [9]. There is no evidence that our results were affected by the drug trial except that symptoms of AMS may have been ameliorated by the active drugs compared with the placebo. There was no change in Tm displacement after 7 days' treatment with acetazolamide or progesterone before ascent to high altitude.

The change in Tm displacement suggesting a rise in intracranial pressure following rapid ascent to 3440 m over 36 h was not associated with any central nervous system symptoms at that altitude and did not correlate with the severity of symptoms at higher altitudes. The relationship of the rise in pressure to the degree of hypoxia at 3440 m but not at higher altitudes would suggest this was an acute effect of hypoxia. Our failure to demonstrate a further rise in intracranial pressure with increasing hypoxia on ascent from 3400 to 4120 and 5200 m may have been due to the timing of the measurements, which were done 4–6 h after arrival at 3440 m but 18–24 h after arrival at the higher altitudes. It is unlikely that the time of day the measurements were made was of any significance because any diurnal variation in intracranial pressure is much smaller than that occurring with postural change and, within an individual, the difference in pressure in the evening compared with morning may be either increased or decreased with no mean change in a group of subjects (unpublished observations). An effect of hypoxia increasing intracranial pressure acutely has been found in animal experiments [10, 11], though the effect is modified if there are simultaneous changes in PCO_2 [12] and is not seen in more chronic exposure to hypoxia [4, 5]. In sheep the peak rise in intracranial pressure occurs after approximately 6 h exposure to hypoxia and thereafter returns to baseline in animals not suffering from AMS [10].

Though raised intracranial pressure has been documented in severe forms of AMS, our findings suggest that raised pressure is a late manifestation of the clinical syndrome and not an early feature of AMS with mild to moderate symptoms. We postulate that there is a continuum from mild to severe AMS but cerebral oedema and increased cerebral blood flow do not lead to raised intracranial pressure until the CSF reabsorptive mechanism is unable to compensate for the increased intracranial contents. Further studies are required to define the time course in man of changes in intracranial pressure on rapid ascent to high altitude. The non-invasive Tm displacement method is clearly suitable for repeated measurements of changes in intracranial pressure in the field.

ACKNOWLEDGMENTS

The work was supported by grants from The Wellcome Trust, The Arthur Thomson Trust and the Special Trustees for the former United Birmingham Hospitals Trust Funds.

REFERENCES

1. Ward MP, Milledge JS, West JB. High altitude medicine and physiology. London: Chapman & Hall Medical, 1989: 369–81.
2. Heath D, Williams DR. High altitude medicine and pathology. London: Butterworths, 1989: 150.
3. Singh I, Khanna PK, Srivastava MC, Lal M, Roy SB, Subramanyam CSV. N Engl J Med 1969; 280: 175–84.
4. Hartig GS, Hackett PH. Cerebral spinal fluid pressure and cerebral blood velocity in acute mountain sickness. In: Sutton JR, Coates G, Houston CS, eds. Hypoxia and mountain medicine. Oxford: Pergamon Press, 1992: 260–5.
5. Curran-Everett DC, Iwamoto J, Meredith MP, Krasney JA. Intracranial pressures and O_2 extraction in conscious sheep during 72h of hypoxia. Am J Physiol 1991; 261: H103–9.
6. Reid A, Marchbanks RJ, Bateman DE, Martin AM, Brightwell AP, Pickard JD. Mean intracranial pressure monitoring by a non-invasive audiological technique: a pilot study. J Neurosurg Psychiatry 1989; 52: 610–12.
7. Reid A, Marchbanks RJ, Burge DM, Martin AM, Bateman DE, Pickard JD AM, Brightwell AP. The relationship between intracranial pressure and tympanic membrane displacement. Br J Audiol 1990; 24: 123–9.
8. Harvey T. Om Mani Padme Hum. Lancet 1993; 342: 363.
9. Maren TH. Carbonic anhydrase: chemistry, physiology and inhibition. Physiol Rev 1967; 47: 595–78.
10. Yang S-P, Bergō GW, Krasney E, Krasney JA. Cerebral pressure-flow and metabolic responses to sustained hypoxia: effect of CO_2. J Appl Phys 1994; 76: 303–13.
11. Yang YB, Sun B, Yang Z, Wang J, Pong Y. Effects of acute hypoxia on intracranial dynamics in unanesthetized goats. J Appl Phys 1993; 74: 2067–71.
12. Jennett S, North JB. Separate and combined effects on intracranial pressure of changes in Po_2 and Pco_2. In: Shulman K, Marmarou A, Miller JD, Becker DF, Hochwald GM, Brock M, eds. Intracranial Pressure, Vol. IV. Berlin: Springer, 1980: 337–9.

Wilderness and Environmental Medicine, **9**, 198–203 (1998)

ORIGINAL ARTICLE

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

C.H.E. IMRAY; N.J. BARNETT; S. WALSH; T. CLARKE; J. MORGAN; D. HALE; H. HOAR; D. MOLE; I. CHESNER; A.D. WRIGHT

From the Medical School, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK.

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-

Reprint requests to Department of Surgery, Walsgrave Hospitals Trust, Clifford Bridge Road, Coventry CV2 2DX, UK (Mr Imray).

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 ÷ total Hb) × 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 ± 9.2 SD) were not different from those on placebo (20.7 ± 8.8 SD). Total AMS scores did not

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

Altitude (m):	*150*	*Sea level*	*2770*	*3650*	*4680*	*4680*
Days of expedition	*(pre)*	*1*	*2*	*3*	*4*	*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.

* $p < 0.05$.

† $p < 0.01$.

‡ $p < 0.001$.

§ $p < 0.0001$.

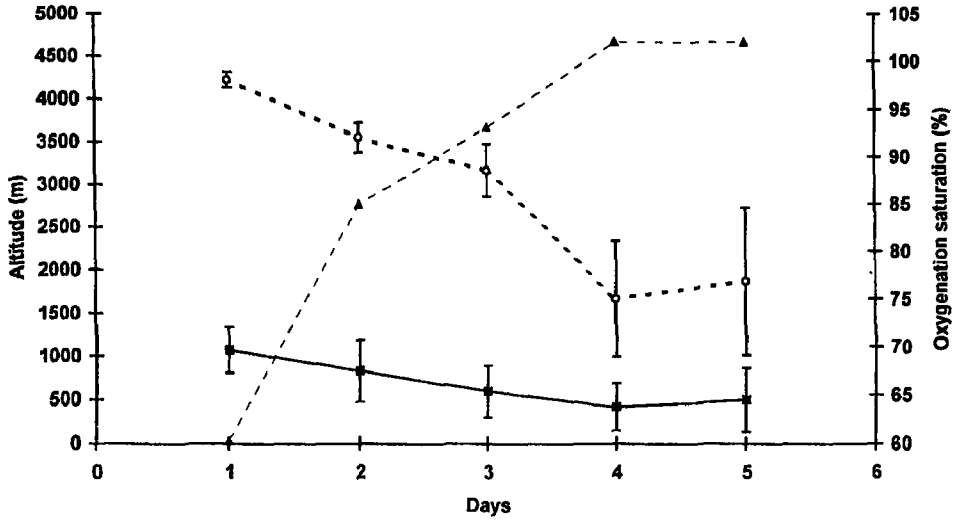


Fig 1. The fall in peripheral oxygen hemoglobin saturation (SpO_2 mean ± SD, open circles with dotted line) and cerebral regional oxygen saturation (rSO_2 mean ± SD, squares and thick solid line). The route profile is shown (triangles and dotted line).

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

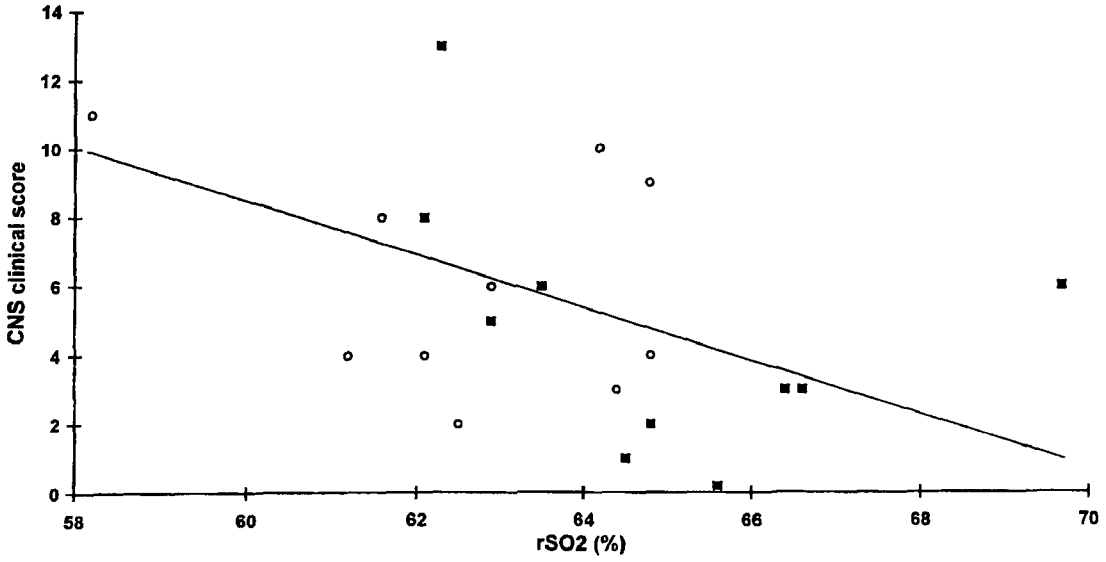


Fig 2. The relationship of rSO_2 at 4680 m and cerebral acute mountain sickness scores for the 10 subjects on medroxyprogesterone in solid squares and the 10 subjects on placebo in open circles ($y = 43.1 - 0.59x$, $r = -0.41$, $p > 0.05 < 0.1$).

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.

Acknowledgments

We are grateful for financial support from The Mount Everest Foundation and the Arthur Thomson Trust and for the loan of equipment by Professor John Coote, BOC Group, Johnson and Johnson Medical Ltd, the Norfolk and Norwich Hospital, and Queen's Hospital, Burton. We gratefully acknowledge the extensive contributions of The Birmingham Medical Research Expeditionary Society in the writing of this article.

References

1. Tavel F. Die Auswirkungen des Sauerstoffmangels auf den menschlichen Organismus bei kurzfristigem Aufenhalt in grosser Höhe. *Helv Physiol Pharmacol Acta,* suppl 1. 1943.
2. Veronneau SJ, Mohler SR, Pennybaker AL, Wilcox BC, Sahiar F. Survival at high altitudes: Wheel-well passengers. *Aviat Space Environ Med.* 1996;67:784–786.
3. Ward PM, Milledge JS, West JB. High altitude cerebral edema and retinal haemorrhage. In: *High Altitude Medicine and Physiology.* 2nd ed. London, UK: Chapman & Hall Medical; 1995:412–418.
4. Birmingham Medical Research Expeditionary Society Mountain Sickness Study Group. Acetazolamide in control of acute mountain sickness. *Lancet* 1981;i:180–183.

5. Moore LG, Harrison GL, McCullough RE et al. Low acute hypoxic ventilatory response and hypoxic depression in acute mountain sickness. *J Appl Physiol.* 1986;60:1407–1412.
6. Lewis DM, Bradwell AR, Shore AC, Beaman M, Tooke JE. Capillary filtration coefficient and urinary albumin leak at altitude. *Eur J Clin Invest.* 1997;27:64–68.
7. Jensen JB, Wright AD, Lassen NA et al. Cerebral blood flow in acute mountain sickness. *J Appl Physiol.* 1990;69:430–433.
8. Wright AD, Imray CHE, Morrissey MSC, Marchbanks RJ, Bradwell AR. Intracranial pressure at high altitude and acute mountain sickness. *Clin Sci.* 1995;89:201–204.
9. McCormick PW, Stewart M, Goetting MG, Balakrishnan G. Regional cerebrovascular oxygen saturation by optical spectroscopy in humans. *Stroke.* 1991;22:596–602.
10. Kirkpatrick PJ, Smielewski P, Lam JMK, Al-Rawi P. Use of near-infrared spectroscopy for the clinical monitoring of adult brain. *J Biomed Optics.* 1996;21:363–372.
11. Williams IM, Mortimer AJ, McCollum CN. Recent developments in cerebral monitoring—near-infrared light spectroscopy. An overview. *Eur J Vasc Endovasc Surg.* 1996;12:263–271.
12. Hackett PH, Oelz O. The Lake Louise concensus on the definition and quantification of altitude illness. In: Sutton JR, Coates G, Houston CS, eds. *Hypoxia and Mountain Medicine.* Burlington, VT: Queen City Printers; 1992:327–330.
13. Baumgartner RW, Bartsch P, Maggiorini M, Waber U, Oelz O. Enhanced cerebral blood flow in acute mountain sickness. *Aviat Space Environ Med.* 1994;65:726–729.
14. Mchedhishvili G. *Arterial Behaviours and Blood Circulation in the Brain.* New York, NY: Plenum Publishing Corp; 1986.
15. Portnoy HD, Chopp M. Hydraulic model of myogenic autoregulation and the cerebrovascular bed; the effects of altering the systemic arterial pressure. *Neurosurgery.* 1983;13:482–498.
16. Williams IM, Vohra R, Farrell A, Picton AJ, Mortimer AJ, McCullum CN. Cerebral oxygen saturation, transcranial Doppler ultrasonography and stump pressure in carotid surgery. *Br J Surg.* 19;81:960–964.
17. Smielewski PJ, Whitfield PC, Czosnyka M, Menon D, Pickard JD. An observational study of near-infrared spectroscopy during carotid endarterectomy. *J Neurosurg.* 1995;82:756–763.
18. Owen-Reece H, Elwell CE, Wyatt JS, Delpy DT. The effect of scalp ischaemia on measurement of cerebral blood volume by near-infrared spectroscopy. *Physiol Meas.* 1996;17:279–286.
19. Grubhofer G, Lassnigg A, Manlik F, Marx E, Trubd W, Heismayr M. The contribution of extracranial blood oxygenation on near-infrared spectroscopy during carotid thromboendarterectomy. *Anaesthesia.* 1997;52:116–120.
20. Evans PD. *Non-invasive Optical Measurement of Oxidative Metabolism and Haemoglobin Parameters in Tissue.* Swansea, UK: University of Wales; 1997. Thesis.
21. Henson LC, Calalang C, Temp JA, Ward DS. Accuracy of a cerebral oximeter in healthy volunteers under conditions of isocapnic hypoxia. *Anesthesiology.* 1998;88:58–65.

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

C. H. E. IMRAY, S. BREAREY, T. CLARKE, D. HALE[1], J. MORGAN, S. WALSH, A. D. WRIGHT and the Birmingham Medical Research Expeditionary Society
The Immunodiagnostic Research Laboratory, The Medical School, University of Birmingham, Edgbaston, Birmingham B15 2TT, U.K.

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±2.3%; means±S.D.; $P < 0.001$). At 4680 m, CO_2 increased regional cerebral oxygenation (63.8±2.5% to 65.9±2.2%; $P < 0.001$) and also increased peripheral oxygen saturation (75.1±6.1% to 83.6±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±7.9% to 98.1±1.5%; $P < 0.001$) and cerebral regional oxygenation (64.6±3.3% to 70.6±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; $PETCO_2$, end-tidal partial pressure of CO_2.

Correspondence: Mr C. H. E. Imray, Department of Surgery, Walsgrave Hospitals Trust, Clifford Bridge Road, Coventry CV2 2DX, U.K. (e-mail chrisimray@aol.com).

[1] Deceased.

function of cerebral capillaries or cerebral tissues in response to hypoxia. In some reports, AMS has been shown to be more closely related to P_{aCO_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; ~ 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 P_{aO_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 ~ 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 × 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

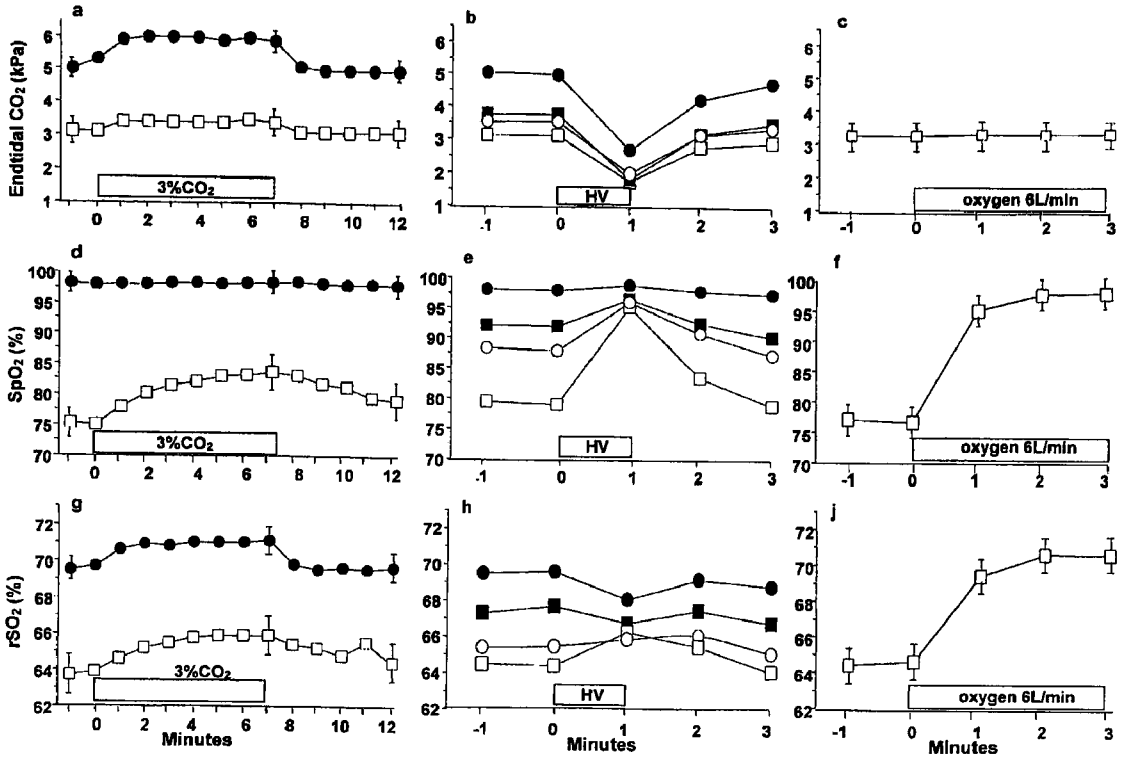


Figure 1 **Changes in P_{ETCO_2}, peripheral O_2 saturation and cerebral regional O_2 saturation in response to CO_2, hyperventilation and oxygen**

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±7.9% to 98.1±1.5%) (Figure 1f) and cerebral regional oxygen saturation (64.6±3.3% to 70.6±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

COMMENT

Oxygenation of the brain at altitude

'Anoxia not only stops the machine, it wrecks the machinery' wrote J. S. Haldane of the effect of hypoxia on the brain. The brain is the most sensitive organ in the body to oxygen lack, in two ways. It stops working at a higher partial pressure of oxygen (P_{O_2}) than any other organ, and it is irretrievably damaged by a short period of oxygen deprivation. It is not surprising, therefore, that life scientists of many disciplines have been interested in the factors that govern the oxygen supply to the brain.

Oxygen delivery is determined by blood flow and by the amount of oxygen in the arterial blood. The latter, in turn, depends upon the arterial oxygen saturation (Sa_{O_2}) and the oxygen capacity or haemoglobin concentration. An ascent to altitude provides a controlled, textbook study in mild oxygen lack, and all the factors affecting oxygen delivery are changed. The lower barometric pressure lowers the inspired P_{O_2}. Arterial P_{O_2} is reduced and Sa_{O_2} is lowered. After some time the well-known increase in haemoglobin concentration (due to both haemoconcentration and increased red cell mass) compensates for this. The lower arterial P_{O_2} results in vasodilatation and increased cerebral blood flow (CBF), but the lower partial pressure of carbon dioxide (P_{CO_2}), due to hyperventilation, has the opposite effect. In the first few days at altitude, hypoxia wins and CBF is increased. Over the next few days CBF declines towards sea-level values at a time when the haematocrit is increasing.

Of course, what really matters is not only the oxygen delivery but also the oxygenation of the brain. Some attempts have been made in the past to measure this by sampling blood draining from the brain by jugular bulb puncture, since the venous P_{O_2} is probably a good measure of the tissue P_{O_2}. However, this is an invasive procedure and not popular with subjects (or ethical committees). In the last few years near-IR spectroscopy has been used to measure the oxygen saturation of the brain (rSo_2). This includes some arterial blood, but is heavily weighted towards the capillary and venous saturation and probably gives us a good measure of brain oxygenation. Many technical difficulties have been overcome and, with care, the method now seems to give reliable results, at least for trends if not for absolute values.

Using this technique, Imray and colleagues from the Birmingham Medical Research Expeditionary Society have looked at the effects of altitude, breathing 3% CO_2, breathing oxygen and voluntary hyperventilation in a group of 20 healthy volunteers on an expedition to 4680 m in the Andes [1]. They are to be congratulated in getting these results with this sophisticated technique in the mountains.

Breathing CO_2 predictably raised end-tidal P_{CO_2} at sea level and at altitude. The resulting hyperventilation raised Sa_{O_2} at altitude, but had no effect on Sa_{O_2} at sea level because it was already on the flat part of the dissociation curve. The effect on rSo_2 was to increase it both at altitude and at sea level, due to the combined effects of increased saturation (at altitude) and a CO_2-driven increase in blood flow. Breathing oxygen at 6 litres · min^{-1} at altitude had the expected effect of increasing Sa_{O_2} and rSo_2 despite, no doubt, some reduction in CBF. The most interesting finding was in relation to voluntary hyperventilation. End-tidal P_{CO_2} fell, of course, and Sa_{O_2} rose (most at the highest altitude), but rSo_2 fell at sea level, was unchanged at 3560 m and rose at 4680 m. What was going on? Presumably at sea level, with very little change in P_{O_2}, the reduction in P_{CO_2} caused a reduction in CBF and hence in rSo_2. At the highest altitude the increase in Sa_{O_2} outweighed the reduction in CBF, and there was a net increase in oxygen delivery. At the middle altitude the two effects just cancelled each other out. This result might have been predicted from the knowledge we have of the effects of hypoxia and CO_2 on CBF; however, since the hypoxic effect is non-linear and any assumptions about these relationships have wide margins of error, any predictions are uncertain. These direct measurements are, therefore, of great interest.

This work leads on to other questions. Imray et al.'s subjects [1] were studied on arrival at altitude. How would acclimatization affect the situation? They were presumably free of acute mountain sickness (AMS) at the time of study. Would AMS have changed the results? Do rSo_2 values correlate with AMS symptom scores? If so, is the correlation better than that with Sa_{O_2}? No doubt the Birmingham team or others will be setting out to answer these and other related questions in the next few years.

Do these results lead to advice for the management of illness at altitude? When we have the answers to some of the above questions, we might be in a better position to advise. The breathing of 3% CO_2 has been advocated on the grounds that it would increase CBF and, via hyperventilation, increase oxygenation. The study by Imray et al. [1] supports this prediction, although the rise in rSo_2 with 3% CO_2 was rather modest and less than with oxygen or voluntary hyperventilation. The practicality of using CO_2 in the field is questionable. Voluntary hyperventilation has been advocated by mountain guides as a means of gaining temporary relief from the symptoms of AMS. However, it cannot be kept up for long, and

during sleep (when saturations are lowest) hyperventilation is not an option. However, the work by Imray et al. [1] gives scientific validity to this old advice, although only at altitudes above 3560 m. Oxygen, we all know, is fine if you've got it! One practical point is that perhaps we ought not to be too worried about slight CO_2 build up (1–2%) when using portable compression (Gamow) bags. However, we must realize that, for every 1% rise in CO_2 in the bag, approx. 1% of O_2 is removed, unlike the situation with CO_2 mixtures made up by adding CO_2 to air, as in the study by Imray et al. [1].

Haldane's younger contemporary, Joseph Barcroft, said 'Mountain sickness is caused by the oxygen that is not there!'. The study by Imray et al. [1] has shown that, by using near-infrared spectroscopy, we can measure the missing oxygen and study factors that affect its absence!

J. S. MILLEDGE
137 Highfield Way, Chorleywood, Herts. WD3 2PL, U.K.
(ON BEHALF OF THE EDITORIAL BOARD)

REFERENCES

1 Imray, C. H. E., Brearey, S., Clarke, T., Hale, D., Morgan, J., Walsh, S., Wright, A. D. and the Birmingham Medical Research Expeditionary Society (1999) Cerebral oxygenation at high altitude and the response to carbon dioxide, hyperventilation and oxygen. Clin. Sci. 98, 159–164

Clinical Science (2001) 100, 151–157 (Printed in Great Britain)

Carbon dioxide contributes to the beneficial effect of pressurization in a portable hyperbaric chamber at high altitude

Christopher H. E. IMRAY*, Timothy CLARKE†, Peter J. G. FORSTER‡, Timothy C. HARVEY§, Helen HOAR‖, Sarah WALSH†, Alexander D. WRIGHT‖ and the Birmingham Medical Research Expeditionary Society

*Department of Surgery, Walsgrave Hospital, Coventry, U.K., †Department of Anaesthetics, James Paget Hospital, Yarmouth, U.K., ‡Department of Medicine, James Paget Hospital, Yarmouth, U.K., §Department of Medicine, Manor Hospital, Walsall, West Midlands, U.K., and ‖The Medical School, University of Birmingham, Birmingham, U.K.

ABSTRACT

Regional cerebral oxygenation (rSo_2) and peripheral oxygen saturation (Spo_2) have been studied in subjects inside a portable hyperbaric chamber at altitude during pressurization. The effects of the accumulation of carbon dioxide within the chamber on rSo_2 and Spo_2 have also been investigated. Three studies of cerebral regional oxygenation were undertaken, using near-IR spectroscopy, in subjects who had ascended to 3475 m in the Alps, 4680 m in the Andes or 5005 m in the Himalayas. At 3475 m and 5005 m the effects of the removal of inspired carbon dioxide by a soda lime scavenger were also studied. On pressurization of the chamber to 19.95 kPa, inspired carbon dioxide rose within the chamber from 0.03% (0.06 kPa) ambient to over 1% (1.3 kPa). At 5005 m, Spo_2 rose from a baseline of 79.5% (S.D. 4.5%) to 95.9% (2.0%) ($P < 0.0001$), and cerebral rSo_2 rose from 64.6% (3.4%) to 69.4% (3.6%) ($P < 0.0001$). The introduction of a soda lime CO_2 scavenger into the breathing circuit resulted in a drop in Spo_2 from 95.9% (2.03%) to 93.6% (2.07%) ($P < 0.001$) and a fall in rSo_2 from 69.4% (3.64%) to 68.5% (3.5%) ($P < 0.01$). Chamber pressure was maintained throughout at 19.95 kPa. Similar changes were seen at the other altitudes. Cerebral rSo_2 increased rapidly following pressurization at all three altitudes. Scavenging of inspired carbon dioxide was associated with a significant fall in cerebral rSo_2 and Spo_2, and we estimate that the contribution of carbon dioxide may account for up to one-third of the beneficial effect of the portable hyperbaric chamber.

INTRODUCTION

Acute mountain sickness (AMS) is a common clinical problem affecting otherwise fit individuals who ascend to high altitude. The prevalence of AMS has been reported to vary from 43 to 63% in the Himalayas [1], and from 9 to 69% in the Alps [2]. The severity depends upon a number of factors, including rate of ascent, altitude achieved, recent previous acclimatization, and the susceptibility of the individual to the syndrome. Although usually relatively benign and self-limiting, the condition can deteriorate and progress to high-altitude cerebral

Key words: carbon dioxide, cerebral oxygenation, high altitude, near-infrared spectroscopy, portable hyperbaric chamber.

Abbreviations: AMS, acute mountain sickness; NIRS, near-infrared spectroscopy; rSo_2, regional oxygen saturation; Spo_2, peripheral oxygen saturation; $Pico_2$, partial pressure of inspired carbon dioxide; $Petco_2$, end-tidal partial pressure of carbon dioxide; Pio_2, partial pressure of inspired oxygen.

Correspondence: Mr C. H. E. Imray, Coventry and Warwickshire County Vascular Unit, Department of Surgery, Walsgrave Hospitals NHS Trust, Clifford Bridge Road, Coventry CV2 2DX, U.K. (e-mail chrisimray@aol.com).

oedema and pulmonary oedema, both of which are potentially fatal syndromes that have been reported in trekkers, mountaineers and military personnel.

A number of strategies have been developed to prevent AMS, including slow rate of ascent, rest days for acclimatization and drug prophylaxis with acetazolamide and dexamethasone. Mild symptoms of AMS may be treated with simple analgesics and rest while acclimatizing. Moderate AMS may require dexamethasone. The best treatment for severe AMS is rapid descent to a lower altitude, but the local terrain or weather conditions may make this difficult. Oxygen is effective, but cylinders are heavy and only a limited supply can be carried. More recently, portable hyperbaric chambers made of lightweight fabric have been developed [3], which may be taken on trekking expeditions to treat AMS. These allow rapid pressurization of a subject up to 19.95 kPa (200 mBar) above ambient pressure by use of a foot or hand pump. For example, at an altitude of 5000 m a simulated descent to 2500 m is achieved within minutes. Early symptom relief and improvement in peripheral oxygen saturation have been reported [4], but there are no data on the effects of compression on cerebral oxygenation.

The introduction of the technique of reflected near-infrared spectroscopy (NIRS) allows continuous, non-invasive monitoring of cerebral oxygenation. The technique was first described in adults in 1991 [5], and has widespread research and clinical applications [6]. Reflected cerebral NIRS uses light in the near-IR spectrum (650–1100 nm) and, like pulse oximeters and mixed-venous oximeters, uses the principles of light transmission and absorption to measure concentrations of oxygenated, deoxygenated and total haemoglobin in cerebral tissue. The cerebral regional oxygen saturation (rSO_2) is derived from the equation:

$$rSO_2 = (\text{oxygenated haemoglobin}/\text{total haemoglobin}) \times 100$$

The non-invasive NIRS technique has recently been used to assess cerebral oxygenation in healthy volunteers under laboratory conditions of normocapnic and hypercapnic hypoxia. It has been reported that cerebral oxygenation, as assessed by NIRS, precisely tracks changes in jugular bulb venous saturation within individuals [7]. The technique has also been validated in studies comparing NIRS with PET (positron-emission tomography) scanning [8], with ^{133}Xe washout techniques [9] and also with internal carotid artery stump pressures [6]. We have reported changes observed on ascent to altitude, and have found the equipment to be robust and suitably sensitive for use in the field [10,12,16].

Hitherto, the beneficial effect of pressurization has been considered to be due solely to an increase in the partial pressure of inspired oxygen (PiO_2). However, pressurization in a small hyperbaric chamber results in an increase in carbon dioxide within the chamber, resulting in an increase in the partial pressure of inspired carbon dioxide ($PiCO_2$). Efforts have been made in the design of the bag to minimize the accumulation of carbon dioxide, either using a carbon dioxide scrubber or by a pressure relief valve to ensure a flow of fresh air. Using the bag as recommended with a foot pump, carbon dioxide within the lung increases, reaching a plateau of mean 0.74% (range 0.56–0.97%) after 3 min [11]. Carbon dioxide itself will improve peripheral oxygen saturation and increase cerebral blood flow, and we have demonstrated that cerebral regional oxygenation is also increased [12]. We postulated that the accumulation of carbon dioxide in the portable hyperbaric chamber may contribute to the beneficial effect of pressurization.

The aim of the present study was to measure cerebral oxygenation and peripheral pulse oximetry in subjects inside a hyperbaric chamber, and to assess the contribution of accumulated carbon dioxide to cerebral and peripheral oxygenation.

METHODS

Subjects and methods

Experiments were performed shortly after arrival at three different altitudes, on three different expeditions. The first experiment was undertaken in 10 healthy, non-smoking subjects (seven men) aged 24–59 years, who ascended from sea level to 4680 m in a minibus over 3 days. At 3 days after arrival at 4680 m, the hyperbaric chamber study was performed. Subjects were placed in a Gamow bag (Chinook Medical Gear, CO, U.S.A.) and the cabling for the various probes (NIRS, digital pulse oximeter) was bound together with tape and led through the airtight zip of the chamber. After 2 min of baseline measurements, the bag was sealed and pressurized to 6.88 kPa (69 mBar) using a foot pump. Pressurization took 2–3 min. Although there was an audible leak of air around the cables, the predetermined pressure was readily achieved and was maintained by operating the foot pump at 20–25 pumps/min. Peripheral oxygen saturation (SpO_2) and heart rate were measured using a hand-held digital pulse oximeter (model 3770; Ohmeda, BOC Group). The end-tidal partial pressure of CO_2 ($PETCO_2$) was measured using a Hewlett Packard capnograph 78356 in two subjects.

A second experiment was performed in nine healthy, non-smoking subjects (six men) aged 24–53 years who ascended to 3475 m in a cable car, having spent one night at 700 m. The pressurization study was undertaken 3 days after ascent using a Certec compression chamber Mark 1 (69210; Sourcieu, Les Mines, France), which works on the same principle as the Gamow bag [13]. The chamber was pressurized to 19.95 kPa (200 mBar) using a

foot pump, with a good seal obtained with only one cable (for NIRS) passing through the airtight zip. Pressurization took 3–4 min. Spo_2, heart rate, $PiCO_2$ and $PETCO_2$ were measured using a battery-powered Propac Encore (Propac Systems Inc, Beaverton, OR, U.S.A.), which was kept within the chamber; readings were made through the viewing window. Measurements were made over 5 min before a paediatric soda lime circuit (Waters 'to and fro') was inserted by the subject within the bag into the breathing circuit for 5 min. After a further 5 min of basal recordings, a piece of tubing with the same dead space as the paediatric soda lime circuit was also inserted into the breathing circuit. A steady state was achieved after each manipulation, and pressure was maintained at 19.95 kPa throughout.

A third experiment using a similar protocol to the 3475 m experiment was undertaken at 5005 m. Nine healthy, non-smoking subjects (eight men) aged 22–55 years ascended from 1345 m to 5005 m on foot over 13 days. The study was undertaken 2 days after arrival at 5005 m using a Certec compression chamber Mark 11 (69210; Sourcieu, Les Mines, France). Spo_2 and heart rate were measured using a battery-powered Propac Encore within the chamber. A steady state was achieved after each manipulation, and pressure was maintained at 19.95 kPa (200 mBar) throughout.

Six subjects were common to two studies, and three subjects were common to all three studies.

Measurement of Spo_2

Spo_2 and heart rate were measured at 1 min intervals using a hand-held digital oximeter (model 3770; Ohmeda, BOC Group) in the 4680 m study and a Propac Encore (Propac Systems Inc.) in the 3475 m and 5005 m studies. Extraneous light was excluded.

Measurement of $PETCO_2$

A BOC face mask was positioned on the face of the subject, with a Clausen harness ensuring a good seal. A capnograph (Hewlett Packard capnograph 78356 at 4680 m and a Propac Encore at 3475 m and 5005 m) was attached to the mask inlet in order to measure $PiCO_2$ and $PETCO_2$.

Measurement of cerebral rSo_2

Continuous non-invasive NIRS was performed using a Critikon 2020 monitor (Johnson and Johnson Medical Ltd). The sensor position was standardized to a point over the right fronto-parietal region, with the sensor margins 3 cm from the midline (avoiding the sagittal sinus) and 3 cm above the orbital crest. The Critikon disposable pads were unsatisfactory, and a Blue-line Tubifast bandage (Seton Healthcare Group plc, Turbiton, Oldham, Lancashire, U.K.) was used to keep the sensor in place. Data samples every 1 s were logged on to a Toshiba Satellite 200 CDS laptop computer. The interlock hold time was set at 120 s. Oxyhaemoglobin, deoxyhaemoglobin and total haemoglobin were measured.

Statistics

Results are given as means (S.D.). The statistical significance of results obtained was assessed by repeated-measures ANOVA, except where indicated in the text (*paired t test*). All calculations were performed using Statview for Windows software (Abacus Concepts, Berkeley, CA, U.S.A.). P values of < 0.05 were considered significant.

Ethics

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

RESULTS

Barometric pressure

Barometric pressure at 200 m was 1008–1015 mBar (100.55–101.25 kPa), at 3475 m it was 641 mBar (63.9 kPa), at 4680 m it was 582 mBar (58.05 kPa) and at 5005 m it was 547 mBar (54.56 kPa).

$Pico_2$

During pressurization at 3475 m, $PiCO_2$ rose from 0.059 (0.18) to 1.33 (0.18) kPa ($P < 0.0001$). On introducing soda lime after pressurization at 3475 m, $PiCO_2$ fell from 1.33 (0.18) to 0.05 (0.13) kPa ($P < 0.0001$), thus validating the efficacy of the Waters 'to and fro' canister (Table 1, Figure 1).

$PETCO_2$

$PETCO_2$ at 3475 m rose on pressurization from a baseline of 3.8 (0.33) to 4.17 (0.52) kPa ($P < 0.0001$). On introducing soda lime after pressurization at 3475 m, $PETCO_2$ fell from 4.17 (0.52) to 4.01 (0.41) kPa ($P < 0.0001$) (Table 1, Figure 1).

Digital pulse oximetry

Baseline Spo_2 at 3475 m was 91.0% (2.8%), that at 4860 m was 75.1% (10.3%) and that at 5005 m was 79.5% (4.5%). Spo_2 rose rapidly following pressurization at all three altitudes, reaching a plateau within 3 min. At 3475 m Spo_2 rose from 91.0% (2.8%) to 97.8% (1.4%) ($P < 0.0001$); at 4680 m Spo_2 rose from 75.1% (10.3%) to 81.7% (8.1%) ($P < 0.05$); and at 5005 m Spo_2 rose from 79.5% (4.5%) to 95.9% (2.0%) ($P < 0.0001$) (Table 2). The introduction of the soda lime

Table 1 Changes in carbon dioxide partial pressures and in Spo_2 and cerebral rSo_2 at 3475m

Values are mean (S.D.). ns, not significant.

Conditions	$Pico_2$ (kPa)	$Peco_2$ (kPa)	Spo_2 (%)	rSo_2 (%)
Baseline	0.059 (0.18)	3.8 (0.33)	91.0 (2.8)	63.4 (4.5)
At 19.95 kPa	1.33 (0.18)	4.17 (0.52)	97.8 (1.4)	66.9 (4.7)
P	< 0.0001	< 0.0001	< 0.0001	< 0.0001
At 19.95 kPa + soda lime	0.05 (0.13)	4.01 (0.41)	96.1 (1.4)	65.7 (5.7)
P compared with 19.95 kPa alone	< 0.0001	< 0.0001	< 0.0001	< 0.05
P compared with baseline	ns	ns	ns	ns
At 19.95 kPa + spacer	1.63 (0.17)	4.16 (0.53)	98.2 (1.5)	66.1 (5.0)
P compared with + 19.95 kPa	< 0.01	ns	ns	ns

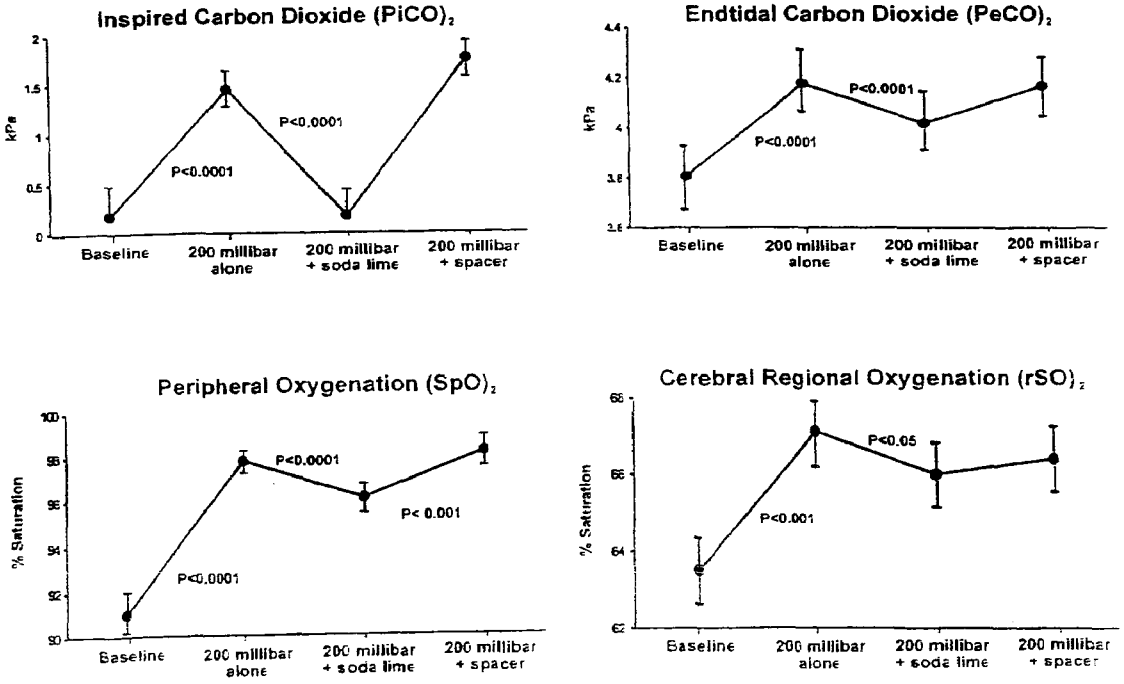


Figure 1 Portable hyperbaric chamber study at 3475 m

See the text for details. 200 mBar = 19.95 kPa.

CO_2 scavenger resulted in a fall in Spo_2 [from 97.8% (1.4%) to 96.1% (1.4%) ($P < 0.0001$) at 3475 m and from 95.9% (2.0%) to 93.6% (2.1%) ($P < 0.001$) at 5005 m].

Cerebral rSo_2

Baseline cerebral rSO_2 at 3475 m was 63.4% (4.5%), that at 4680 m was 62.5% (3.4%) and that at 5005 m was 64.6% (3.4%). Cerebral rSO_2 following pressurization showed similar rises at all three altitudes (Tables 1 and 2). At 3475 m with pressurization to 19.95 kPa, rSO_2 rose from 63.4% (4.5%) to 66.9% (4.7%) ($P < 0.0001$). The introduction of the CO_2 scavenger resulted in a decrease in rSO_2 to 65.7% (5.7%) ($P < 0.049$). At 4680 m, rSO_2 rose with pressurization to 6.88 kPa from 62.5% (3.4%) to 65.4% (3.2%) ($P < 0.0001$). At 5005 m rSO_2 rose with pressurization to 19.95 kPa from 64.6% (3.4%) to 69.4% (3.6%) ($P < 0.0001$). The introduction of the CO_2 scavenger resulted in a decrease in rSO_2 to 68.5% (3.5%) ($P < 0.001$) (Table 3).

Cerebral oxygenation is dependent in part on the haematocrit. There was no significant rise in the total cerebral haemoglobin at altitude in the 4680 m study [16], although there was a trend towards a rise at altitude [sea level, 112.3 (11.6) μmol/l of tissue; 150 m, 105.2 (11.2) μmol/l of tissue; 4680 m, 116.8 (16.6) μmol/l of

Table 2 Changes in Spo_2 and cerebral rSo_2 during pressurization

Values are mean (S.D.). *P* values (paired *t* test) refer to data at 5 min (3475 m and 5005 m) or 4 min (4680 m) compared with baseline.

	19.95 kPa at 3475 m		6.88 kPa at 4680 m		19.95 kPa at 5005 m	
Time (min)	Spo_2 (%)	rSo_2 (%)	Spo_2 (%)	rSo_2 (%)	Spo_2 (%)	rSo_2 (%)
Baseline	91.0 (2.8)	63.4 (4.5)	75.1 (10.3)	62.5 (3.4)	79.5 (4.5)	64.6 (3.4)
1	97.0 (2.2)	66.6 (4.1)	79.2 (12.7)	64.4 (3.3)	93.6 (2.3)	68.6 (3.4)
2	97.4 (1.7)	66.2 (4.4)	80.4 (10.6)	64.4 (3.1)	95.5 (2.2)	68.9 (3.4)
3	97.3 (1.7)	66.7 (4.3)	81.7 (7.6)	65.2 (3.3)	95.7 (2.1)	69.1 (3.3)
4	97.3 (1.7)	67.1 (4.1)	81.7 (8.1)	65.4 (3.2)	96.0 (2.5)	69.2 (3.5)
5	97.8 (1.4)	66.9 (4.7)	–	–	95.9 (2.0)	69.4 (3.6)
P value	< 0.005	< 0.01	< 0.05	< 0.01	< 0.0001	< 0.0001

Table 3 Changes in Spo_2 and rSo_2 at 5005 m

Values are mean (S.D.).

Conditions	Spo_2 (%)	rSo_2 (%)
Sea level	97.4 (1.0)	68.6 (3.1)
5005 m baseline	79.5 (4.5)	64.6 (3.4)
P compared with sea level	< 0.0001	< 0.0001
At 19.95 kPa	95.9 (2.0)	69.4 (3.6)
P compared with 5005 m baseline	< 0.0001	< 0.0001
At 19.95 kPa + soda lime	93.6 (2.1)	68.5 (3.5)
P compared with + 19.95 kPa	< 0.001	< 0.001
P compared with 5005 m baseline	< 0.0001	< 0.0001

tissue]. At 5005 m there was a rise in total haemoglobin from 107.5 (26.3) to 132.1 (37.4) μmol/l of tissue ($P < 0.04$; paired *t* test).

DISCUSSION

Oxygenation of the brain is likely to be critical in determining performance and illness at high altitude [12]. The first commercially successful, high-altitude bag was described by Gamow et al. in 1990 [11]. This portable hyperbaric chamber, weighing approx. 7 kg, has rapidly increased in popularity, based initially upon anecdotal reports and then upon clinical studies assessing efficacy [4,14]. Treatment of sick subjects within the very confined space of the chamber can be difficult, and prolonged treatment makes considerable demands on the individuals required to maintain pressure with the foot pump. The chambers are now carried on many high-altitude trekking and mountaineering expeditions, and are being used to treat AMS, sometimes as an alternative to descent. The chambers are designed to operate at pressures between 15.96 and 21.95 kPa, being pressurized by a foot or hand pump. In order to prevent the build-up of carbon dioxide within the chamber, air has to be pumped in at 40–50 litres/min. Even with this rapid turnover of air, the carbon dioxide levels rise to approx. 0.7% [11,15]. Soda lime has been used to prevent carbon dioxide build-up, with the aim of reducing the effort of pumping, but is not usually employed. Treatment of subjects with AMS at 4559 m in a portable compression chamber at 19.25 kPa for 1 h has been shown to improve Spo_2 during treatment and to decrease clinical AMS scores immediately after treatment, but with no benefit 12 h later [15].

NIRS is a relatively new non-invasive technique for measuring cerebral regional oxygenation. It has been used to assess cerebral regional oxygenation in healthy volunteers under laboratory conditions of normocapnic and hypercapnic hypoxia. We have reported [12] the use of NIRS techniques in field studies, making repeated measurements after physiological manipulations. Cerebral rSo_2 fell on ascent from sea level to 4680 m [16]. To date, there are no data regarding cerebral oxygenation within a portable hyperbaric chamber at altitude.

The first of our present studies (at 4680 m) was a simple observational study to determine whether the technique of cerebral NIRS could be used to measure the presumed rise in cerebral oxygenation inside a hyperbaric chamber. A pressure of only 6.88 kPa was achieved, partly due to leakage around the cabling but also because of a misunderstanding of the optimal operating pressures. However, a rise in P_{ETCO_2} was observed in two subjects. The magnitude of the rise in P_{iCO_2} was similar to that observed by others [11] and, in view of the leaks around the cabling in this experiment, the increase in the level of CO_2 is likely to have been an underestimate compared with the use of the chamber in a standard fashion.

In the second study (3475 m), a pressure of 19.95 kPa resulted in a rise in Spo_2 and a rise in cerebral rSo_2 (Figure 1). The rises in both parameters occurred within 2–3 min of achieving the desired pressure. The contribution of the rise in carbon dioxide within the closed space of the hyperbaric chamber on both peripheral and cerebral oxygenation was clearly significant, as shown by the changes that occurred when the soda lime carbon dioxide

scavenger was introduced. With the soda lime in the circuit, there was a small but significant fall in both SpO_2 and cerebral rSO_2 (Table 1). Removal of the soda lime from the circuit returned these values to the previous levels. The fall in SpO_2 on the introduction of a carbon dioxide scavenger has been recorded previously [17], but not commented on, by others. The introduction of a spacer into the circuit within the Gamow bag resulted in a return of both cerebral and peripheral oxygenation to pre-CO_2-scavenger levels, suggesting that the dead space of the soda lime canister was not as clinically significant as the soda lime itself. It should be noted that the build-up of approx. 1% CO_2 within the chamber during normal use will result in a fall of approx. 1% of O_2 in the bag removed [18].

The third experiment (5005 m) was undertaken at an altitude more representative of the altitudes at which portable compression chambers are usually used. Unfortunately, malfunctioning of the capnograph meant no data were obtained regarding $PiCO_2$ and $PETCO_2$. However, the rapid improvement in cerebral oxygenation that was observed at 4680 m and 3475 m was reaffirmed, as was the effect of the soda lime CO_2 scavenger in decreasing both SpO_2 and cerebral rSO_2 (Table 3).

The higher baseline cerebral rSO_2 seen at 5005 m than at 4680 m initially appears anomalous. The NIRS technique is particularly suitable for multiple measurements of trends rather than single absolute measurements of cerebral oxygenation. The higher baseline rSO_2 seen at 5005 m is probably partly a reflection of the much lower rate of ascent on this particular expedition. Subjects were much better acclimatized, having taken 13 days to ascend to 5005 m, whereas ascent to 4680 m was over 3 days and that to 3475 m was in a single day. Baseline SpO_2 at 4680 m following a rapid ascent (3 days) was 75.1% (10.3%), whereas at 5005 m, following a much slower ascent (13 days), it was 79.5% (4.5%). The subjects would probably have had a higher haematocrit at 5005 m. The observed rise in total cerebral haemoglobin from 107.5 (26.3) μmol/l of tissue at sea level to 132.1 (37.4) μmol/l ($P < 0.04$) supports this hypothesis.

The concept that carbon dioxide might be beneficial at altitude is not a new one [19]. More recently, supplemental carbon dioxide has been suggested in the treatment of acute mountain sickness [20], but this has not been confirmed by others [21]. Carbon dioxide has two powerful effects at all altitudes. First, by stimulating the respiratory centre, the rate and depth of respiration are increased. This can profoundly affect SpO_2 [12] and can also increase the arterial partial pressure of O_2 [22]. Secondly, carbon dioxide is a powerful cerebral vasodilator, causing a rapid increase in cerebral blood flow and increasing trans-cranial Doppler middle cerebral artery velocities at altitude [23]. The combination of increases in PiO_2 and $PiCO_2$ appears to have a synergistic effect. For these reasons, it seems likely that the accumulation of carbon dioxide in a portable hyperbaric chamber is beneficial, and that carbon dioxide extraction may be counter-productive. The use of supplemental 3% carbon dioxide at ambient pressures at altitude has been studied [22]. However, the optimum concentrations of carbon dioxide at differing altitudes need to be determined, and we suggest that measurement of cerebral regional oxygenation is a useful end-point to monitor, as it is likely to predict response to treatment.

In conclusion, these studies have demonstrated for the first time that compression in a portable hyperbaric chamber at altitude improves cerebral oxygenation, and that the improvement is due in part to the increase in PiO_2; in addition, the increase in $PiCO_2$ has a measurable physiological effect.

ACKNOWLEDGMENTS

The Mount Everest Foundation and the Arthur Thomson Trust supported this study.

REFERENCES

1 Hackett, P. M., Rennie, D. and Levine, H. F. (1976) The incidence, importance, and the prophylaxis of acute mountain sickness. Lancet ii, 1149–1154
2 Maggiorini, K., Buhler, B., Walter, K. and Oelz, O. (1990) Prevalence of acute mountain sickness in the Swiss Alps. Br. Med. J. 301, 853–855
3 Kayser, B., Dominique, J., Herry, J.-P. and Bärtsch, P. (1993) Pressurisation and acute mountain sickness. Aviat. Space Environ. Med. 64, 928–931
4 Bärtsch, P., Merki, B., Hofsetter, D., Maggiorini, M., Kayser, B. and Oelz, O. (1993) Treatment of acute mountain sickness by simulated descent: a randomised controlled trial. Br. Med. J. 306, 1098–1101
5 McCormick, P. W., Stewart, K., Goetting, M. G. and Balakrishnan, G. (1991) Regional cerebrovascular oxygen saturation by optical spectroscopy in humans. Stroke 22, 596–602
6 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
7 Henson, L. C., Calaing, 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
8 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
9 Holzschuh, M., Woertgen, C., Metz, C. and Brawanski, A. (1997) Comparison of changes in cerebral blood flow and cerebral oxygen saturation measured by near-infrared spectroscopy (NIRs) after acetazolamide. Acta Neurochir. 139, 58–62
10 Imray, C. H. E. and Knickenberg, C. J. (1997) Letter to Anaesthesia. Anaesthesia 52, 805
11 Gamow, I., Geer, G. D., Kasie, J. F. and Smith, H. M. (1990) Methods of gas-balance control in the treatment of high altitude illness. J. Wilderness Med. 1, 165–180
12 Imray, C. H. E., Brearey, S., Clarke, T. et al. (2000) Cerebral oxygenation at high altitude and the response to carbon dioxide, hyperventilation and oxygen. Clin. Sci. 98, 159–164

13 Dubois, C., Herry, J.-P. and Kayser, B. (1994) Portable hyperbaric medicine: some history. J. Wilderness Med. 5, 190–198
14 Kasic, J. F., Yaron, M., Nicholas, R. A., Lickteig, J. A. and Roach, R. (1991) Treatment of acute mountain sickness: hyperbaric versus oxygen therapy. Ann. Emergency Med. 20, 1109–1112
15 Keller, H. R., Maffiorini, M., Bärtsch, P. and Oelz, O. (1995) Simulated descent v dexamethasone in treatment of acute mountain sickness: a randomised trial. Br. Med. J. 310, 1232–1235
16 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
17 Saito, S., Shimada, H. and Yamamori, K. (1994) A transportable hyperbaric chamber with soda lime for the treatment of high altitude disorders. J. Wilderness Med. 5, 295–301
18 Milledge, J. S. (2000) Oxygenation of the brain at altitude. Clin Sci. 98, 165–166
19 Childs, S. B., Hamlin, H. and Henderson, Y. (1935) Possible value of inhalation of carbon dioxide in climbing great altitude. Nature (London) 135, 457–458
20 Harvey, T. C., Raichle, M. E., Winterborn, M. H. et al. (1988) Effect of carbon dioxide in acute mountain sickness: a rediscovery. Lancet ii, 639–641
21 Bärtsch, P., Baumgatner, 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
22 Hale, D., Walsh, S., Clarke, T. et al. (1999) Carbon dioxide or oxygen at altitude? The effect on arterial blood gases at sea level and on acute exposure to altitude. Adv. Exp. Biol. 474, 385 (abstract)
23 Tiivas, C., Williams, D., Harvey, T. et al. (1999) Carbon dioxide and cerebral blood flow at sea level and on acute exposure to altitude. Adv. Exp. Biol. 474, 433 (abstract)

Received 1 March 2000/21 August 2000; accepted 18 October 2000

Effects of breathing air containing 3% carbon dioxide, 35% oxygen or a mixture of 3% carbon dioxide/35% oxygen on cerebral and peripheral oxygenation at 150 m and 3459 m

C. H. E. IMRAY*, S. WALSH†, T. CLARKE†, C. TIIVAS*, H. HOAR†, T. C. HARVEY‡, C. W. M. CHAN*, P. J. G. FORSTER§, A. R. BRADWELL†, A. D. WRIGHT‡ and the Birmingham Medical Research Expeditionary Society†

*University Hospitals Coventry and Warwickshire NHS Trust, Department of Vascular Surgery, Clifford Bridge Road, Walsgrave, Coventry CV2 2DX, U.K., †Immunodiagnostic Research Laboratory, The Medical School, University of Birmingham, Vincent Drive, Edgbaston, Birmingham B15 2TT, U.K., ‡Department of Medicine, Manor Hospital, Walsall, U.K., and §Department of Medicine, James Paget Hospital, Great Yarmouth, Norfolk, U.K.

ABSTRACT

The effects of gas mixtures comprising supplementary 3% carbon dioxide, 35% oxygen or a combination of 3% CO_2 plus 35% O_2 in ambient air have been compared on arterial blood gases, peripheral and cerebral oxygenation and middle cerebral artery velocity (MCAV) at 150 m and on acute exposure to 3459 m in 12 healthy subjects. Breathing 3% CO_2 or 35% O_2 increased arterial blood oxygen at both altitudes, and the CO_2/O_2 combination resulted in the most marked rise. MCAV increased on ascent to 3459 m, increasing further with 3% CO_2 and decreasing with 35% O_2 at both altitudes. The CO_2/O_2 combination resulted in an increase in MCAV at 150 m, but not at 3549 m. Cerebral regional oxygenation fell on ascent to 3459 m. Breathing 3% CO_2 or 35% O_2 increased cerebral oxygenation at both altitudes, and the CO_2/O_2 combination resulted in the greatest rise at both altitudes. The combination also resulted in significant rises in cutaneous and muscle oxygenation at 3459 m. The key role of carbon dioxide in oxygenation at altitude is confirmed, and the importance of this gas for tissue oxygenation is demonstrated.

INTRODUCTION

Increasing numbers of people travel to high altitude for recreation and to work. Acute ascent to altitude results in a number of physiological responses. The respiratory centre is sensitive to changes in the arterial partial pressure of carbon dioxide ($PaCO_2$) and, to a lesser extent, to changes in the arterial partial pressure of oxygen

Key words: acute mountain sickness, blood gases, carbon dioxide, cerebral blood flow, high altitude, middle cerebral artery velocity, near-IR spectroscopy, oxygen.

Abbreviations: AMS, acute mountain sickness; MCAV, middle cerebral artery velocity; NIRS, near-IR spectroscopy; $PaCO_2$, arterial partial pressure of CO_2; PaO_2, arterial partial pressure of O_2; $PETCO_2$, end-tidal partial pressure of CO_2; $PiCO_2$, partial pressure of inspired CO_2; rSO_2, regional oxygen saturation.

Correspondence: Mr Chris Imray (e-mail chrisimray@aol.com).

(Pa_{O_2}). As the atmospheric pressure drops, the fall in Pa_{O_2} stimulates the respiratory centre, triggering the hypoxic ventilatory drive and resulting in an increase in the rate and depth of respiration [1]. There is a resulting improvement in Pa_{O_2}, but the increased ventilatory rate lowers Pa_{CO_2}, resulting in subsequent inhibition of the respiratory centre. Pa_{CO_2} is the critical determinant of the activity of the respiratory centre. Part of the acclimatization process is a change in the CO_2 or hypercapnic ventilatory response, and with increasing time at altitude the ventilatory response to a set CO_2 stimulus becomes heightened [2].

Hypoxia also alters cerebral haemodynamics in normal subjects. At altitude, arterial hypoxaemia dilates cerebral blood vessels and increases cerebral blood flow. However, hyperventilation reduces Pa_{CO_2}, and this has a powerful vasoconstrictor effect on cerebral blood flow. An understanding of the dynamic balance of these factors might give an insight into the mechanisms involved in the acclimatization process and the development of acute mountain sickness (AMS).

The introduction of the technique of reflected near-IR spectroscopy (NIRS) allows the continuous non-invasive monitoring of cerebral oxygenation. The technique was first described in adults in 1991 [3], and has widespread clinical applications. Reflected NIRS uses light in the near-IR spectrum (650–1100 nm), and, like pulse oximeters and mixed venous oximeters, uses the principles of light transmission and absorption to measure concentrations of oxygenated and deoxygenated haemoglobin in cerebral tissue. As such, the technique provides information not currently available by the use of any other modality. Although NIRS techniques remain mainly a research tool, valuable additional information about cerebral oxygenation is obtained. The technique of NIRS has been shown to precisely track changes in measured jugular venous bulb saturation in healthy volunteers under conditions of isocapnic hypoxia [4]. The technique has also been validated by comparing NIRS with PET (positron-emission tomography) scanning [5], with ^{133}Xe washout techniques [6] and with measurement of internal carotid artery stump pressures [7]. NIRS has been found to be a reliable and reproducible method for the evaluation of cerebrovascular reactivity, and hypercapnia has been shown to cause vasodilatation that is limited to the resistive vessels of the brain [8].

NIRS has been used at altitude to investigate cerebral oxygenation during acute exposure of subjects to altitudes of 4680 m [9]. Dynamic studies assessing the effects of various physiological manipulations, such as hyperventilation, oxygen therapy and CO_2 supplementation, have also been performed. Air enriched with 3% CO_2 markedly improved cerebral oxygenation [10]. The NIRS technique has been described to date in the assessment of cerebral tissue, and the Critikon 2020 spectrometer uses a two-sensor technique to enable the contribution of the scalp/skull to be eliminated, and thus data on tissue oxygenation at a depth of 2.5–5 cm is collected. There is no theoretical reason why other tissues cannot be investigated in a similar fashion, and a recent paper suggests that NIRS may be more accurate than ankle brachial pressure indices in assessing claudication in diabetic subjects [11]. Thus NIRS allows the continuous non-invasive monitoring of cerebral oxygenation, and is particularly suitable for multiple measurements of trends rather single absolute measurements.

The aim of the present study was to investigate the effects of supplementation with 3% CO_2, 35% O_2 and a CO_2/O_2 combination on cerebral oxygenation on acute exposure to an altitude of 3459 m. Changes in blood gases, pulse oximetry and cerebral artery velocity were measured in order to assess their contributions to changes in cerebral oxygenation.

METHODS

Subjects and methods

Twelve healthy, non-smoking volunteers (10 men), aged 24–53 years, were studied at 150 m and, 1 month later, on the morning after ascent to 3459 m by cable car. Vygon arterial lines (20 G; CE0459) were inserted into the radial artery using a standard Seldinger technique under aseptic conditions, and the lines were flushed with heparinized saline. Gas mixtures were prepared in Douglas bags and led through a closed system to a BOC face-mask. This was positioned over the face using a Clausen harness to ensure a good seal. A one-way valve prevented rebreathing.

Approval for the studies was granted by the Research and Ethics Committee of the South Birmingham Health Authority, and subjects gave informed consent.

Assessment of AMS

Lake Louise AMS questionnaires [12] were completed on the evening of arrival at 3459 m and on the following morning.

Gas mixtures

Gas mixtures were prepared in advance in 500-litre Douglas bags. At both altitudes, 3% CO_2 was made using 3 vol. of CO_2 to 97 vol. of air. The 35% O_2 and the 3% CO_2/35% O_2 gases were also made up based upon volume measurements. However, in view of the potential inaccuracy of the gas cylinder rotameters at altitude, CO_2 gas mixtures were initially checked using a Hewlett Packard capnograph 78356 A. A second confirmation of the composition of the gas mixtures was obtained by checking the partial pressures of inspired CO_2 (Pi_{CO_2}) and inspired O_2 using a Propac Encore Monitor (Propac

Systems Inc., Beaverton, OR, U.S.A.). Gas mixtures were based upon absolute pressures.

Pulse oximetry, capnography and cutaneous oximetry

$PiCO_2$, the end-tidal partial pressure of CO_2 ($PETCO_2$), pulse oximetry (peripheral O_2 saturation), heart rate and blood pressure were monitored at 1 min intervals using a Propac Encore Monitor.

Trans-cranial Doppler

Continuous trans-cranial Doppler assessment of middle cerebral artery velocity (MCAV) was measured by an experienced vascular technologist (C.T.) using a 2 MHz pulsed-wave, range-gated Doppler ultrasound SciMed Logidop 3 instrument (SciMed, Bristol, U.K.). The left middle cerebral artery was identified by recognition of the characteristic waveform and typical flow velocity profile, and was insonated at 45–60 mm through the temporal bone window. The time-averaged mean MCAV ($cm \cdot s^{-1}$) was recorded every 1 min.

Cerebral NIRS

Continuous non-invasive cerebral NIRS was performed using a Critikon cerebral spectroscope 2020 (Johnson and Johnson Medical Ltd, Newport, U.K.). The dual detector sensor position was standardized to a point over the right fronto-parietal region, with sensor margins 3 cm from the midline and 3 cm above the supra-orbital crest, taking care to avoid the sagittal sinus. Critikon disposable adhesive pads were found to be unsatisfactory, and a Blue-line Tubifast bandage (Seton Healthcare Group plc, Oldham, Lancs., U.K.) was used to keep the sensor in place, and maintain a standard probe pressure. Data sampled every 1 s was logged on to a Toshiba Satellite 200 CDS laptop computer. The interlock hold time was set at 120 s. Cerebral regional oxygen saturation (rSO_2) is derived from the equation:

$$rSO_2 = \left\{ \frac{\text{oxygenated haemoglobin}}{\text{total haemoglobin}} \right\} \times 100.$$

Peripheral NIRS

Continuous non-invasive muscle NIRS was carried out using a second Critikon 2020 cerebral spectroscope, with the sensor placed in a standard position over the right soleus muscle using a Blue-line Tubifast bandage. 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.

Blood gases

Arterial blood gases were analysed on an AVL OPTI 1 Blood Gas/pH Analyser (AVL List G.m.b.h., Graz, Austria).

Study protocol

Subjects rested in the supine position for 10–15 min prior to any measurements. After an initial 2 min baseline period breathing ambient air (Baseline 1), subjects breathed 3 % CO_2 for a 5 min period. There was then a 7 min washout period, breathing ambient air (Baseline 2). This was followed by 5 min of 35 % oxygen, and finally subjects breathed a 3 % CO_2/35 % O_2 enriched gas mixture for 5 min. Non-invasive measurements of pulse, pulse oximetry, $PETCO_2$, $PiCO_2$ and blood pressure were made every 1 min. Blood gases were analysed during the penultimate 1 min before changing to a new gas mixture. Although subjects were blinded to the gas mixtures, no attempt was made to change the order of gases, and many individuals noticed the gas mixtures containing CO_2.

Statistics

Statistical significance was assessed by the use of the paired Student's t test, repeated-measures ANOVA, regression analysis and the Wilcoxon signed-rank test (StatView for Windows; Abacus Concepts, Inc., Berkley, CA, U.S.A.). P values of < 0.05 were considered significant.

RESULTS

Atmospheric pressure on the study day at 150 m was 1014.6 mBar (101.2 kPa), and that at 3459 m was 660 mBar (65.8 kPa). Subjects had minimal AMS symptoms the night after ascent to 3459 m, with no scores greater than 2.

Heart rate, blood pressure and $PETCO_2$

Heart rate rose on ascent to 3459 m, but there was no change in blood pressure (Table 1). At 3459 m, heart rate was reduced on breathing 35 % O_2 and with the CO_2/O_2 combination. Systolic and diastolic blood pressures were reduced with 35 % O_2, and diastolic blood pressure decreased with CO_2/O_2. $PETCO_2$ decreased on ascent to 3459 m, and increased with 3 % CO_2 and with the CO_2/O_2 combination (Table 1).

Pulse oximetry and arterial blood gases

Peripheral O_2 saturation (pulse oximetry) decreased on ascent to 3459 m ($P < 0.001$) (Table 2), and increased at both 150 m and 3459 m on breathing 3 % CO_2, 35 % O_2 or the CO_2/O_2 combination. On ascent to 3459 m, arterial pH ($P < 0.005$), PaO_2 ($P < 0.0001$) and $PaCO_2$ ($P < 0.001$) were reduced. PaO_2 was increased at both 150 m and 3459 m on 3 % CO_2 or on 35 % O_2, and was increased still further by the CO_2/O_2 combination (Table 2, Figure 1).

Table 1 Changes in heart rate, blood pressure and P_{ETCO_2} at the end of each 5 min period of supplementary gas breathing

Heart rate, blood pressure and P_{ETCO_2} were measured after breathing ambient air, 3% CO_2, 35% O_2 and a mixture of the two gases, at both 150 m and 3459 m. Values are presented as means (S.D.). Significance of differences (Student's t test): $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.005$ compared with Baseline 1; $\dagger P < 0.001$ compared with 35% O_2.

Parameter	Baseline 1	3% CO_2	Baseline 2	35% O_2	3% CO_2/35% O_2
Heart rate (beats/min)					
150 m	60.25 (10.3)	61.6 (9.4)	61.7 (8.9)	59.5 (9.3)	60.4 (7.4)
3459 m	67.6 (7.4)	67.1 (5.2)	68.1 (6.7)	61.4 (5.9)*	63.1 (5.1)*
Blood pressure (mmHg)					
150 m					
Systolic	133.7 (15.4)	134.9 (12.6)	132.3 (11.2)	133.4 (13.0)	135.6 (15.1)
Diastolic	73.8 (7.0)	71.4 (7.4)	70.7 (8.2)	72.4 (10.4)	75.0 (7.6)
3459 m					
Systolic	136.4 (13.1)	136.0 (15.1)	135.2 (15.3)	131.0 (14.3)***	134.9 (15.7)
Diastolic	72.3 (11.0)	70.1 (11.6)	67.9 (12.8)**	66.4 (12.3)**	64.0 (14.6)**
P_{ETCO_2} (kPa)					
150 m	5.3 (0.28)	5.9 (0.41)*	5.2 (0.31)	5.1 (0.49)	5.6 (0.59)*†
3450 m	4.3 (0.20)	4.6 (0.28)*	4.4 (0.25)	4.34 (0.24)	4.5 (0.24)*†

Table 2 Changes in pulse oximetry and arterial blood gases at the end of each 5 min period of supplementary gas breathing

Pulse oximetry (peripheral O_2 saturation) and arterial blood gases were measured after breathing ambient air, 3% CO_2, 35% O_2 or a mixture of the two gases, at both 150 m and 3459 m. Values are presented as means (S.D.). Significance of differences (Student's t test): $^*P < 0.01$, $^{**}P < 0.0001$ compared with Baseline 1; $\dagger P < 0.01$, $\dagger\dagger P < 0.0005$ compared with 35% O_2.

Parameter	Baseline 1	3% CO_2	Baseline 2	35% O_2	3% CO_2/35% O_2
Pulse oximetry (kPa)					
150 m	97.5 (1.5)	98.5 (1.0)*	98.0 (1.3)	99.3 (0.7)*	99.5 (0.2)*†
3459 m	91.3 (3.0)	93.3 (3.0)*	90.8 (3.4)	99.6 (0.8)*	100.0 (0.0)*†
pH					
150 m	7.40 (0.03)	7.39 (0.01)	7.42 (0.02)	7.40 (0.024)	7.39 (0.03)
3459 m	7.49 (0.02)	7.47 (0.02)**	7.49 (0.02)	7.47 (0.04)	7.45 (0.03)*
Pa_{O_2} (kPa)					
150 m	13.4 (0.9)	15.4 (1.1)**	14.0 (0.6)	22.8 (4.0)*	24.5 (3.4)*†
3459 m	6.5 (0.5)	7.2 (0.6)**	6.6 (0.6)	14.3 (4.3)*	19.0 (3.4)*††
Pa_{CO_2} (kPa)					
150 m	5.06 (0.05)	5.55 (0.35)**	5.23 (0.48)	5.18 (0.54)	5.37 (0.63)**
3459 m	3.78 (0.36)	4.12 (0.36)	3.81 (0.46)	3.96 (0.49)	4.25 (0.41)

MCAV and cerebral rSo_2

Trans-cranial Doppler MCAV increased on ascent to 3459 m ($P < 0.01$) (Table 3), and further increases were found on breathing 3% CO_2. MCAV decreased at both altitudes on 35% O_2, and intermediate results were found for the CO_2/O_2 combination. Cerebral rSo_2 fell on ascent to 3459 m (Table 3). Breathing either 3% CO_2 or 35% O_2 increased cerebral rSo_2 at both 150 m and 3459 m. The combination of CO_2/O_2 resulted in the most marked rise at both altitudes (Table 3, Figure 2).

Muscle rSo_2

Baseline muscle rSo_2 fell from 73.0% (S.D. 2.3%) to 68.4% (3.7%) ($P < 0.001$) on ascent to 3459 m. There was no significant rise in muscle rSo_2 at 150 m [73.3% (2.2%)] or at 3459 m [68.9% (3.6%)] on breathing 3% CO_2. At 3459 m, muscle rSo_2 rose to 70.3% (3.6%) ($P < 0.001$) on breathing 35% O_2. Muscle rSo_2 rose to 74.0% (2.5%) ($P < 0.02$) at 150 m and to 71.2% (3.9%) ($P < 0.001$) with the CO_2/O_2 combination.

DISCUSSION

The beneficial effect of carbon dioxide was suggested as long ago as 1855, when Miescher-Rusch wrote: "over the oxygen supply of the body, carbon dioxide spreads its protecting wings – especially as it cares for the brain

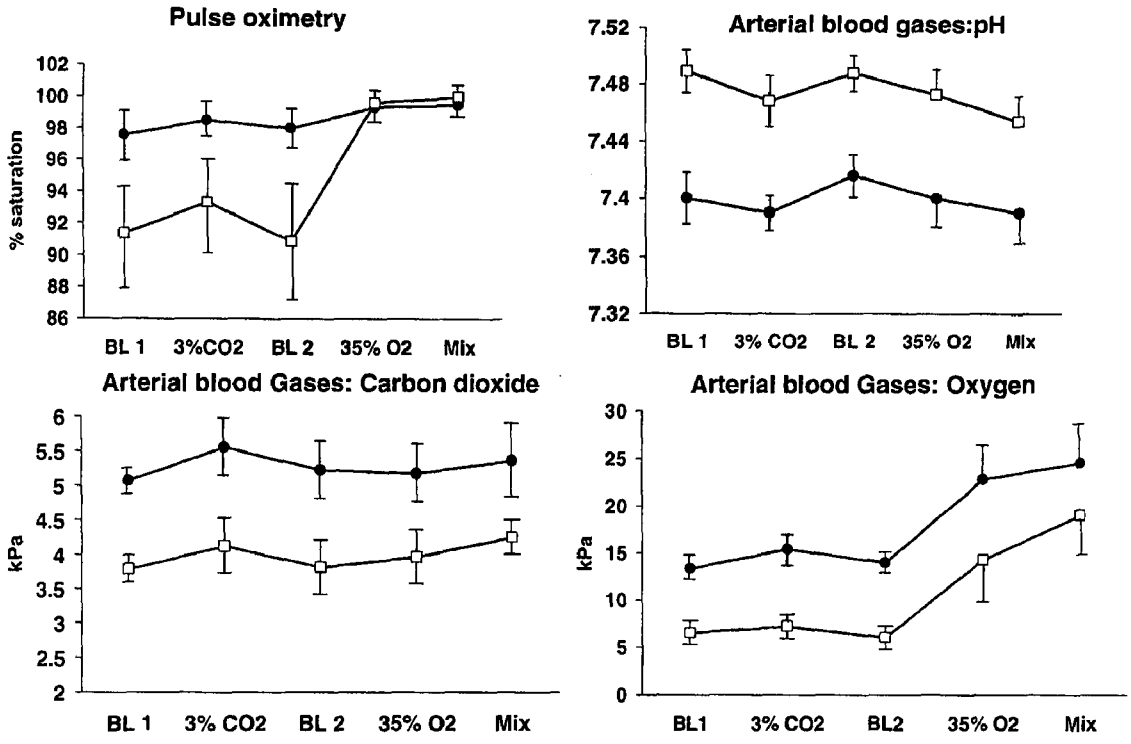


Figure 1 **Pulse oximetry and arterial blood gases in 20 subjects at 150 m (●) and at 3459 m (□)**

Values are means ± S.D. BL1, first baseline; BL2, second baseline. The results at the end of 5 min of breathing 3% CO_2 in ambient air, at the end of 5 min of breathing 35% O_2 in ambient air and at the end of 5 min of breathing 3% CO_2 + 35% O_2 (mix) in ambient air are shown. Compared with BL1, 3% CO_2 resulted in an increase in pulse oximetry at both altitudes ($P < 0.0001$), a fall in pH at 3459 m ($P < 0.05$), an increase in Pao_2 at both altitudes ($P < 0.01$) and a rise in $Paco_2$ at 150 m ($P < 0.01$). Compared with BL1, 35% O_2 resulted in an increase in pulse oximetry ($P < 0.0001$) and Pao_2 ($P < 0.0001$) at both altitudes. Compared with BL1, the 3% CO_2/35% O_2 mixture resulted in an increase in pulse oximetry at both altitudes ($P < 0.0001$), a decease in pH at 3459 m ($P < 0.0001$), increases in Pao_2 at 150 m ($P < 0.01$) and at 3459 m ($P < 0.001$), and an increase in $Paco_2$ at 150 m ($P < 0.01$).

Table 3 **Changes in MCAV and rSo_2 at the end of each 5 min period of supplementary gas breathing**

MCAV and rSo_2 were measured after breathing ambient air, 3% CO_2, 35% O_2 and a mixture of the two gases, at both 150 m and 3459 m. Values are presented as mean (S.D.). Significance of differences (Student's t test): $^*P < 0.01$ compared with Baseline 1; †$P < 0.001$ compared with 35% O_2.

Parameter	Baseline 1	3% CO_2	Baseline 2	35% O_2	3% CO_2/35% O_2
MCAV (cm/s)					
150 m	58.8 (14.2)	68.1 (13.7)*	55.6 (14.6)	54.0 (16.5)*	64.8 (13.4)*†
3549 m	63.1 (18.6)	68.6 (19.2)*	61.4 (18.3)	58.1 (21.0)*	62.0 (20.8)
rSo_2 (%)					
150 m	69.9 (2.6)	70.6 (2.5)*	69.7 (2.6)	70.3 (2.6)*	71.0 (2.6)*†
3459 m	65.6 (2.8)	66.7 (3.2)*	65.7 (3.2)	68.8 (2.9)*	70.2 (3.8)*†

which, for unknown reasons, may not lack air in warm blooded animals whereas skin and muscle may tolerate the ischaemia of a tourniquet for more than half an hour" [13]. In 1898, Angelo Mosso administered CO_2 gas mixtures to relieve hypoxic symptoms in a subject exposed to pressures as low as 250 torr (33.3 kPa; equivalent to an altitude of ~ 8800 m) in a hypobaric chamber [14]. In 1988, Harvey et al. [15] demonstrated in an uncontrolled trial that air enriched with 3% CO_2 improved cerebral blood flow, as assessed by the use of ^{133}Xe. This was associated with an improvement in the symptoms of AMS. However, Bartsch et al. [16], in a controlled trial, found no increase in cerebral blood flow (assessed by trans-cranial Doppler) or reduction in AMS symptoms when symptomatic subjects inhaled air containing 3% CO_2. Similarly, Yang et al. [17] showed that,

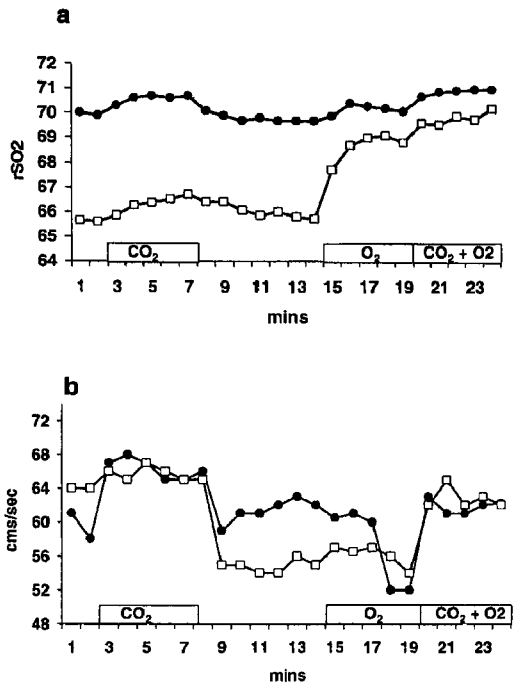


Figure 2 Sequential measurements of rSo_2 (a) and MCAV (b) during inhalation of 3% CO_2, 35% O_2 or 3% CO_2/35% O_2 in ambient air at 150 m (●) and 3459 m (□)

Compared with baseline, breathing 3% CO_2 resulted in an increase in rSo_2 ($P < 0.01$) and an increase in MCVA ($P < 0.01$) at both altitudes. Compared with baseline, 35% O_2 resulted in an increase in rSo_2 ($P < 0.01$) and a decrease in MCVA ($P < 0.01$) at both altitudes. Compared with baseline, the 3% CO_2/35% O_2 mixture resulted in an increase in rSo_2 at both altitudes ($P < 0.01$) and an increase in MCVA at 150 m ($P < 0.01$).

although 3% CO_2-enriched air improved cerebral blood flow in animals (as assessed using radiolabelled microspheres) and that CO_2 is an important determinant of cerebral blood flow at all altitudes, symptoms of AMS were not reduced by supplemental CO_2.

There are several mechanisms by which carbon dioxide might improve tissue oxygenation. Hypercapnia results in increased cardiac output and an alteration in intrapulmonary shunting, with a net increase in PaO_2 [18]. As a result of increases in cardiac output and regional blood flow, including mesenteric flow, there is improved oxygen delivery to the tissues [19]. Hypercapnia also shifts the oxyhaemoglobin dissociation curve to the right, further improving oxygen delivery to the tissues. In patients with coronary artery disease, there is evidence that, acting directly, hypercapnia dilates peripheral arterioles, reducing the systemic vascular resistance index, increasing the cardiac index and augmenting myocardial blood flow [20]. Although the peripheral chemoreceptors are sensitive to changes in $PaCO_2$, the main sensor for changes in $PaCO_2$ is the central medullary chemoreceptor, which is located just beneath the surface of the fourth ventricle. The blood–brain barrier is readily permeable to dissolved CO_2, but is less permeable to H^+ and even less so to HCO_3^-. A rise in $PaCO_2$ is rapidly reflected by a rise in the partial pressure of CO_2 in the cerebrospinal fluid, and this causes a rapid increase in the cerebrospinal fluid H^+ concentration. This is sensed by the chemoreceptors, resulting in increased stimulation of the respiratory centre and increased ventilation [1]. Activation of the central nervous system evokes sympatho-adrenal responses, resulting in increased myocardial contractility, tachycardia and hypertension.

The most important determinants of cerebral blood flow in normotensive individuals are PaO_2 and $PaCO_2$, which interact with opposing effects. Ascent to altitude results in a hypoxic vasodilatation and an increase in cerebral blood flow, whereas the resulting decrease in $PaCO_2$ causes vasoconstriction and a reduction in cerebral blood flow. In 1966, Sevringhaus et al. [21], using a nitrous oxide-based technique, showed that cerebral blood flow increased by 24% in the first 6–12 h at altitude, but this fell to 13% above sea-level values at 3–5 days. There appears to be general agreement that there is an initial rise in cerebral blood flow on acute exposure to high altitude, and that this returns gradually towards the baseline level with acclimatization. Whether cerebral blood flow is any higher in subjects suffering from AMS may depend on the degree of hypoxia, possibly explaining why an increase was found in one study [22] but not in another [23].

Our present studies were therefore designed to quantify the effects of supplementary carbon dioxide at altitude, not only on blood gases and blood velocity, but also on tissue oxygenation. The choice of a concentration of 3% CO_2 was made because it is safe and tolerated at similar altitudes [10], although other studies within portable hyperbaric chambers suggest that concentrations as low as 1% have significant effects [25]. Although the percentage of $PiCO_2$ was kept constant at both sea level and altitude, the changes in observed $PETCO_2$ were considerably smaller at altitude, and consequently this may have reduced the effect.

In our present study, breathing air containing 3% CO_2 increased trans-cranial Doppler cerebral blood flow and cerebral oxygenation as measured by NIRS, at both 150 m and 3459 m. We also confirmed that breathing 35% O_2 reduced the trans-cranial Doppler cerebral blood velocity at both altitudes, but more so at 3459 m than at 150 m. However, for the first time, 35% O_2 was shown to increase cerebral rSO_2 at both altitudes, with a greater rise at 3459 m. The mixture of 3% CO_2/35% O_2 resulted in a small increase in MCAV compared with ambient air at 150 m, but no change in at 3459 m. The gas mixture resulted in the largest increase in cerebral rSO_2 at both 150 m and 3459 m, but this was greater at 3459 m, which appeared to be due to a combination of increased partial pressure of inspired O_2 through an effect on gas

exchange improving arterial oxygenation and $PiCO_2$ causing cerebral vasodilatation. The greatest effect of additional CO_2 is most probably increased gas exchange due to increased ventilation, but this was not measured in the present study.

Whether CO_2 supplementation alone has a useful role at altitude remains uncertain [15,16], but our results show that the combination of CO_2 and O_2 has a synergistic effect, and could be useful in the management of AMS. Indeed, this may already be the case in the use of lightweight portable fabric hyperbaric chambers that have been shown to be beneficial in the treatment of AMS [24]. More recent work demonstrated that once a steady state had been achieved with pressurization of the chamber to 200 mBar (19.95 kPa), $PiCO_2$ rose from 0.059 (S.D. 0.18) to 1.33 (0.18) kPa [25]. When a soda lime CO_2 scrubber was introduced into the breathing circuit within the chamber, there was a reduction in both digital pulse oximetry and cerebral oxygenation (measured by NIRS). The build-up of CO_2 within the chamber to a pressure of 1.33 (0.18) kPa appeared to account for up to one-third of the beneficial effect of the portable hyperbaric chamber on cerebral oxygenation [25]. Before conducting clinical trials of supplementary CO_2 and O_2, the optimum proportions of the two gases need to be found. We believe that tissue oxygenation should be the end point measured, in view of the opposing effects of O_2 and CO_2 on vascular beds and the different responses in different vascular beds.

In conclusion, we have studied for the first time the effects of supplementary oxygen and carbon dioxide on cerebral oxygenation at altitude, as measured by NIRS. Bert [26] and Mosso [14] were both correct to conclude that oxygen and carbon dioxide respectively have profound effects on oxygen delivery to the brain. Mosso, however, believed that it was the lack of CO_2 or 'acapnia' that was the cause of AMS, and based on today's evidence this is not correct. Theoretically, the greatest benefit may be obtained from a combination of the two gases, and this should be assessed in clinical trials in the management of AMS. In the meantime, the best treatment of AMS remains descent, and if this is not possible, oxygen therapy, dexamethasone and acetazolamide, which are of proven benefit.

ACKNOWLEDGMENTS

We are grateful for support from The Arthur Thomson Trust. Ms Dionne Logan provided secretarial support.

REFERENCES

1 Ward, M. P., Milledge, J. S. and West, J. B. (1995) The ventilatory response to hypoxia and carbon dioxide. In High Altitude Medicine and Physiology, 2nd edn, pp. 69–97, Chapman and Hall Medical, London

2 Lloyd, B. B., Jukes, M. G. M. and Cunningham, D. J. C. (1958) The relationship of alveolar oxygen pressure and the respiratory response to carbon dioxide in man. Q. J. Exp. Physiol. **43**, 214–227

3 McCormick, P. W., Stewart, M., Goetting, M. G. and Balakrishnan, G. (1991) Regional cerebrovascular oxygen saturation measured by optical spectroscopy in humans. Stroke **22**, 596–602

4 Henson, L. C., Calalang, C., Temp, J. A. and Ward, D. S. (1998) Accuracy of cerebral oximeter in healthy volunteers under conditions of isocapnic hypoxia. Anesthesiology **88**, 58–65

5 Villinger, 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

6 Holzschuh, M., Woertgen, C., Metz, C. and Brawanski, A. (1997) Comparison of changes in cerebral blood flow and cerebral oxygen saturation measured by near-infrared spectroscopy (NIRS) after acetazolamide. Acta Neurochir. (Wein) **139**, 58–62

7 Williams, I. M., Vohra, R., Farrell, A., Picton, A. J., Mortimer, A. J. and McCollum, C. N. (1994) Cerebral oxygen saturation, transcranial Doppler ultrasonography and stump pressure in carotid surgery. Br. J. Surg. **81**, 960–964

8 Totaro, R., Barattelli, G., Quaresima, V., Carolei, A. and Ferrari, M. (1998) Evaluation of potential factors affecting the measurement of cerebrovascular reactivity by near-infrared spectroscopy. Clin. Sci. **95**, 497–504

9 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

10 Imray, C. H. E., Brearey, S., Clarke, T. et al. (2000) Cerebral oxygenation at high altitude and the response to carbon dioxide, hyperventilation and oxygen. Clin. Sci. **98**, 159–164

11 Komiyama, T., Shigematsu, H., Yashuhara, H. and Muto, T. (2000) Near-infrared spectroscopy grades the severity of intermittent claudication in diabetics more accurately than ankle pressure measurement. Br. J. Surg. **87**, 459–466

12 Hackett, P. H. and Oelz, O. (1992) The Lake Louise consensus on the definition and quantification of altitude sickness. In Hypoxia and Mountain Medicine (Sutton, J. R., Coates, G. and Houston, C. S., eds), pp. 327–330, Queen City Printers, Burlington

13 Miescher-Rusch, F. (1885) Bemerkungen zur Lehre von der Athembewegungen. Arch. Anat. Physiol. Physiol. Abth. 355–361

14 Mosso, A. (1898) Life of Man on the High Alps, pp. 287–307, Fischer Unwin, London

15 Harvey, T. C., Raichle, M. E., Winterborn, M. H. et al. (1988) The effect of carbon dioxide in acute mountain sickness: a rediscovery. Lancet ii, 639–641

16 Bartsch, P., Baumgartener, R. W., Waber, U., Marggorini, M. and Oelz, O. (1990) Comparison of carbon-dioxide-enriched, oxygen-enriched and normal air in the treatment of acute mountain sickness. Lancet **336**, 772–775

17 Yang, S.-P., Bergo, G. W., Krasney, E. and Krasney, J. A. (1994) Cerebral pressure-flow and metabolic responses to sustained hypoxia: effect of CO_2. J. Appl. Physiol. **76**, 303–313

18 Hickling, K. G. and Joyce, C. (1995) Permissive hypercapnia in ARDS and its effects on tissue oxygenation. Acta Anaesthesiol. Scand. **39** (Suppl. 107), 201–208

19 Cardenas, V. J., Zwischenberger, J. B., Tao, W. et al. (1996) Correction of blood pH attenuates changes in hemodynamics and organ blood flow during permissive hypercapnia. Crit. Care Med. **24**, 827–834

20 Kazmaier, S., Weyland, A., Buhre, W. et al. (1998) Effects of respiratory alkolosis and acidosis on myocardial blood flow and metabolism in patients with coronary artery disease. Anesthesiology **89**, 831–837

21 Sevringhaus, J. W., Chiodi, H., Eger, E. I., Brandstater, B. and Hornbein, T. F. (1966) Cerebral blood flow in man at high altitude. Role of cerebrospinal fluid pH in normalization of flow in chronic hypocapnia. Circ. Res. **19**, 274–282
22 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
23 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
24 Bartsch, P., Merki, B., Hofsetter, D., Maggiorini, M., Kayser, B. and Oelz, O. (1993) Treatment of acute mountain sickness by simulated descent: a randomised controlled trial. Br. Med. J. **306**, 1098–1101
25 Imray, C. H. E., Clarke, T., Forster, P. J. G. et al. (2001) Carbon dioxide contributes to the beneficial effect of pressurization in a portable hyperbaric chamber at high altitude. Clin. Sci. **100**, 151–157
26 Bert, P. (1878) La Pression Barometrique, Paris Masson; English translation (1943) by M. A. Hitchcock and F. A. Hitchcock, Columbus Ohio College Book Company, Columbus

Received 17 April 2002/10 September 2002; accepted 26 November 2002

STV

Mini-revue

Sang Thrombose Vaisseaux 2003 ;
15, n° 1 : 17-27

Perfusion cérébrale en haute altitude

Christopher H. E. Imray [1], Colin W. M. Chan [1], Alexander D. Wright [2]
et le *Birmingham medical research expeditionary society* [3]

[1]Warwickshire County vascular unit, department of surgery, University Hospitals Coventry and Warwickshire NHS Trust, Clifford bridge road, Walsgrave, Coventry CV2 2DX, Royaume-Uni, [2]Department of Medicine, Manor Hospital, Walsall, Royaume-Uni, [3]Immunodiagnostic Research Laboratory, The Medical School, University of Birmingham, St Vincent's Drive, Edgbaston, Birmingham B15 2TT, Royaume-Uni

En novembre 1783, Pilatre de Rozier et le marquis d'Arlandre entreprirent le premier voyage dans le ballon des frères Montgolfier. Ils sont montés à 900 m environ et le vol dura près de vingt minutes au-dessus de Paris. Cet événement historique montra qu'une rapide excursion en altitude était possible et inaugura l'ère du vol en équipage. Ce fut le début d'une période « d'exploration physiologique », et l'excitation qui s'empara de la société fut sans doute semblable à celle de l'exploration spatiale des années cinquante et soixante. L'orgueil national fut flatté par ces aventures et chaque aérostier cherchait à voler de plus en plus haut. À cette époque, les risques étaient méconnus.

En mars 1874, les éminents aérostiers du moment, Joseph Croce-Spinelli et Théodore Sivel furent soumis dans le caisson de compression hypobare Sorbonne, de Paul Bert, à une pression 304 mmHg (7 000 m) pendant plus d'une demi-heure. On note alors que la basse de pression exerçait une action très importante sur la vision, l'audition et le calcul arithmétique simple *(figure 1)*.

Plus tard, Paul Bert écrivit aux aérostiers qu'il aurait calculé que la réserve d'oxygène qu'ils s'apprêtaient à emporter dans leur vol en haute altitude n'était pas adaptée. Malheureusement, la lettre leur parvint trop tard. Le 15 avril 1875, Croce-Spinelli et Gaston Tissandier s'envolèrent à bord du « Zénith ». Vers 7 000 m, tous trois perdirent connaissance et deux d'entre eux décédèrent. Le survivant, Gaston Tissandier, devait écrire plus tard : « J'en arrive au moment fatidique, quand nous fûmes saisis par les terribles effets de la décompression atmosphérique... Aussitôt, je voulus prendre le tuyau d'oxygène, mais je ne pouvais pas lever le bras... Je voulus crier « Nous sommes à 8 000 m » mais ma langue était paralysée. Soudain mes yeux se refermèrent et je tombai inanimé » [1]. Ces deux premiers accidents mortels en haute altitude suscitèrent une grande émotion nationale.

Ascension en haute altitude

Les transports aériens modernes permettent à des personnes plus ou moins expérimentées, souvent animées de projets fantaisistes, de se rendre rapidement dans des régions lointaines et non exemptes de dangers. Un grand nombre d'entre elles font des programmes serrés et se joignent aux groupes d'ascension rapide au lieu de grimper selon leurs possibilités individuelles.

Correspondance et tirés à part :
E-mail : chrisimray@aol.com

Traduit par : Claude Franceschi, Hôpital Saint-Joseph, Service de chirurgie vasculaire, 185, rue Raymond Losserand, 75014 Paris cedex 14.

Mots clés : débit cérébral, haute altitude, dioxyde de carbone, mal des montages aigu, œdème cérébral de haute altitude, œdème pulmonaire de haute altitude

Abbréviations : dioxyde de carbone, CO_2 ; Oxygène O_2 ; pression artérielle partielle d'oxygène, PaO_2 ; pression artérielle partielle de dioxyde de carbone, $PaCO_2$

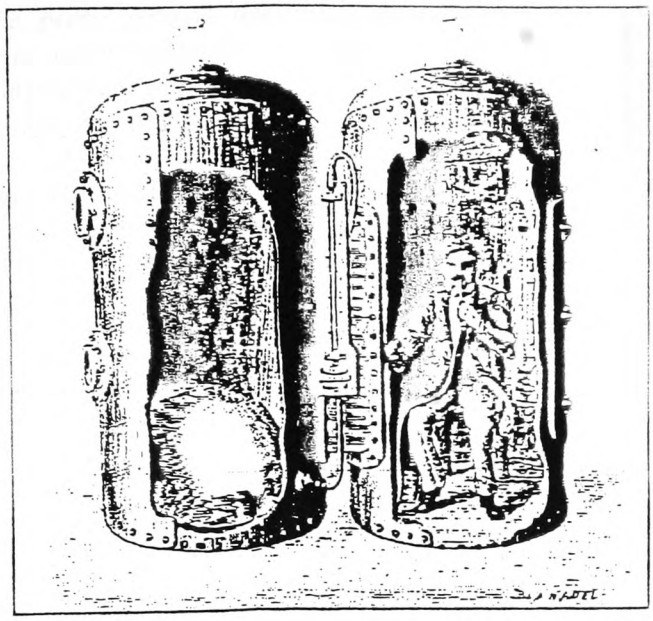


Figure 1. Caisson de compression hypobare de Paul Bert.

Le nombre de maladies liées à l'altitude croît sans cesse avec le nombre toujours plus grand de personnes qui vont se promener ou travailler en altitude Une foule croissante de randonneurs et de grimpeurs montent tant sur des sommets européens comme le Mont Blanc (4 808 m) ou d'autres plus reculés comme le Kilimandjaro (5 895 m) en Tanzanie. On s'attend à ce que des soldats soient envoyés combattre en haute altitude, comme c'est le cas de la frontière très disputée entre l'Inde et le Pakistan (4 000-5 000 m). Des mines ont été exploitées en haute altitude pendant des siècles en Amérique du Sud, record battu par la mine de soufre d'Aucanquilcha au Chili [2]. Des télescopes aussi sont installés très haut en raison des conditions de visualisation astronomique plus favorables grâce à une atmosphère moins épaisse, et une pollution atmosphérique et lumineuse plus faible. Le mont Mauna Kea (4 200 m) à Hawaii tient le record du nombre avec 13 télescopes et le Chajantor (5 050 m) au nord du Chili devrait recevoir le gigantesque Atacam Large Millimeter Array (Alma) *(figures 2* et *3)*.

L'ascension provoque de nombreuses réactions physiologiques. Le centre respiratoire est sensible aux variations de la $PaCO_2$, et à un moindre degré à la PaO_2.

Quand la pression atmosphérique baisse, la PaO_2 chute, le centre de contrôle de l'hypoxie déclenche une hyperventilation qui relève la PaO_2 mais fait chuter la $PaCO_2$. La $PaCO_2$ est le facteur stimulant majeur du centre respiratoire. Sa chute entraîne une respiration périodique. L'acclimatation réside en partie dans le changement de réponse

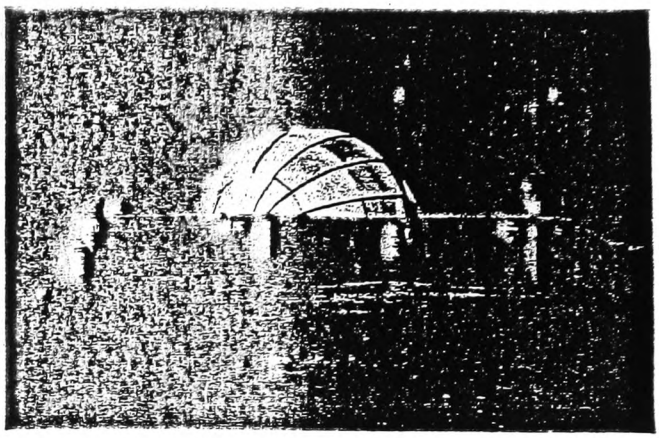


Figure 2. Site proposé pour l'installation du télescope géant ALMA (Chanjantor, Chili, 5 000 m d'altitude).

du centre respiratoire, dont le seuil de réponse à la $PaCO_2$ s'élève au bout d'un certain temps de station en altitude. L'hypoxie comme l'hypocarbie modifient l'hémodynamique cérébrale chez le sujet normal. L'hypoxie dilate les vaisseaux et augmente fortement le débit cérébral. Mais l'hyperventilation réduit la $PaCO_2$ qui à son tour entraîne une forte vasoconstriction. La compréhension de la dynamique de l'équilibre de ces deux facteurs devrait éclairer mieux les mécanismes mis en œuvre, le processus d'acclimatation et de mal aigu des montagnes.

Mal aigu des montagnes

En 1913, Thomas Ravenhill de l'Université de Birmingham, décrivit pour la première fois une maladie en rapport avec l'altitude. Il était médecin des mines chiliennes quand il donna la première description précise de ce qu'il appela le « mal des montages ». Il en fit la première classification et fut aussi le premier à distinguer l'œdème cérébral et l'œdème pulmonaire de haute altitude [3]. Son

Figure 3. Camion gros porteur, mine de cuivre du Chili (4 200 m d'altitude).

article fut perdu pendant une cinquantaine d'années et redécouvert par WH Hall en 1964, au cours d'une recherche bibliographique approfondie.

Le mal aigu des montagnes est fréquent au cours des ascensions rapides. Il se traduit par des céphalées, un état léthargique et nauséeux, qui peuvent en rester là ou bien évoluer vers l'œdème cérébral l'œdème pulmonaire de haute altitude. Dans ce dernier cas, les sujets meurent souvent et rapidement d'une affection que l'on sait parfaitement bien prévenir. La prévalence du mal aigu des montagnes est évaluée entre 43 et 62 % en Himalaya, et entre 9 et 69 % dans les Alpes [4]. La sévérité dépend de nombreux facteurs parmi lesquels le taux de montée, l'altitude atteinte, l'acclimatation antérieure et la susceptibilité individuelle.

On peut éviter le mal aigu des montagnes par une ascension lente qui permet à l'organisme de s'adapter au manque d'O_2. Au-dessus de 3 000 m, la moyenne de vitesse d'ascension ne devrait pas dépasser 300 m par jour. Des journées de repos doivent être observées pour respecter ce taux de montée, qui plus rapide peut devenir dangereux. L'altitude à laquelle on dort est importante à considérer et ne doit pas être supérieure de 300 m à celle de la nuit précédente, même si on est monté plus haut dans la journée : grimper haut et dormir bas.

En plus de la vitesse de montée lente et du repos pour l'acclimatation, nombre de stratégies ont été mises en place pour prévenir le mal aigu des montagnes, parmi lesquelles les substances médicamenteuses comme l'acétalozamide [5] et la dexaméthasone. L'acétalozamide 250 ou 500 retard est commencée 24 à 48 h avant l'ascension. On a dit récemment que 750 mg par j en trois prises seraient plus efficaces [6]. Il doit être continué pendant une semaine au moins si l'ascension dure moins de temps. Les effets secondaires sont la polyurie et les paresthésies. Un mal aigu des montagnes modéré, pourrait requérir de la dexamethasone 8 mg immédiatement puis 4 mg par jour, *per os* ou intraveineux.

Un supplément d'O_2 améliore le mal aigu des montagnes, et c'est le traitement à conseiller [7].

Des caissons hyperbares portables comme le sac Gamow (Chinook Medical Gear, PO Box 176, Edwards CO 81362, États-Unis) ou le sac Certec (Sourcieux-les-Mines, 69210 L'Arbresle, France) peuvent être utilisés pour le traitement individuel du mal aigu des montagnes.

Le sujet est enfermé dans le sac, fermé par une glissière étanche, puis de l'air est pompé vers l'intérieur jusqu'à 200 mbar au-dessus de la pression ambiante, ce qui revient à une descente de 200 m et ferait régresser rapidement les symptômes. Le traitement doit être maintenu pendant plus de 2 h. Il est destiné à permettre une descente réelle dans de meilleures conditions [8]. Avec ou sans sac, le traitement de l'œdème cérébral de haute altitude repose sur l'oxygène, la descente et aussi la dexaméthasone *(figure 4)*.

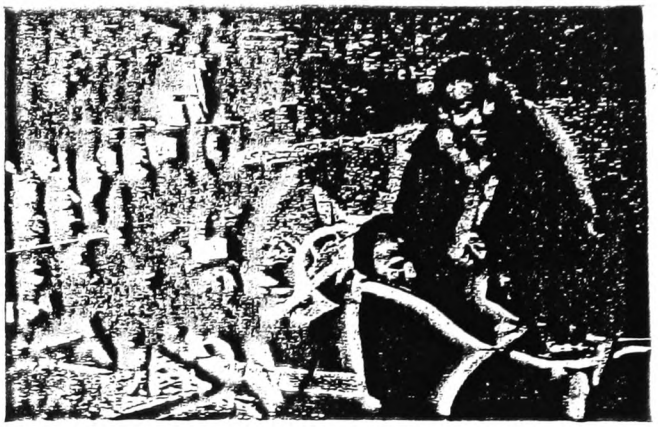


Figure 4. Caisson hyperbare portable (sac Gamow, États-Unis).

Apports de sang en haute altitude

Oxygène

Paul Bert est le père incontesté de la physiologie d'altitude moderne. Il fut le premier à expérimenter le caisson hyper- et hypobare chez l'homme et l'animal. Il démontra que l'apport d'O_2 faisait régresser les effets de l'hypobarie. Son traité *« La pression barométrique »* constitua un apport complet et autorisé à l'histoire et aux effets de l'hypobarie [1]. Il fut un grand promoteur de l'oxygène dans le traitement du mal aigu des montagnes.

Quoique Paul Bert fut le premier à la décrite en 1878, ce fut Alexandre Kellas qui évaluera, pour la première fois sur le terrain, les effets de l'oxygène sur l'hypoxie en 1920, sur le Kamet. Cependant, il sentit que la route de l'Everest pourrait être prise sans supplément d'oxygène en raison des faibles difficultés techniques. Il écrivit « un homme, pourvu qu'il soit en bonne condition physique et mentale, peut monter à l'Everest sans préparation particulière ni oxygène supplémentaire, tant qu'il n'est pas confronté à de trop grandes difficultés ». Malgré cela, on utilisa l'oxygène dans la *British Everest Expedition* de 1922 et dans l'expédition malheureuse qui entraîne la mort de George Mallory et Sandy Irvine pendant qu'ils redescendaient de 8 500 m. En mai 1952, Raymond Lambert et Tenzing Norgay retournèrent tout près du sommet de l'Everest. Ils utilisèrent de l'oxygène à 2 L/min. Le Britannique Griffith Pugh en déduisit qu'il faudrait 4 L/min pour monter au-dessus de 8 000 m. Edmund

Hilary et Tenzing conquirent l'Éverest en 1953 avec 4 à 6 L d'oxygène/min.

En 1950, Maurice Herzog et Louis Lachenal furent les premiers à monter à 8 091 m, sur l'Annapurna, sans oxygène, ce qui donna raison à Kellas qui disait cela possible. Mais leur retour catastrophique devait aussi souligner combien la marge entre succès et défaite peut être étroite à ces altitudes. Reinhold Messner et Peter Habeler, en 1978, sont montés à 8 848 m (Éverest) sous oxygène. En 1999, plus de 1 000 individus ont grimpé l'Éverest. Le taux de mortalité, chez les sujets qui y ont grimpé avec oxygène, était de 3,2 % pour les hommes et 7,4 % pour les femmes. Il était de 6 % chez ceux qui y sont montés sans oxygène.

L'apport d'oxygène a pour avantage, la rapidité de sa mise en œuvre et de son action. Il ne demande ni abord IV ni ingestion orale, ce qui est d'une grande utilité sur le terrain. Il présente hélas l'inconvénient de devoir être transporté dans des bouteilles lourdes et encombrantes, au point qu'il n'est plus transporté dans la majorité des ascensions et reste réservé à la médecine.

Dioxyde de carbone

On mit longtemps à se rendre compte de l'intérêt biologique du dioxyde de carbone qui n'est pas moins vital que l'oxygène. En 1885, Miescher-Rusch écrivit « le dioxyde de carbone déploie ses ailes protectrices sur les apports en oxygène, particulièrement quand il s'occupe du cerveau qui, pour des raisons inconnues, ne résiste pas à l'absence d'air chez les animaux à sang chaud, alors que le muscle et la peau supportent l'ischémie pendant plus d'une demi-heure de garrot ».

Angelo Mosso, professeur de physiologie à Turin, en 1879, marqua un vif intérêt pour la physiologie d'altitude. Il pressentit que nombre de symptômes de l'hypoxie/hypobarie aiguë étaient dus à un manque d'oxygène. Cette intuition ne suscita aucun intérêt à cette époque, de sorte que le rôle de l'oxygène, dans la circulation cérébrale et dans le mal aigu des montagnes, fut oublié pendant une très longue période. Il faut aussi, en 1898, un acteur de la construction de la station de recherche en haute altitude de Cabana Margherita, sur le Monte Rosa (4 559 m). Là haut, il nota une respiration périodique de Cheyne Stokes tant chez son frère Ugolino que chez son chien Nerino ! Le refuge est le plus haut d'Europe et devrait rester un site important pour la recherche pendant près d'un siècle.

Selon l'hypothèse que le déficit en oxygène entraînerait hyperpnée et acapnie, malgré une respiration subnormale, le CO_2 fut proposé comme un traitement alternatif à « l'acapnie » d'altitude. En 1898, Angelo Mosso entreprit sa remarquable expérience en caisson hypobare en ajoutant un supplément de 0,9 % de CO_2 au mélange gazeux, afin de soulager les symptômes d'un sujet exposé à une altitude de 6 500 m. Le même sujet fut ensuite exposé à Torr 250 (8 800 m) avec un supplément de 2,2 % de CO_2 sans aucun effet pathologique.

Douglas, Holdane et autres redonnèrent de l'importance à l'hypocapnie et Childs suggéra plus tard que le CO_2 pourrait être bénéfique lors des ascensions en haute altitude [9]. Harvery *et al.* et le *Birmingham Medical Research Expeditionary Society* « redécouvrirent » la conception originale de Mosso selon laquelle l'apport de CO_2 supplémentaire pouvait être bénéfique pour le traitement du mal aigu des montagnes [10]. Un supplément de 3 % en CO_2 améliorait l'oxymétrie digitale (SpO_2) et la gazométrie artérielle (PaO_2) chez les sujets atteints de mal aigu des montagnes à 5 680 m, de même que s'amendaient les céphalées en rapport avec une augmentation du débit cérébral au xénon 133. Par contre, Bartsch trouvait que si 3 % de CO_2 améliorait légèrement la PaO_2, il n'améliorait pas les symptômes du mal des montages aigu, ni ne modifiait le débit cérébral ou doppler transcrânien [7]. L'utilité du CO_2 seul en altitude reste à prouver.

En revanche le rôle bénéfique du mélange CO_2/O_2 semble plus que probable dans le traitement du mal aigu des montagnes. Comme nous l'avons dit, les caissons hyperbares, légers et portables, ont montré leur effet positif dans le mal aigu des montagnes [8]. Jusqu'à présent, on supposait que les effets positifs de la pressurisation étaient dus à l'augmentation de la pression artérielle en oxygène de l'air inspiré (PiO_2). Pourtant un tout récent travail a démontré que pendant le palier de pressurisation de 200 mbar, la $PiCO_2$ s'est élevée de 0,059 (0,18) à 1,33 (0,18) kPa. Quand un épurateur au soda citron fut introduit dans le circuit respiratoire du caisson, il apparut une réduction de l'oxymétrie digitale et de l'oxygénation aux infrarouges. Le CO_2 apparut responsable du tiers de l'effet bénéfique du caisson hyperbare sur l'oxygénation cérébrale [11]. L'utilisation de l'épurateur de CO_2 au soda citron fut, dans le passé, préconisée pour réduire les efforts de pompage. Cet article récent montre que cette pratique n'est pas à conseiller.

Débit cérébral en altitude

La mesure du débit cérébral en altitude à l'oxyde d'azote existe depuis 1948 et demeure la technique de référence [12]. Le débit sanguin cérébral reste stable dans un grand nombre de situations [13] grâce au couplage débit/métabolisme cérébral. Cet effet s'exprime régionalement

par le débit qui s'élève avec le métabolisme tissulaire, comme on le voit par exemple lors de la stimulation du cortex visuel. Ce couplage se manifeste aussi pendant le sommeil par une baisse globale du débit cérébral. La tomographie à émission de positons a montré une constance des débits dans différentes régions du cerveau [14]. Les régions cérébelleuses, frontales et occipitales ont un débit sanguin supérieur à celui de la substance blanche. La consommation d'oxygène, comme le débit sanguin, est supérieure dans la substance grise.

Chez le sujet normotendu, la PaO_2 et la $PaCO_2$ sont les principaux régulateurs du débit cérébral. Chez le rat ventilé en normocapnie, une chute de la PaO_2 de 130 mmHg à 60 mmHg modifie peu le débit cérébral, alors qu'une chute plus prononcée à 25 mmHg le multiplie par cinq [15]. La baisse de $PaCO_2$ réduit le débit cérébral par un puissant effet vasoconstricteur. Sur le modèle animal à $PaCO_2$ constante, une chute de $PaCO_2$ de 40 à 10 mmHg réduit le débit cérébral de 40 %. Des études dynamiques au cours du sommeil et de l'exercice en caissons hypobares devront nous apporter des lumières conséquentes. Ainsi, les voyages en haute altitude seront plus sûrs pour le nombre grandissant de ceux qui s'exposent au risque sérieux de mal aigu des montagnes, d'œdème cérébral et d'œdème pulmonaire de haute altitude.

En attendant, les maladies induites par l'altitude devraient être évitées par un profil ascensionnel lent. Si un sujet est atteint de mal aigu des montagnes, il faut d'abord descendre. Si cela n'est pas possible, oxygénothérapie, acétazolamide, dexamethasone et caisson hyperbare seront mis à profit.

Comme nous l'avons déjà évoqué, les effets de l'altitude sur les sujets normaux est plus complexe que cela. Non seulement l'hypoxie dilate les vaisseaux cérébraux, mais elle augmente la fréquence et l'ampliation respiratoire ce qui a pour effet une réduction de la $PaCO_2$ qui à son tour réduit le débit cérébral selon le niveau d'altitude.

La conviction que l'altitude augmente le débit cérébral est largement répandue. En 1966, Sevringhaus démontra avec la technique à l'oxyde d'azote de Seymour Kety que le débit cérébral augmentait de 24 % dans les 6 à 12 premières heures en altitude et rechutait de 13 % en 3 à 5 j [16]. Ces observations ont été confirmées au doppler transcrânien avec une élévation de 20 % en 18 à 44 h, puis un retour aux valeurs du niveau de la mer en 4 à 12 j. Il n'y aurait pas de différence de débit cérébral au doppler trans-crânien entre le niveau de la mer et 4 300 m au cours d'une épreuve prolongée. Des preuves ultérieures d'augmentation du débit cérébral en altitude ont été montrées dans une étude rapportant une réduction du temps moyen

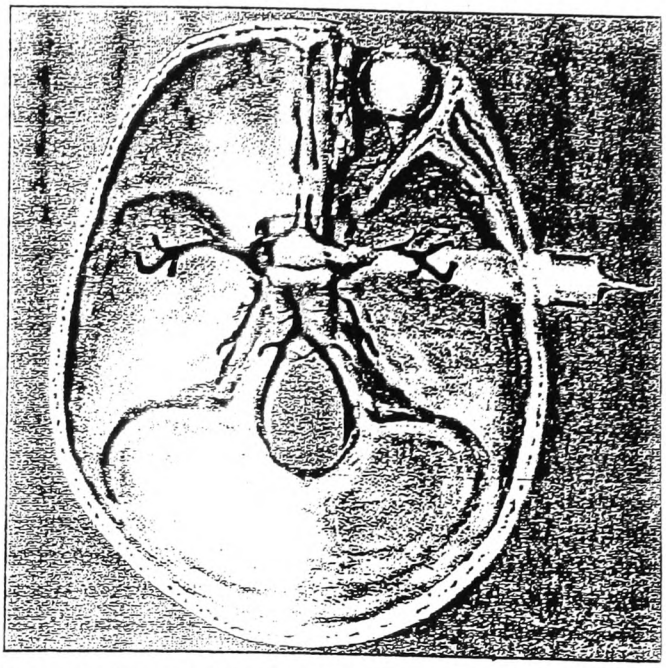


Figure 5. Coupe de la boîte crânienne au doppler transcranien.

de circulation rétinienne de la fluorescéine. L'accord est général sur le fait que le débit cérébral augmente au début du séjour en altitude pour revenir progressivement à des valeurs normales sous l'effet de l'acclimatation *(figure 5)*. Yang *et al.* [17] ont publié un travail qui montre, au moyen de microbilles marquées, que l'air enrichi de 3 % de CO_2 augmente le débit cérébral chez l'animal sans pour autant réduire les symptômes du mal aigu des montagnes.

Bien que le mal aigu des montagnes s'accompagne d'une augmentation du débit cérébral, l'œdème cérébral de haute altitude et le mal aigu des montagnes en général résultent plutôt de l'extravasation capillaire. Des désaccords persistent quant aux modifications du débit cérébral dans le mal aigu des montagnes. Jensen *et al.* ont montré une augmentation du débit cérébral au xénon 133 chez tous les sujets, indépendamment de la survenue de mal aigu des montagnes [18]. Pourtant certains pensent que le mal aigu des montagnes est lié à l'élévation du débit cérébral [19]. L'augmentation du débit cérébral a été imputée à la baisse de la PaO_2 chez les sujets atteints de mal aigu des montagnes. Plus récemment, la même équipe a démontré en caisson de décompression l'absence de lien entre le débit cérébral et le mal aigu des montagnes [20].

On a montré que lors du mal aigu des montagnes, la réponse vasoconstrictive à l'hyperventilation était augmentée. La vélocité de l'artère cérébrale moyenne au doppler transcrânien a été rapportée d'autant plus élevée que la PaO_2 était plus basse [21]. La haute altitude perturbe aussi l'autorégulation cérébrale. L'effet de l'élé-

variation de la pression artérielle moyenne sans perfusion de phényléphrine sur la vélocité de l'artère cérébrale moyenne au DTC a été étudiée à 4 243 m. La non variation de la vélocité devait attester d'une parfaite auto-régulation. Pourtant tous les sherpas et la majorité des habitants des basses terres ont montré une perte d'autorégulation. La perfusion de phenyl-éphrine a provoqué des élévations tensionnelles nettement plus importantes qu'au niveau de la mer [22].

La céphalée d'altitude fut initialement attribuée à l'élévation du débit cérébral mais Reeves *et al.* ont démontré qu'il n'y avait pas de corrélation entre ces deux phénomènes lors de simulations d'altitude de 4 800 m [23]. Les symptômes de mal aigu des montagnes s'apparentent à ceux de l'hypertension intracrânienne par la nausée, la photophobie et l'ataxie. La responsabilité de l'hypertension intracrânienne lors du mal aigu des montagnes semble fortement évidente. La pression intracrânienne était plus élevée au cours du mal aigu des montagnes qu'après sa guérison [24]. Les sujets décédés de mal aigu des montagnes ont un œdème cérébral à l'autopsie. La tomodensitométrie montre des zones diffuses de basse densité correspondant à l'œdème en cas d'œdème cérébral de haute altitude [25]. Cependant l'évaluation de la pression intracrânienne par la mesure du déplacement du tympan, a montré plus de corrélation avec l'altitude qu'avec le mal aigu des montagnes [26].

La rupture de la barrière hémato-encéphalique semblerait déterminante au même titre que lors de l'œdème cérébral. La barrière hémato-encéphalique est sensible aux neurotransmetteurs, à l'oxyde d'azote, à l'histamine, à la substance P, aux radicaux libres, à la 5-hydroxytryptamine, aux cytokines et aux facteurs de croissance endothéliale. L'hypoxie locale déclenche une cascade de réponses cellulaires sous forme d'élévation de lactate, de rupture de la membrane basilaire capillaire et d'extravasation plasmatique. Le facteur de croissance vasculaire endothéliale (VEGF) semblerait le plus important agent de rupture de la membrane basale et de formation de l'œdème. On a montré la régulation du VEGF par hypoxie chez le rat [27] et aussi chez l'homme après l'effort. La régression de la céphalée d'altitude sous dexamethasone apporte la preuve indirecte de l'œdème cérébral et de la perméabilité capillaire dans la céphalée d'altitude, dans la mesure où la dexamethasone supprime la peroxydation lipidique, bloque la production de VEGF et réduit la perméabilité endothéliale.

Jusqu'à aujourd'hui il n'a pas été rapporté la preuve d'une augmentation globale du débit cérébral en altitude. D'autant que le PETscan montrant de fortes variations régionales du débit cérébral au niveau de la mer, il devrait

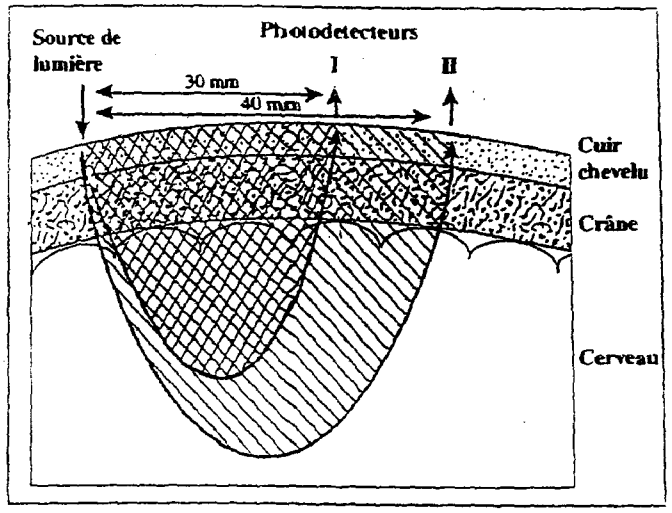


Figure 6. Coupe schématique de la boîte crânienne en spectrographie par réflexion au proche infrarouge.

en être de même en altitude. Le PETscan sur des sujets en caisson hypobare devrait apporter des arguments supplémentaires.

Jusqu'à présent, toute l'attention a été portée sur le débit cérébral, sans doute en raison des possibilités de mesure (NO, DTC, xénon 133). L'ascension augmente le débit cérébral et provoque une hypoxie. On a récemment émis l'hypothèse que l'élévation du débit devait maintenir un taux constant d'oxygène délivré au cerveau [28]. Ce taux est à l'évidence déterminant en toutes altitudes sur l'état cérébral.

L'introduction récente de la spectrographie par réflexion au proche infrarouge permet un monitorage continu et non invasif de l'oxygénation cérébrale. La technique fut pour la première fois décrite chez l'adulte en 1991 [29] et largement diffusée depuis. La spectrographie au proche infrarouge utilise la bande 650-1 000 nm du spectre infrarouge selon les principes de transmission et d'absorption qui permettent de mesurer l'hémoglobine cérébrale, oxygénée et non oxygénée. Elle utilise les mêmes principes que l'oxymétrie pulsée et mixte. La spectrographie au proche infrarouge est désormais utilisée sur le cerveau et nombreux sont ceux qui utilisent la technique à deux sondes car elle permet d'éliminer le crâne et d'explorer l'oxygénation tissulaire cérébrale sur 2,5 à 5 cm de profondeur. Ainsi, cette technique fournit-elle des informations que l'on ne peut obtenir autrement en routine (*figure 6*).

Bien qu'instrument de recherche, la spectrographie au proche infrarouge a pu mesurer précisément les variations de saturations dans la veine jugulaire chez des sujets sains soumis à une hypoxie isocapnique [30]. Elle a aussi été validée en comparaison avec le PETscan, le xénon 133 et

les mesures de pression intracarotidienne [31]. Elle s'est montrée fiable et reproductible dans l'évaluation de la réactivité cérébro-vasculaire, et a démontré que l'hypercapnie ne dilate que les vaisseaux résistifs du cerveau [32].

Les techniques de spectrographie au proche infrarouge se sont montrées récemment robustes et fiables en altitude. L'oxygénation cérébrale régionale (SO_2R) baisse régulièrement de 70,2 (2,4) % à 150 m, à 63,6 (2,3) % à 4 680 m. Parralèllement il existe aussi une chute de 98,1 (0,9) % à 75,1 (5,9) % de l'oxymétrie périphérique pulsée. La pression de CO_2 passe de 5,9 (0,6) kPa à 3,4 (0,3) kPa [33].

La spectrographie proche à infrarouge a été utilisée en altitude pour étudier les effets de l'hyperventilation, l'oxygénothérapie et l'apport de CO_2. L'enrichissement de l'air en CO_2 (3 %), a fortement augmenté l'oxygénation cérébrale, tant au niveau de la mer qu'à 4 680 m, alors que l'oxygène à 6 L/min l'a augmenté seulement à 4 680 m. L'hyperventilation volontaire réduisit l'oxygénation cérébrale au niveau de la mer et à 2 270 m, fut sans effet à 3 650 m mais l'améliora à 4 680 m. Au niveau de la mer, elle réduisit la $PaCO_2$ qui provoqua une vasoconstriction cérébrale entraînant à son tour une baisse du débit cérébral et donc de l'oxygénation cérébrale. À 4 650 m, elle a augmenté la $PaCO_2$ de façon si marquée que l'effet vasoconstricteur cérébral a du être surpassé [34].

Fonction cérébrale en haute altitude

L'oxygénation tissulaire est un facteur critique de l'adaptation à toutes altitudes. Elle dépend du débit, de l'oxygénation artérielle, de la courbe de dissociation de l'oxyhémoglobine et l'hémoglobinurie.

Paul Bert fut le premier à décrire l'altération des fonctions cérébrales chez les sujets en hypobarie aiguë. Il nota des troubles de la vision, de l'audition et de la concentration qui régresseront sous oxygène [1].

L'altitude de 4 000-5 000 m apparaît être le seuil critique de détérioration des fonctions cérébrales. Le rythme de l'ascension, l'entraînement préalable et les susceptibilités individuelles ont aussi leur importance. Au début ce sont les tâches complexes, telles l'étude de nouveautés qui sont perturbées. Ceci fut décrit en premier et en détail par Mac Forland dans les Andes dans les années 30. Les fonctions mentales des plus simples au plus complexes étaient nettement altérées [35].

L'altération de la fonction cérébrale par l'hypoxie est largement admise au niveau de la mer, une baisse de la PaO_2 à 75 % de la normale altère les performances mentales, à 65 % la mémoire récente, à 50 % le jugement et provoque une perte de connaissance à 30-40 % [36].

Au cours de l'expédition Silver Hut au Népal en 1964, Gill *et al.* a rapporté une baisse de l'efficacité mentale à 5 800 m chez les sujets triant des cartes à jouer. L'effet positif de l'acclimatation sur la psychomotricité a été montré chez les soldats de l'armée indienne stationnés en haute altitude. La psychomotricité et la mémoire des chiffres qui étaient perturbées chez les travailleurs de Mauna Kea se sont améliorées avec le temps d'acclimatation [38].

Afin d'améliorer la fonction neurophysiologique à une altitude simulée de 5 000 m, on a apporté un supplément d'oxygène de 6 % avec pour résultat une élévation de la SaO_2 (93,3 % *versus* 81,6 %), un temps de réaction plus bref, une meilleure régulation oculomotrice et un sentiment de bien-être [39].

Le projet de télescope Alma à 5 000 m au Chili prévoit une nouvelle façon de protéger le personnel. Au lieu d'une pleine acclimatation à l'altitude, on délivrera un supplément d'oxygène avec l'air conditionné dans les zones critiques. Des réservoirs d'oxygène semblables à ceux de Scuba seront utilisés à l'extérieur pour les travaux de maintenance. À chaque 1 % d'oxygène supplémentaire correspond une baisse apparente d'altitude de 300 m. On peut ainsi abaisser virtuellement le télescope de 5 000 à 3 200 m grâce à 6 % d'oxygène supplémentaire. Cette altitude virtuelle apparaît comme raisonnable pour des astronomes qui devront quotidiennement rejoindre leur base à San Pedro da Atacama (2 400 m). La sécurité du personnel dépendra de l'efficacité des dispensateurs d'oxygène et de la fiabilité des moyens d'évacuation sanitaire. Les experts se partagent pour dire qu'il s'agit d'un véritable progrès, ou d'une aventure dangereuse.

La notion de désordres nerveux résiduels irréversibles après exposition aux altitudes extrêmes fut controversée. Une baisse statistiquement significative de la mémoire des chiffres (fonction cognitive) et de la frappe digitale (fonction motrice) a été relevée chez des sujets dans les suites immédiates d'une expédition dans l'Everest. Ces anomalies ont régressé pendant les 12 mois suivants mais sans retourner à l'état précédent l'expédition [40]. Des troubles cognitifs persistants ont été décrits chez les grimpeurs qui sont montés à plus de 8 500 m sans supplément d'oxygène. L'IRM a montré une atrophie corticale définitive chez ce type de grimpeurs, prouvant avec force l'effet délétère de l'altitude en absence de supplémentation en oxygène [41].

La littérature expérimentale suggère que l'hypoxie seule est rarement la cause de la mort neuronale. Des chats soumis à une PaO_2 de 17 mmHg pendant 25 min ne présenteraient aucun signe à l'exception d'une baisse tensionnelle. L'hypotension a entraîné des infarcisse-

ments, notamment dans les régions déshydratées. L'hypercapnie semble protéger par le cerveau des dégâts hypoxiques, comme le montre l'importance de la $PaCO_2$ relevée par Gray et Horner chez les survivants à l'hypoxie. Dans l'ischémie focale, la ventilation hypercarbonique a montré un effet de réduction de la taille des zones infarcies [42]. *A contrario*, l'hypocapnie avec alcalose respiratoire pourrait fragiliser le cerveau à l'hypoxie [43].

Le CO_2 induit des effets circulatoires directs et indirects. L'hypocapnie augmente le débit cardiaque et perturbe les shunts pulmonaires avec une nette élévation de la PaO_2 [44]. L'augmentation du débit cardiaque et régional, mésentérique compris, améliore l'oxygénation tissulaire. Chez le coronarien, il est évident que l'hypercapnie dilate les artérioles périphériques abaissant les résistances périphériques, augmentant l'index cardiaque et le débit myocardique.

L'hypcapnie est pathogène aussi au niveau de la mer. Les revues cliniques et expérimentales s'accumulent pour montrer l'effet protecteur du CO_2 sur les lésions tissulaires à concentration élevée et délétère à faible concentration. Une hypothèse récente postule que la chute de la PaO_2 consécutive à l'hyperventilation pourrait participer au syndrome de détresse respiratoire de l'adulte [45]. L'hyperventilation prophylactique des traumatisés du crâne n'est pas étrangère à l'aggravation des signes neurologiques [45]. Expérimentalement, l'ictus ischémique chez l'animal est plus grave en cas d'hypocapnie.

On ne dispose pas de données concernant l'effet du CO_2 sur l'oxygénation tissulaire périphérique en altitude. Au niveau de la mer, les effets indirects de la vasoconstriction sur les tissus périphériques sont corrigés par la baisse des résistances circulatoires secondaires à l'effet vasodilatateur direct du CO_2. L'hypocapnie déplace la courbe de dissociation de l'hémoglobine vers la gauche ce qui réduit le largage d'O_2 vers les tissus, en même temps que la vasoconstriction hypocapnique en réduisant le débit [46]. Le CO_2 produit des effets différents selon les secteurs vasculaires. Il est connu comme un puissant vasodilatateur cérébral au niveau de la mer, mais cet effet est encore très discuté en altitude [7, 10].

Les chemorécepteurs périphériques sont sensibles aux variations de la $PaCO_2$, mais le récepteur principal est centro-médullaire juste au-dessous du 4^e ventricule. La barrière hémato-encéphalique très perméable au CO_2 dissout moins aux H^+ et encore moins au HCO_3^-. Une élévation de la $PaCO_2$ est rapidement suivie d'une élévation de la PCO_2 du LCR, ce qui entraîne une augmentation rapide de H^+. Cela tient aux chemorécepteurs qui stimulent le centre respiratoire, entraînant une augmentation de la ventilation. La stimulation du SNC provoque une réponse adreno-sympathique responsable de tachycardie, d'hypertension et d'hypercontractibilité myocardique. L'acclimatation agit pour partie en réglant la réponse des chemorécepteurs à un niveau plus bas de CO_2. L'acetazolamide inhibe l'anhydrase carbonique et pourrait ainsi en augmentant le CO_2 intra-cellulaire, préserver le débit cérébral pendant la période d'hyperventilation de l'acclimatation.

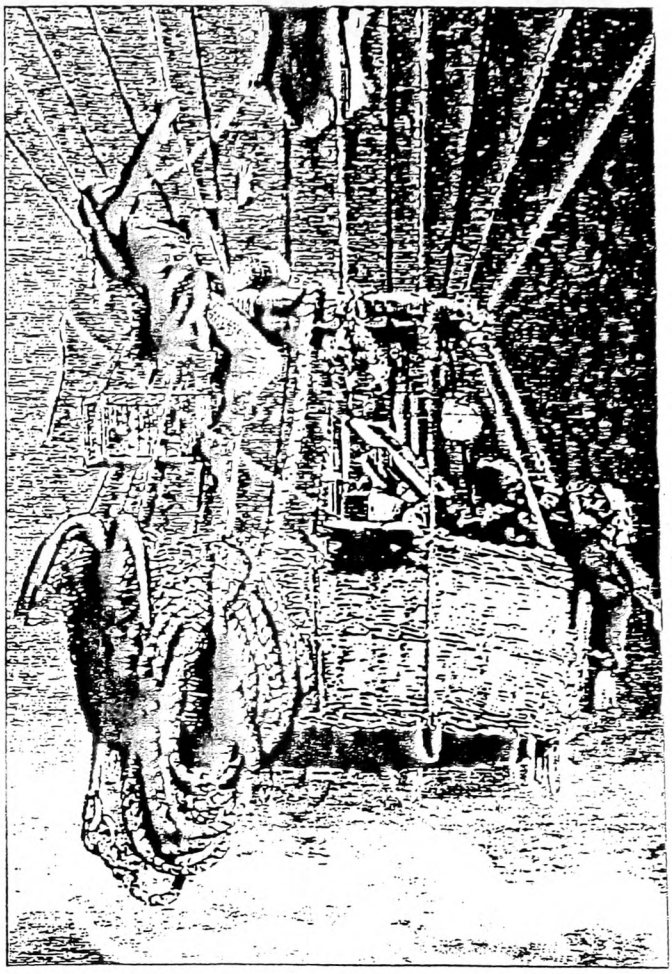


Figure 7. Vol en ballon de Glaisher et Coxwell en 1871.

Événements neurologiques focaux en altitude

La littérature médicale rapporte de nombreux accidents neurologiques, ictus ou AIT en altitude. Un grand nombre semble avoir régressé avec la redescente ou l'oxygène, comme l'a rapporté Tissaudia de son vol en « Zénith » en 1875 [1].

Glaisher, 1871 *(figure 7)*.

« ...Puis je regardais le baromètre qui était à 9 ¾ pouces, descendant de plus en plus vite, correspondant à une

altitude de plus de 29 000 pieds. Peu après je posais mon bras sur la table, plein de toute sa vigueur mais je le trouvais très faible quand j'ai voulu m'en servir, il a dû perdre momentanément sa force...entraperçut M. Coxwell qui voulut parler mais sans succès... aucune gène succéda à ma perte de sensibilité.... Il fallait que je marche encore 7 à 8 miles... »

Shipton, 1933

Pendant l'expédition britannique sur l'Éverest en 1933, Eric Shipton reporta un évident épisode d'aphasie à 7 000 m. Il écrivit plus tard

«... je voulais dire « donnez-moi une tasse de thé » j'aurais dit quelque chose de complètement différent comme « wagon, chat, met... »... j'étais parfaitement lucide... mais ma langue refusait de faire les mouvements qu'il fallait... ».

Jean-Paul Richalet, 1997

Plus récemment, Richalet décrivit en détail le déficit neurologique de trois sujets enfermés dans l'expérimental et très sophistiqué caisson hypobare Opération Éverest III (Comex'97). Un sujet de 23 ans devint dysphasique et incapable d'écrire à l'altitude simulée de 8 000 m. À 8 848 m d'altitude simulée, un deuxième sujet de 25 ans fut aphasique et incapable de bouger la jambe gauche. Et un troisième de 25 ans aussi, présentait des symptômes plus généraux avec sensation bizarre et incapacité de reconnaître ses amis. Tous trois ont vite récupéré sans oxygène. L'examen neurologique et l'IRM qui suivirent, furent normaux. JP Richalet propose plusieurs interprétations depuis la vasoconstriction hypocapnique, le spasme de la migraine accompagnée, la thrombose, l'embolie jusqu'à l'embolie paradoxale par le foramen oval [47].

L'éminent physiologiste d'altitude John West suggéra que « la sensation de paralysie partielle était due aux extrêmes faiblesse et fatigue engendrées par l'hypoxie ». Cependant, si l'on tient compte du grand nombre de cas rapportés, on doit retenir pour vrais les déficits neurologiques transitoires. Les embolies ne correspondent pas à l'âge des sujets et les hémorragies ne pouvaient se résoudre si rapidement. Le *sludge* microvasculaire secondaire à l'hématocrite élevée et amplifié par la déshydratation a été avancé comme hypothèse d'explication, mais il n'est pas compatible avec une régression rapide sans oxygène ou en descente.

Un mécanisme possible de déficit facial transitoire en altitude régressant sous oxygène serait la combinaison hypoxie-hypoperfusion (si l'on définit comme hypoperfusion dans ces situations, un déficit cérébral incapable de maintenir un débit d'oxygène suffisant pour oxygéner les tissus). L'oxygénation artérielle (PaO_2) et le contrôle du débit cérébral ($PaCO_2$) sont également cruciaux. La réserve circulatoire cérébrale (évaluée par DTC et spectrographie au proche infrarouge) et la capacité vasodilatatrice du cerveau étant réduites à 3 459 m, on peut penser que la vasodilatation a atteint son maximum à cette altitude. On peut en déduire raisonnablement que le potentiel de vasodilatation cérébrale est épuisé en haute altitude et ne permet plus d'accroissement supplémentaire du débit cérébral, de sorte que tout besoin supplémentaire ne peut être satisfait et se solde par un AIT d'hypoperfusion, tel décrit par Richalet [47].

Figure 8. Utilisation de la spectrographie par réflexion au proche infrarouge en chirurgie carotidienne.

Notre expérience de clampage carotidien sous anesthésie locale nous porte à cette conclusion. Le clampage chez les patients qui avaient besoin d'un shunt, altère d'abord les plus hautes fonctions tels que le sens de l'humour noir, l'engagement de la conversation et le souvenir des codes postaux, et seulement après les fonctions plus grossières tels la parole, le mouvement et finalement la conscience. Le rétablissement de la circulation par shunt ou déclampage, rétablit rapidement les plus hautes fonctions cérébrales chez ces sujets, la perte des fonctions survient souvent en cascade *(figure 8)*.

On a établi une corrélation négative statistiquement significative entre une réponse ventilatoire hypoxique élevée précédent l'Opération Éverest II Expédition et une fonction neuro-comportementale affaiblie qui en a suivi. Une explication a été suggérée : les sujets dont la réponse ventilatoire hypoxique était la plus élevée étaient ceux qui allaient réduire le plus leur PaO_2, responsable d'une plus intense vasoconstriction cérébrale et donc d'une hypoxie cérébrale plus sévère [48].

L'ictus amnésique transitoire d'altitude a été récemment décrit. Les deux cas décrits ont comporté des troubles amnésiques — les deux sujets ne savaient plus où ils étaient ni pourquoi, et ne se souvenaient plus de la date du

jour- mais aucun déficit neurologique local. Tout rentra dans l'ordre pendant la descente, sans laisser de séquelles [49].

Conclusion

Chez le normotendu, le débit cérébral augmente quand l'oxygène artériel baisse et quand le CO_2 artériel s'élève. Le passage en altitude fait baisser à la fois le CO_2 et l'oxygène. Il existe alors un équilibre entre les effets vasodilatateurs de l'hypoxie et les effets vasoconstricteurs de l'hypocapnie. Mais cet équilibre est complexe et dynamique. Il varie de plus selon chaque individu.
Paul Bert comme Angelo Mosso semblent bien ne pas s'être trompés en croyant que CO_2 et oxygène jouent chacun un rôle déterminant dans l'adaptation des individus en altitude. L'oxygène augmente les capacités de transport sanguin et de diffusion aux tissus. Le CO_2 augmente la fréquence et l'ampliation respiratoire, déplace la courbe de dissociation de l'oxyhémoglobine vers la gauche, améliore les shunts pulmonaires et provoque une importante vasodilatation cérébrale.
La compréhension des mécanismes de la circulation cérébrale est actuellement au point mort et par trop simpliste. Les avancées prochaines viendront grâce aux techniques non invasives tels que les spectrographies au proche infrarouge, PETscan et IRM ■

Références

1. Bert P. *La pression barométrique*. Paris : Masson, 1878.

2. West JB. Highest inhabitants in the world. *Nature* 1986 ; 324 : 517.

3. Ravenhill TH. Some experiences of mountain sickness in the Andes. *J Trop Med Hyg* 1913 ; 16 : 313-20.

4. Maggiorini M, Buhler B, Walter K, Oelz O. Prevalence of acute mountain sickness in the Swiss Alps. *Br Med J* 1990 ; 301 : 853-5.

5. Birmingham Medical research expeditionary society mountain sickness group. Acetazolamide in control of acute mountain sickness. *Lancet* 1981 ; 1 : 180-3.

6. Dumont L, Mardirosoff C, Tramer MR. Efficacy and harm of pharmacological prevention of acute mountain sickness : quantitative systematic review. *Brit Med J* 2000 ; 321 : 267-72.

7. Bartsch P, Baumgartener RW, Waber U, Marggorini M, Oelz O. Comparison of carbondioxide-enriched, oxygen-enriched and normal air in the treatment of acute mountain sickness. *Lancet* 1990 ; 336 : 772-5.

8. Bartsch P, Merki B, Hofstetter D, Maggoiorini M, Kayser B, Oelz O. Treatment of acute mountain sickness by simulated descent : a randomized controlled trial. *Brit Med J* 1993 ; 306 : 1098-101.

9. Childs SB, Hamlin H, Henderson Y. Possible value of inhalation of carbon dioxide in climbing great altitudes. *Nature* 1935 : 135 : 457-8.

10. Harvey TC, Winterborn MH, Lassen NA, *et al.* and the Birmingham medical research and expeditionary society. Effect of carbon dioxide in acute mountain sickness : a rediscovery. *Lancet* 1988 ; II : 639-41.

11. Imray CHE, Clarke T, Forster PJG, *et al.* Carbon dioxide contributes to the beneficial effect of pressurization in a portable hyperbaric chamber at high altitude. *Clin Sci* 2001 ; 100 : 151-7.

12. Kety SS, Schmidt CF. The nitrous oxide method for the quantitative determination of cerebral blood flow in man : theory, procedure and normal values. *J Clin Invest* 1948 ; 27 : 476-83.

13. Lassen NA. Control of cerebral circulation in health and disease. *Circ Res* 1974 ; 34 : 749-60.

14. Tyrrell P. Tomographic measurement of cerebral blood flow and metabolism with positron emitting isotopes in man. *In :* Harper AM, Jennett SC, eds. *Cerebral Blood Flow and Metabolism*. Manchester : Manchester University Press, 1990, pp 90-107.

15. Borgstrom L, Johannsson H, Siesko BK. The relationship between arterial PO_2 and cerebral blood flow in hypoxic hypoxia. *Acta Physiol Scand* 1975 ; 93 : 423-32.

16. Sevringhaus JW, Chiodi H, Eger EI, Brandstater B, Hornbein TF. Cerebral blood flow in man at high altitude. Role of cerebrospinal fluid pH in normalization of flow in chronic hypocapnia. *Circ Res* 1966 ; 19 : 274-82.

17. Yang SP, Bergo GW, Krasney E, Krasney JA. Cerebral pressure-flow and metabolic responses to sustained hypoxia : effect of CO_2. *J Appl Physiol* 1994 ; 76 : 303-13.

18. Jensen JB, Wright AD, Lassen NA, *et al.* Cerebral blood flow in acute mountain sickness. *J Appl Physiol* 1990 ; 69 : 430-3.

19. Baumgartner RW, Bartsch P, Maggiorini M, Waber U, Oelz O. Enhanced cerebral blood flow in acute mountain sickness. *Aviat Space Environ Med* 1994 ; 65 : 726-9.

20. Baumgartner RW, Spyridopoulos S, Bartsch P, Maggiorini M, Oelz O. Enhanced cerebral blood flow in acute mountain sickness. *J Appl Physiol* 1999 ; 86 : 1578-82.

21. Jansen GFA, Krins A, Basnyat B. Cerebral vasomotor reactivity at high altitude in humans. *J Appl Physiol* 1999 ; 86 : 681-6.

22. Jansen GFA, Krins A, Basnyat B, Bosch A, Odoom JA. Cerebral autoregulation in subjects adapted and not adapted to high altitude. *Storke* 1999 ; 31 : 2314-8.

23. Reeves JT, Moore LG, McCullough RE, *et al.* Headache at high altitude is not related to the internal carotid arterial blood velocity. *J Appl Physiol* 1985 ; 59 : 905-15.

24. Singh I, Khanna PK, Srivastra MC, Lal M, Roy SB, Subramanyam CSV. Acute Mountain Sickness. *N Eng J Med* 1969 ; 280 : 175-84.

25. Fukushima M, Yasaki K, Shibamoto T, *et al.* Findings of brain computed tomography in patients with high altitude pulmonary edema. *In :* Sutton JR, Houston CS, Jones NL, eds. *Hypoxia, exercise and altitude*. New York : Liss, 1983, pp 456-7.

26. Wright AD, Imray CHE, Morrisey MSC, Marchbanks RJ, Bradwell AR. Intracranial pressure at high altitude and acute mountain sickness. *Clin Sci* 1995 ; 89 : 201-4.

27. Xu F, Sevringhaus JW. Rat brain VEGF expression in alveolar hypoxia ; possible role in high-altitude cerebral edema. *J Appl Physiol* 1998 ; 85 : 53-7.

28. Wolff CB. Cerebral blood flow and oxygen delivery at high altitude. *High Altit Med Biol* 2000 ; 1 : 33-8.

29. McCormick PW, Stewart M, Goetting MG, Balakrishnan G. Regional cerebrovascular oxygen saturation measured by optical spectroscopy in humans. *Storke* 1991 ; 22 : 596-602.

30. Henson LC, Calalang C, Temp JA, Ward DS. Accuracy of cerebral oximeter in healthy volunteers under conditions of isocapnic hypoxia. *Anesthesiology* 1998 ; 8858-65.

31. Williams IM, Vohra R, Farrel A, Picton AJ, Mortimer AJ, McCollum CN. Cerebral oxygen saturation, transcranial Doppler ultrasonography and stump pressure in carotid surgery. *Br J Surg* 1994 ; 81 : 960-4.

32. Totaro R, Barattelli G, Quaresima V, Carolei A, Ferrari M. Evaluation of potential factors affecting the measurement of cerebrovascular reactivity by near-infrared spectroscopy. *Clin Sci* 1998 ; 95 : 497-504.

33. Imray CHE, Barnett NJ, Walsh S, *et al.* Near-infrared spectroscopy in the assessment of cerebral oxygen at high altitude. *Wild Environ Med* 1998 ; 9 : 198-203.

34. Imray CHE, Brearey S, Clarke T, *et al.* Cerebral oxygenation at high altitude and the response to carbon dioxide, hyperventilation and oxygen. *Clin Sci* 2000 ; 98 : 159-64.

35. MacFarland RA. Psycho-physiological studies at high altitude in the Andes I. The effect of rapid ascents by aeroplane and train. *Comp Phychol* 1937 ; 23 : 191-225.

36. Blass JP, Gibson GE. The consequences of mild grade hypoxia. *Adv Neurol* 1979 ; 2 : 229.

37. Gill MB, Poulton EC, Carpenter A, *et al.* Falling efficiency in sorting cards during acclimatization at 19 000 ft. *Nature* 1964 ; 203 : 436.

38. Forster PJG. Telescopes in high places. *In :* Heath D, ed. *Aspects of Hypoxia.* Liverpool : Liverpool University Press, 1986, pp 217-33.

39. Gerard AB, McElroy MK, Taylor MJ, *et al.* Six percent oxygen enrichment of room air at simulated 5 000 m altitude improves neuropsychological function. *High Altit Med Biol* 2000 ; 1 : 51-61.

40. West JB. Do climbs to extreme altitude cause brain damage. *Lancet* 1986 ; ii : 387-8.

41. Garrido E, Castello A, Ventura AL, *et al.* Conical atrophy and other brain magnetic resonance imaging (MRI) changes after extremely high altitude climbs without oxygen. *Int J Sports Med* 1993 ; 14 : 232-4.

42. Simon RP, Niiro M, Gwinn R. Brain acidosis induced by hypercarbic ventilation attenuating focal ischemic injury. *J Pharm Exp Ther* 1993 ; 267 : 1428-31.

43. Tombaugh GC, Sapolsky RM. Short review. Evolving concepts about the role of acidosis in ischemic neuropathology. *J Neurochem* 1993 ; 61 : 793-803.

44. Hickling KG, Joyce C. Permissive hypercapnia in ARDS and its effects on tissue oxygenation. *Acta Anaesthesiol Scand* 1995 ; 107 : 201-8.

45. Laffey JG, Kavanagh BP. Carbon dioxide and the critically ill - too little of a good thing ? *Lancet* 1999 ; 354 : 183-6.

46. Muizelaar JP, Marmarou A, Ward JD, *et al.* Adverse effects of prolonged hyperventilation in patients with severe head injury : a randomized trial. *J Neurosurg* 1991 ; 75 : 731-9.

47. Richalet JP. Operation Everest III (Comex'97) *In :* Roach RC, Wagner PD, Hackett PH ed. *Hypoxia : Into the next millenenium.* New York : Kluwer Academic/Plenum, 1999 ; 297-317, 372-3.

48. Hornbein TF, Townes BD, Schoene RB, *et al.* The cost to the central nervous system of climbing to extremely high altitude. *N Eng J Med* 1989 ; 321 : 1714-9.

49. Litch JA, Bishop RA. Transient global amnesia at high altitude. *N Eng J Med* 1999 ; 340 : 1444.

Chapter 4

PARTITIONING OF ARTERIAL AND VENOUS VOLUMES IN THE BRAIN UNDER HYPOXIC CONDITIONS

Christopher B Wolff and Christopher H E Imray *

1. INTRODUCTION

Cerebral oxygen delivery is sustained in the face of, at least moderate, hypoxia.[1] The measurements required to show this have, in the past, been especially invasive, with a requirement for jugular venous bulb sampling and carotid arterial administration of a marker to allow measurement of flow by dye dilution[2]. With the advent of middle cerebral arterial blood velocity measurement (Doppler) and arterial oxygen saturation measurement (pulse oximetry) the procedure is greatly simplified, at least on a relative basis: SaO_2 multiplied by middle cerebral artery velocity will, arguably, give individual changes in oxygen delivery for, at least, the distribution supplied by the middle cerebral artery. This will, for normal subjects, usually change in proportion to global changes.

Cerebral near infrared spectroscopy (NIRS) provides a measure of the proportion of blood which is oxygenated in a given, mainly, cortical region. It does not, however, distinguish how much is in the arterial or the venous part of that vascular bed. The proportions of blood in the arterial and venous compartments in the brain have been estimated at 28% of the total for the arterial and 72% for the venous value.[3] This gives a relationship between the arterial and venous blood volumes ($p = Va/Vv$) of 28/72 or 0.39 (so $p = 0.39$). There will be a range of values above and below this for individual local tissues.

The present article examines how well oxygen delivery is sustained with increasing altitude (and/or reduced oxygen saturation) from earlier measurements of middle cerebral artery velocity (MCAV), and explores how well a model of arterial/venous distribution fits with SaO_2 and NIRS data (rSO_2) from the same experimental series.[4-6]

* Christopher B Wolff Applied Physiology, Sherrington School, Block 9, St Thomas's Hospital, Lambeth Palace Road, LONDON, SE1 7EH, UK. Email: chriswolff@doctors.org.uk (44) 0207 9289292 x2151
Christopher H E Imray The Immunodiagnostic Research Laboratory, The Medical School, University of Birmingham, Edgbaston, Birmingham, V15 2TT.

Oxygen Transport to Tissue XXV, edited by
Thorniley, Harrison, and James, Kluwer Academic/Plenum Publishers, 2003.

3. METHODS AND MODEL

3.1. Measurements

Methods of measurement for rSO_2, SaO_2 and MCAV are outlined in the studies quoted.[4-6] SaO_2 was measured using a Propac Encore Monitor (Beaverton, USA), rSO_2, a Critikon 2020 monitor (Johnson and Johnson, Newport, UK) and middle cerebral artery velocity (MCAV), a Logidop 3 TCD monitor (SciMed, Bristol, UK). Oxygen delivery is calculated here as a percentage of the putative sea level value:

$$100 \times (MCAVtest \times SaO_2test) / (MCAVsea \times SaO_2sea).$$

3.2. Model

In this section we derive an expression (the model) for fractional oxygen concentration in the blood volume described by infrared transmission (rSO_2) in terms of SaO_2, the relative volumes of arterial and venous blood ($p = Va/Vv$) and the proportional extraction (E) of oxygen from its perfusate. rSO_2 represents the volume of oxygenated blood divided by the total blood volume (i.e. HbO_2 / (Hb + HbO_2). Hence, $rSO_2 = (SaO_2.Va + SvO_2.Vv) / (Va + Vv)$. From this we can obtain rSO_2 in terms of p: $rSO_2 = (SaO_2.p + SvO_2) / (p + 1)$. $E = VO_2 / DO_2 = (SaO_2 - SvO_2) / SaO_2$ so we can substitute $SaO_2(1 - E)$ for SvO_2. This gives the equation:

$$rSO_2 = (SaO_2.p + SaO_2(1 - E)) / (p + 1) \qquad \text{Equation 1 (the model)}$$

(An alternative is: $rSO_2 = SaO_2(1 - E(1 - f))$, where $f = Va / (Va + Vv)$)

3.3. Fitting the Model with Measured Data

An example of a set of values for rSO_2 obtained from this model for a sea level SaO_2 of 97%, appears in the results section (Table 1). Values are calculated for each measured SaO_2 (at sea level on air, at altitudes 2400m, 3549m and 5050m and at sea level with subjects breathing 12.5% oxygen). Each set is presented graphically (Figures 2 and 3 in Results) as a plot of rSO_2 against p, with isobars for E. The value of each measured rSO_2 is drawn as a horizontal line across the theoretical plot.

RESULTS

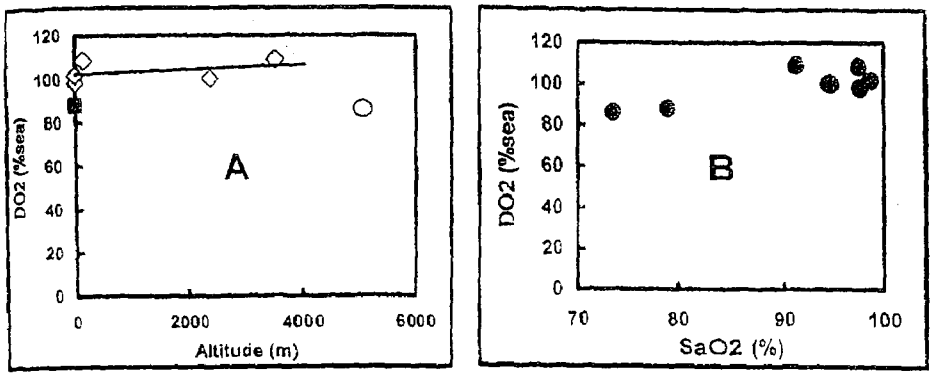
4.1. Oxygen delivery

Oxygen delivery is shown in Figure 1. It is constant over the range from sea level to 3549m (A) and is lower at 5050m and at sea level in subjects breathing 12.5% oxygen. The lower DO_2 is related also to SaO_2 in Figure 1 B.

4.2. The Model and Measured SaO_2 and rSO_2 Values

Table 1 shows rSO_2 values for SaO_2 97% (sea level) (calculated from the model).

igure 2 shows the values from Table 1 in graphical form. Isobars for E appear as a grid n a plot of rSO_2 against p. The measured rSO_2 value is also plotted as a horizontal bar nd crosses E = 0.4 and 0.5 E isobars around p values of 0.4 to 0.8.



igure 1. Oxygen delivery as a percentage of the sea level value (mean of two values). A regression line has en fitted to values at all altitudes (◇) other than 5050m (○) in A and its slope is not significant (equation: DO_2%sea = 102 - 0.011altitude). The 5050m point and the one recorded at sea level on 12.5% O_2 (■) show reduced delivery. In B DO_2 values are plotted against SaO_2.

Table 1. Values of rSO_2 calculated from equation 1 for a range of p and E values at sea level (SaO_2 97%). Mean measured rSO_2 is given in the last column. Values in bold are nearest to measured values.

p	E = 0.2	E = 0.25	E=0.32	E=0.4	E=0.5	rSO2 (sea)
2	0.905	0.889	0.867	0.841	0.808	0.696
1.5	0.892	0.873	0.846	0.815	0.776	0.696
1	0.873	0.849	0.815	0.776	0.728	0.696
0.8	0.862	0.835	0.798	0.754	**0.701**	0.696
0.7	0.856	0.827	0.787	0.742	**0.685**	0.696
0.6	0.849	0.818	0.776	0.728	0.667	0.696
0.5	0.841	0.808	0.763	0.711	0.647	0.696
0.4	0.831	0.797	0.748	0.693	0.624	0.696
0.3	0.821	0.783	0.731	0.672	0.597	0.696

In Figure 3 theoretical rSO_2 is again plotted against p with the same set of E isobars as in Figure 2. For A (2400m) and B (3549m) the horizontal line indicating measured rSO_2 crosses the same E isobars at the same relation to p as in Figure 1 (for sea level on air). In C (sea level breathing 12.5% O_2) and D (5050m) the line for the measured rSO_2 has moved to cross further up the grid of E isobars where E is lower.

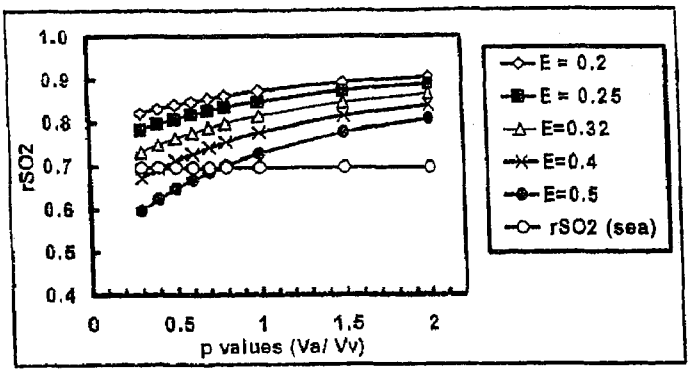


Figure 2. Calculated rSO_2 is shown against p (Va/Vv) for a series of values for oxygen extraction (E). The measured sea level value is also entered (○) as a horizontal line.

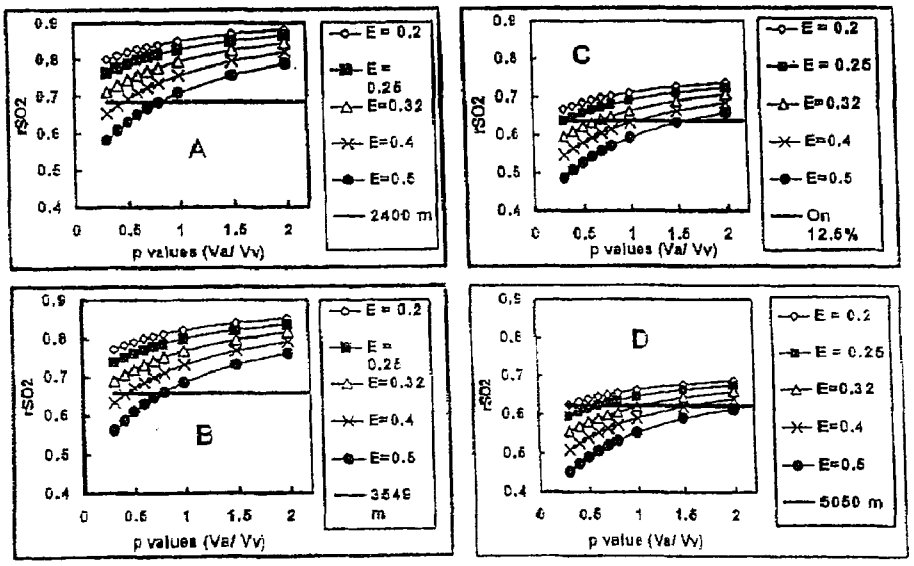


Figure 3. Theoretical rSO_2 values for given E isobars; A. At 2400 m: SaO_2 = 0.946 (rSO_2 was 68.5%); B. Control at 3549 m: SaO2 91.3% (rSO2 was 65.7%); C. Hypoxic, 12.5 % O_2 at sea level: Sa = 79%; (rSO_2 was 63.7%). D. At 5050 m: SaO_2 = 73.6% (rSO_2 was 62.1%). Horizontal bar: measured rSO_2.

4. DISCUSSION

The measured results (SaO_2, and MCAV) here show a constant DO_2 at lower altitudes (up to 3549m). However, DO_2 is reduced under more hypoxic conditions found at 5050m and on 12.5% oxygen at sea level. Hence, there is a 'break point' between 3549m and 5050m (or between 79% and 91% arterial oxygen saturation).

The same 'break point' is seen when measured rSO_2 values are fitted to the model, in it there is a change from a fixed relation between the oxygen extraction (E) and the io of Va to Vv (symbol p).

The two major changes in cerebral vascular function (the E/p relationship and rebral DO_2) occurring at the same break point lends support to the simple model.

It is now possible to obtain SvO_2 for tissue being examined with near infrared ectroscopy.[7] This means that with future investigations it will be possible to calculate p om SaO_2 and SvO_2, and also to calculate E, according to equation 1 (the model). It will e interesting to see whether the derived values for p (Va/Vv) then agree with values om the literature (around 0.4) over the more normal physiological range below the reak point.[3,8-9] It will also be possible, if the model is then validated, to see whether the on-physiological phenomena beyond the break point mainly involve reduced oxygen xtraction (E) or whether, and to what extent, the cerebral arterial to venous volume ratio Va/Vv) changes.

It might be thought that changes in cerebral blood volumes alter a reserve of oxygen, ut can only be transient. A sustained alteration in DO_2 (a rate) requires a change in lood flow or oxygen content of the blood.

Use of p here (Va/Vv) is one way to depict the arterial volume relationships but one an also use Va/(Va + Vv), termed f above (see 3.2. Model). Hence, the model has also [redacted] given as an equation in f for those who prefer this format.

It is thought that, despite the simplicity of the model, formal demonstration of the relationships can be useful in the interpretation of cerebral NIRS data and in comparison of normal and abnormal function.

5. REFERENCES

1. C.B. Wolff, P. Barry and D.J. Collier Cardiovascular and respiratory adjustments at altitude sustain cerebral oxygen delivery – Severinghaus revisited. *Comparative Biochemistry and Physiology Part A* 132, 221-229(2002).
2. Severinghaus, J.W., Chiodi, H., Eger, E.I., Brandstater, B. and Hornbein, T.F. Cerebral blood flow in man at high altitude. *Circulation Research* 19, 274-282. (1966.)
3. P.W. McCormick, M. Stewart, M.G. Goetting and G. Balakrishnan, Regional cerebrovascular oxygen saturation measured by optical spectroscopy in humans. *Stroke* 22, 596-602 (1991)
4. C.H.E. Imray, A.W. Wright, C. Chan, A.R. Bradwell and the Birmingham Medical Research and Expeditionary Society (BMRES). Carbon dioxide increases cerebral oxygen delivery when breathing hypoxic gas mixtures. *High Altitude Medicine & Biology* 3 (1), p106 A30, 2002 (abstract).
5. C.H.E. Imray, S. Walsh, T. Clarke, H. Hoar, T.C. Harvey, C.W.M. Chan, P.J.G. Forster and the BMRES. 3% Carbon dioxide increases cerebral oxygen delivery at 150m & 3549m. *High Altitude Medicine & Biology* 3 (1), p106 A31, 2002 (abstract).
6. C.H.E. Imray, H. Hoar, A.D. Wright, A.R. Bradwell C. Chan, and the BMRES. Cerebral oxygen delivery falls with voluntary forced hyperventilation at altitude. *High Altitude Medicine & Biology* 3 (1), p106 A32, 2002 (abstract).
7. [redacted]well, C.E., Cope, M., Edwards, A.D., Wyatt, J.S., Delpy, D.T., Reynolds, E.O.R. Quantification of adult cerebral haemodynamics by near infrared spectroscopy. *J. Appl. Physiol.* 77, 2753-2760(1994).
8. T.Q. Duong and S-G. Kim, In vivo MR measurements of regional arterial and venous blood volume fractions in intact rat brain. *Magnetic Resonance in Medicine* 43, 393-402 (2000).
9. H.Ito, I.Kanno, H, Iida, J. Hatazwa, E. Shimosegawa, H. Tamura and T. Okudera, Arterial fraction of cerebral blood volume in humans measured by positron emission tomography. *Annals of Nuclear Medicine* 15 (2), 111-116 (2001).

Wilderness and Environmental Medicine, **15**, 25–31 (2004)

ORIGINAL RESEARCH

Medroxyprogesterone at High Altitude. The Effects on Blood Gases, Cerebral Regional Oxygenation, and Acute Mountain Sickness

Alex D. Wright, MB; Margaret F. Beazley, MB; Arthur R. Bradwell, MB; Ian M. Chesner, MB; Richard N. Clayton, MD; Peter J. G. Forster, MB; Peter Hillenbrand, MB; Christopher H. E. Imray, MB; for the Birmingham Medical Research Expeditionary Society

From the Department of Medicine, The Medical School, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK.

Objective.—To study the effect of medroxyprogesterone on blood gases and cerebral regional oxygenation at high altitude, alone and in conjunction with acetazolamide, and to assess the effect on acute mountain sickness (AMS).

Design.—Two placebo-controlled trials during rapid ascent to high altitude.

Participants.—In the first trial, 20 participants, and in the second trial, 24 participants.

Setting.—During rapid ascent to 4680 m and on rapid ascent to 5200 m.

Intervention.—In the first trial, participants were randomized to receive medroxyprogesterone 30 mg or a placebo twice a day. In the second trial, participants were randomly assigned to one of 4 groups: a placebo twice daily, medroxyprogesterone 30 mg twice daily, acetazolamide 250 mg plus a placebo twice daily, or acetazolamide 250 mg plus medroxyprogesterone 30 mg twice daily.

Main Outcome Measures.—Blood gas changes and symptom scores of AMS in both trials and cerebral regional oxygen saturations in the first trial only.

Results.—Medroxyprogesterone improved peripheral oxygen saturations in both trials and improved Pa_{O_2} in combination with acetazolamide. Cerebral regional oxygen saturation was not altered by medroxyprogesterone. The reduction in symptom scores and in the extent of AMS was not significant in this limited study.

Conclusions.—Medroxyprogesterone acts as a respiratory stimulant, but the clinical benefit regarding the development of AMS was unproven at high altitude. Combined medroxyprogesterone and acetazolamide gave the best Pa_{O_2}.

Key words: acute mountain sickness, progesterone, high altitude, oxygenation, acetazolamide

Introduction

Individuals vary in their rate of acclimatization and in their susceptibility to acute mountain sickness (AMS); hence, it is difficult to set a safe rate of ascent for a group so that no one is affected by AMS.[1] Ascent profiles are also determined by transport arrangements and time constraints. As a result, prophylactic measures to prevent AMS are often required. This has led to the use of drugs such as acetazolamide, which is of proven value in the prevention of AMS[2] and has also been used in the acute treatment of AMS.[3] However, acetazolamide does not fully protect against AMS, and side effects such as paresthesias sometimes limit its application. Other drugs that have been used in the treatment of established AMS, such as nifedipine for high-altitude pulmonary edema[4] and dexamethasone for high-altitude cerebral edema,[5] have also been tried in the prevention of AMS. Nifedipine is ineffective,[6,7] and although dexamethasone is protective,[8] the potential side effects when using the recommended dose of 12 mg daily are of concern when it is used for prevention.

Acetazolamide increases ventilation at altitude, thereby increasing arterial and tissue oxygen concentrations.[2]

Presented at the 11th International Hypoxia Symposium, Jasper, Alberta, 1999.

Corresponding author: Arthur R. Bradwell, MB, IDRL, The Binding Site Ltd, PO Box 4073, Birmingham B29 6AT, UK (e-mail: a.r.bradwell@bham.ac.uk).

Reprints not available from the author.

This may be particularly important in persons who have poor hypoxic ventilatory responses.[9] It is possible that other respiratory stimulants would be effective, but so far, only almitrine has been reported as improving arterial oxygen saturation but also worsening periodic breathing in short-term studies at high altitude.[10] Progesterone is known to increase hypoxic ventilatory responses with an improvement in oxygen saturation and a reduction in hematocrit for persons residing at 3100 m[11] and to benefit patients with hypoventilation syndromes and sleep apnea.[12] In animals, progesterone reduces brain edema,[13] possibly by tightening the blood-brain barrier through the inhibition of Na+/K+-adenosine triphosphatase (ATPase). Progesterone has few side effects when taken in short courses. These features suggest it has potential in the prevention of AMS and would be useful in combination with acetazolamide.

The purpose of these studies was to assess the effect of medroxyprogesterone alone and in combination with acetazolamide on blood gases at altitude. We wished to assess the effect of medroxyprogesterone on cerebral regional oxygenation and in the prevention of AMS.

Methods

PILOT STUDY

An initial open pilot study was performed in Birmingham (150 m), to determine the side effects and changes in acid-base parameters of medroxyprogesterone alone, acetazolamide alone, and both drugs in combination. Five participants were given acetazolamide 500 mg daily for 7 days, followed by a 1-week washout, and then medroxyprogesterone 60 mg daily for 7 days, followed by a 1-week washout, and finally, acetazolamide 500 mg with medroxyprogesterone 60 mg daily for 7 days. Drug effects were recorded, and acid-base measurements were made on arterialized, capillary blood samples at the beginning of the study and at the end of each treatment period.

HIGH-ALTITUDE STUDY 1

Twenty healthy persons, 17 men and 3 women aged 24 to 59 years, were randomly allocated to groups on a double-blind basis that were administered an encapsulated placebo (ascorbic acid) or medroxyprogesterone 30 mg twice daily. Information on side effects was obtained prospectively each day using a structured interview. After an overnight stay at sea level (La Serena, Chile), rapid ascent in a minibus was achieved after 3 days to 2770, 3650, and 4680 m (Paso del Agua Negra).

HIGH-ALTITUDE STUDY 2

Twenty-four healthy persons, 22 men and 2 women aged 22 to 65 years, were randomly allocated to groups that were administered one of 4 treatments, with 6 persons in each group:

1. Placebo (ascorbic acid, 3 tablets of 50 mg twice daily),
2. Medroxyprogesterone (3 tablets of 10 mg twice daily),
3. Acetazolamide (250 mg twice daily) plus a placebo (3 tablets twice daily), or
4. Acetazolamide (250 mg twice daily) plus medroxyprogesterone (3 tablets of 10 mg twice daily).

The medroxyprogesterone part of the trial was double blinded and placebo controlled, while acetazolamide was an open trial. Information about drug side effects was obtained prospectively by use of a self-administered, symptoms questionnaire completed twice daily and, retrospectively, by a structured interview held on the last day of the trial. All participants flew to 1300 m (Kathmandu) and, 2 nights later, to 2800 m (Lukla). Subsequent ascent was by trekking, with overnight stops at 3440 m (Namche Bazaar), 4120 m (2 nights at Pheriche), and then 5200 m (Gorek Shep).

In both altitude studies, stratification of approximately two thirds of the participants according to previous susceptibility to AMS was performed before random allocation to treatment groups. Randomization was performed independently by the hospital pharmacy. Female participants were started on their allocated medication, medroxyprogesterone or a placebo, from the first day of their menstrual cycle prior to the drug trials and were randomly allocated to groups so that at least 1 participant was in the active medroxyprogesterone group. Compliance with assigned therapy was assessed by counting unused tablets.

Symptoms of AMS were recorded using the Lake Louise self-reporting AMS questionnaire twice daily.[14] A score of 3 or more at any one time indicated significant AMS. In study 1, the scores from 7 participants who completed questionnaires, starting from their arrival at 2770 m until the second evening at 4680 m, were used to calculate a total AMS score. In study 2, the scores from 10 participants who completed questionnaires, starting from their arrival at 3440 m until the second morning at 5200 m, were used to calculate a similar total score. In both studies, participants were interviewed each day by 2 physicians experienced in high-altitude medicine. As necessary, participants were withdrawn from the drug trial and given acetazolamide according to clinical indications. One participant in study

Table 1. Acid-base data for the pilot study (mean and SD)

Pilot study	*pH*	*$PaCO_2$, kPa*	*HCO_3, mmol/L*
Baseline (no drugs)	7.4116 (0.22)	5.32 (0.24)	24.9 (1.05)
Medroxyprogesterone	7.4314 (0.028)	4.5 (0.27)†	23.9 (1.6)
Acetazolamide	7.3596 (0.037)*	4.51 (0.15)†	20.6 (2.2)*
Medroxyprogesterone plus acetazolamide	7.3747 (0.036)*	3.89 (0.18)†‡	20.2 (1.7)*

†$P < .001$ compared with baseline.
*$P < .05$.
‡$P < .001$ compared with acetaxolamide alone.

1 required additional dexamethasone on the second day at 4680 m. Results from these participants have been included in the original randomized groups on an intention-to-treat basis.

BLOOD GASES

In study 1, blood gases were measured on arterialized capillary samples using a Medical Analyzer (model 348; Chiron Diagnostics, Emeryville, CA) at 2770 and 4680 m, and oxygen saturation in blood and heart rate were measured at 1-minute intervals at all altitudes using a digital pulse oximeter (Ohmeda 3770; BOC Group, Hatfield, UK). In study 2, blood gases were measured on arterialized capillary samples using a Corning Blood Gas Analyzer (model 238; Ciba Corning, Medford, MA) at 3440, 4120, and 5200 m.

CEREBRAL REGIONAL OXYGENATION

In study 1, cerebral regional oxygen saturations were measured using near-infrared spectroscopy (Critikon 2020; Johnson & Johnson Medical Ltd, Ascot, UK).[15] Cerebral regional oxygenation was calculated using $[Hbo_2 \div \text{total Hb}] \cdot 100$.

STATISTICS

Significant differences in oxygen saturations and blood gas data were determined by repeated-measures analysis of variance. Significant differences among the 4 treatment groups in study 2 were determined by 2-way analysis of variance using repeated measures.[16] Other differences were determined by the Student's *t* test. *P*-values <.05 were considered significant.

Ethical approval was given by the Research Ethics Committee of the South Birmingham Health Authority, and permission to use medroxyprogesterone was given by the Department of Health Medicines Control agency. Participants gave informed consent.

Results

PILOT STUDY

All participants noted mild hyperventilation on medroxyprogesterone, particularly when combined with acetazolamide, but there were no other side effects. $Paco_2$ was reduced to a similar extent by both acetazolamide and medroxyprogesterone, and a combination of the 2 drugs gave an additive effect (Table 1). pH was not significantly changed on medroxyprogesterone, but it decreased on acetazolamide and remained reduced when the 2 drugs were combined.

HIGH-ALTITUDE STUDY 1

All participants had some symptoms of AMS, and 7 of the 10 participants on medroxyprogesterone compared with 9 of the 10 participants on the placebo achieved a score of 3 or more on at least one questionnaire at high altitude. Total AMS scores for the 4 days at altitude were not significantly different for participants on medroxyprogesterone (mean, 16.0; SD, 9.2) compared with those on the placebo (mean, 20.7; SD, 8.8). Mean peripheral oxygen saturations were higher throughout the study for participants on medroxyprogesterone ($P = .049$), but cerebral regional oxygen saturations were not different (Figure 1). Pao_2 levels were not measured because of equipment failure. End tidal CO_2 was significantly reduced throughout the study for participants on medroxyprogesterone ($P < .001$) (Figure 2).

$Paco_2$ was significantly reduced at 2770 m for participants on medroxyprogesterone (mean, 3.96 kPa; SD, 0.3) when compared to the placebo group (mean, 4.31 kPa; SD, 0.27; $P < .05$) but was not significantly different at 4680 m (mean, 3.58; SD, 0.37, compared with mean, 3.75; SD, 0.18, respectively). At both altitudes, arterial pH values were not different between the 2 groups (mean, 7.468; SD, 0.035, compared with mean, 7.483; SD, 0.035, respectively).

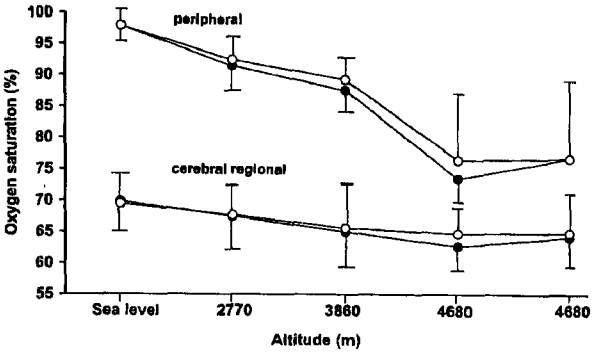


Figure 1. Peripheral oxygen saturation (top 2 lines) and cerebral regional oxygenation (bottom 2 lines) before and during ascent to high altitude. Measurements were made at daily intervals after an overnight stay at that altitude. A second measurement was made after an additional 24 hours at 4680 m. Means (SD) of 10 participants on the placebo (•) and 10 participants on medroxyprogesterone (o). Peripheral oxygen was greater for participants on medroxyprogesterone (P = .049). Cerebral regional oxygenation was not significantly different for participants on medroxyprogesterone.

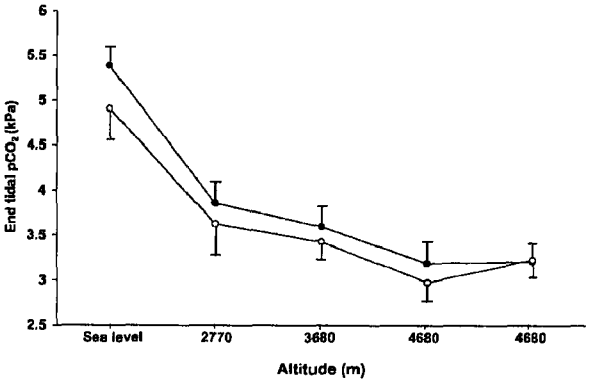


Figure 2. End tidal P_{CO_2} before and during ascent to high altitude. Measurements were made at daily intervals after an overnight stay at that altitude. A second measurement was made after an additional 24 hours at 4680 m. Means (SD) of 10 participants on the placebo (•) and 10 participants on medroxyprogesterone (o) were significantly different (P < .001).

HIGH-ALTITUDE STUDY 2

All participants had some symptoms of AMS. All of the participants on the placebo, 3 of the 6 participants on medroxyprogesterone, 3 of the 5 participants on acetazolamide, and 4 of the 6 participants on the combination of drugs achieved an AMS score of 3 or more on at least one questionnaire at high altitude. Total AMS scores were not significantly lower on medroxyprogesterone (16.2; SD, 16.3) or acetazolamide (26.3; SD, 16.0) or on the combination of the 2 drugs (17.0; SD, 8.0) when compared with the placebo (28.3; SD, 11.4). As clinically indicated, 4 participants were withdrawn from the drug trial at 4120 m; 1 participant taking the placebo and 2 participants taking medroxyprogesterone were started on acetazolamide and continued ascent, and 1 participant taking acetazolamide descended with an unrelated illness that has been described elsewhere.[17]

There was an overall difference in Pa_{O_2} among the 4 treatment groups (F = 5.05, P < .01) (Table 2). Pa_{O_2} was higher for participants on the combined therapy than for those on the placebo (F = 8.48, P < .02) but not for participants on medroxyprogesterone or acetazolamide alone. There was an overall difference in Pa_{CO_2} among the 4 treatment groups (F = 10.02, P < .01); both medroxyprogesterone and acetazolamide reduced Pa_{CO_2} (F = 10.24, P < .01). Pa_{CO_2} for participants on combined therapy was lower than for those on acetazolamide alone (F = 9.43, P < .01). There was an overall difference in plasma bicarbonate among the 4 treatment groups (F = 8.79, P < .01); both medroxyprogesterone and acetazolamide lowered plasma bicarbonate when compared with placebo (F = 13.7, P < .01). Plasma bicarbonate for participants on combined therapy was not different from plasma bicarbonate for those on acetazolamide alone. pH was reduced for participants on acetazolamide alone and on combined therapy (P < .05) but was not significantly different from pH for those on medroxyprogesterone when compared with placebo.

DRUG SIDE EFFECTS AND COMPLIANCE

In study 1, medroxyprogesterone was well tolerated, and at the end of the trial, none of the male participants was able to indicate whether he was taking the active medication. Peripheral edema was detected in the same number of participants on medroxyprogesterone and the placebo. Compliance with allocated therapy was 86% for the placebo and 93% for medroxyprogesterone.

In study 2, all participants on acetazolamide reported slight-to-moderate paresthesias; in 7 participants, it was intermittent throughout the study, and in 5 participants, it tended to ameliorate at higher altitudes. Two participants on the placebo reported paresthesias, but none of the participants on medroxyprogesterone alone reported paresthesias. The severity and pattern of paresthesias were identical to those for the participants on combined therapy when compared with those on acetazolamide alone. Four participants, 2 on medroxyprogesterone alone and 2 on combined therapy, reported the sensation of deeper breathing or hyperventilation at rest. There was no evidence that medroxyprogesterone alone or in combination was associated with any increase in periph-

Table 2. Blood gas data in high-altitude study 2 (mean and SD for each group on each of the test dates)*

	Blood gases, altitude (m)			
	Day 2, 2660	*Day 4, 3440*	*Day 6, 4120*	*Day 8, 5200*
PaO_2, kPa				
Placebo	7.27 (0.41)	6.160 (0.59)	5.63 (0.65)	4.71 (0.43)
Medroxyprogesterone	6.93 (0.43)	6.2 (0.44)	5.57 (0.36)	5.07 (0.4)
Acetazolamide	7.17 (0.51)	6.49 (0.11)	6.17 (0.76)	4.91 (0.43)
Az + Mp†	7.77 (0.52)	6.93 (0.31)	6.09 (0.4)	5.37 (0.41)
H^+ion, nmol/L				
Placebo	7.483 (0.01)	7.475 (0.019)	7.483 (0.038)	7.453 (0.044)
Medroxyprogesterone	7.478 (0.035)	7.478 (0.023)	7.477 (0.019)	7.473 (0.043)
Acetazolamide	7.428 (0.017)	7.418 (0.033)	7.427 (0.039)	7.427 (0.035)
Az + Mp	7.46 (0.018)	7.442 (0.021)	7.457 (0.018)	7.423 (0.018)
$PaCO_2$, kPa				
Placebo	4.83 (0.6)	3.67 (0.32)	3.29 (0.36)	3.16 (0.83)
Medroxyprogesterone	4.09 (0.48)	3.11 (0.29)	3.07 (0.13)	2.49 (0.2)
Acetazolamide	4.37 (0.58)	3.09 (0.25)	3.04 (0.36)	2.8 (0.53)
Az + Mp	4.04 (0.31)	2.77 (0.27)	2.53 (0.19)	2.11 (0.23)
HCO_3, mmol/L				
Placebo	28.4 (2.0)	23.3 (0.7)	22.3 (1.6)	20.3 (1.5)
Medroxyprogesterone	25.3 (1.8)	21.5 (0.7)	21.0 (1.1)	19.2 (2.1)
Acetazolamide	23.6 (2.3)	19.0 (1.4)	19.0 (1.5)	18.4 (2.9)
Az + Mp	24.2 (0.7)	18.9 (1.2)	18.8 (0.9)	16.1 (1.0)

*PaO_2 was higher in participants on combined therapy ($P < .02$); pH was reduced in participants on acetazolamide and on combined therapy ($P < .05$). $PaCO_2$ was reduced in participants on medroxyprogesterone and acetazolamide ($P < .01$) and was further reduced in participants on combined therapy ($P < .01$).

†Az + Mp indicates acetazolamide plus medroxyprogesterone.

eral edema. Loss of libido was reported by 1 participant assigned to the placebo group and by 1 participant on combined therapy. Minor breakthrough vaginal bleeding occurred in the 1 female participant on medroxyprogesterone. Compliance with allocated therapy was 99% for the placebo, 98% for medroxyprogesterone, and 98% for acetazolamide.

Discussion

Medroxyprogesterone did not prevent AMS as defined by a Lake Louise score of 3 or more in the small numbers studied. In both studies, although there was a trend toward lower AMS scores on medroxyprogesterone and more participants had no AMS (score, <3) on medroxyprogesterone than on the placebo or acetazolamide, the differences were not significant. It is possible that a more sensitive scoring system than the Lake Louise questionnaire is required,[18] as our own modified environmental system questionnaire showed greater differences among the treatment groups in study 2 (data not shown); however, this was not used in study 1. A formal combination of the results of the 2 high-altitude studies was not possible because the rate of ascent and the amount of exercise were different. Larger numbers of participants are required to overcome the variable susceptibility to AMS. Ideally, a crossover study should be performed using participants as their own controls in order to prove the efficacy of medroxyprogesterone, but acclimatization would introduce another variable.

Progesterone stimulates an estrogen-dependent receptor at hypothalamic sites and influences the respiratory center via a neural pathway.[19] Progesterone also stimulates peripheral chemoreceptors.[20] Our studies confirmed the expected effect of a reduction in $PaCO_2$ and an improvement in peripheral oxygen saturation. The failure to show an improvement in cerebral regional oxygenation may have been due to the small effects observed, but it is also possible that the effect of a fall in carbon dioxide reduced cerebral blood flow and offset any improvement in peripheral oxygen saturation. Although we assumed that the small clinical effects of medroxyprogesterone were due to increased oxygenation, it is pos-

sible that other effects such as the inhibition of Na+/K+-ATPase are important.

The side effect profile for medroxyprogesterone was acceptable and better than that for acetazolamide. Suppression of plasma gonadotrophins and testosterone was noted with these high doses of medroxyprogesterone in the pilot study but with no immediate clinical effect. The time course of these altitude studies was similar to that of the pilot study. Medroxyprogesterone in female participants, however, was difficult to use and required confirmation that the woman was not pregnant as well as the initiation of therapy at the onset of menstruation. It also risked some breakthrough uterine bleeding.

These studies used pharmacologic doses of medroxyprogesterone, which may have effects different from physiologic levels of progesterone.[21] Women have been variously described as protected,[22,23] equally susceptible,[24] or at greater risk[25] of acquiring AMS when compared with men. However, studies have not always been limited to the luteal phase of the menstrual cycle. Whether the high concentrations of progesterone occurring during pregnancy or the relatively lower doses of progesterone used in contraceptive preparations are beneficial remains unknown. The role of progesterone in the treatment of the severe forms of AMS has not been assessed, but it is unlikely to be effective as monotherapy, given the modest effects seen in our studies.

Conclusions

In conclusion, the improvement in peripheral oxygenation on medroxyprogesterone was small and was not detected in cerebral regional oxygenation. Larger numbers of participants would be required to demonstrate a reduction in AMS scores and the prevention of AMS. The practical difficulties of using this drug in female participants preclude this.

Acknowledgements

We are grateful for support from The Wellcome Trust, The Arthur Thomson Trust, The Mount Everest Foundation, and Ciba Corning Diagnostics UK Ltd and for the supply of Provera for study 2 by Upjohn Ltd. Prof Peter Jones, Keele University, and Dr Andrew Krentz assisted with the statistical analyses. Mrs Margaret Richards provided secretarial and other support.

References

1. Shlim DR, Houston R. Helicopter rescues and deaths among trekkers in Nepal. *JAMA.* 1989;261:1017–1019.
2. BMRES Mountain Sickness Study Group. Acetazolamide in the control of acute mountain sickness. *Lancet.* 1981;i:180–183.
3. Wright AD, Winterborn MH, Forster PJ, et al. Carbonic anhydrase inhibition in the immediate therapy of acute mountain sickness. *J Wilderness Med.* 1994;5:49–55.
4. Bärtsch P, Maggiorini M, Ritter M, Noti C, Vock P, Oelz O. Prevention of high-altitude pulmonary oedema by nifedipine. *N Engl J Med.* 1991;325:1284–1289.
5. Hackett P, Roach R, Wood R, et al. Dexamethasone for prevention and treatment for acute mountain sickness. *Aviat Space Environ Med.* 1988;59:950–954.
6. Bradwell AR, Imray CHE, Wright AD, Delamere J, and the BMRES. Acetazolamide or nifedipine in acute mountain sickness prophylaxis. In: Sutton JR, Houston CS, Coates G, eds. *Hypoxia and Molecular Medicine.* Burlington, VT: Queen City Printers Inc; 1993:294.
7. Hohenhaus E, Niroomand F, Goerre S, Vock P, Oelz O, Bärtsch P. Nifedipine does not prevent acute mountain sickness. *Am J Respir Crit Care Med.* 1994;150:857–860.
8. Johnson TS, Rock PB, Fulco CS, et al. Prevention of acute mountain sickness by dexamethasone. *N Engl J Med.* 1984;310:683–686.
9. Moore LG, Harrison GL, McCullough RE, et al. Low acute hypoxic ventilatory response and hypoxic depression in acute altitude sickness. *J Appl Physiol.* 1986;40:1407–1412.
10. Hackett PH, Roach RC, Harrison GL, Schoene RB, Mills WJ. Respiratory stimulants and sleep periodic breathing at high altitude. Almitrine versus acetazolamide. *Am Rev Respir Dis.* 1987;135:896–898.
11. Kryger M, McCullough RE, Collins D, et al. Treatment of excessive polycythemia of high altitude with respiratory stimulant drugs. *Am Rev Respir Dis.* 1978;117:455–464.
12. Milerad J, Lagercrantz H, Lofgren O. Alveolar hypoventilation treated with medroxyprogesterone. *Arch Dis Childhood.* 1985;60:150–155.
13. Roof RL, Duvdevani R, Stein DG. Progesterone treatment attenuates brain oedema following contusion injury in male and female rats. *Restorative Neurol Neurosci.* 1992;4:425–427.
14. Roach RC, Bärtsch P, Oelz O, Hackett PH, and the Lake Louise AMS Scoring Consensus Committee. The Lake Louise acute mountain sickness scoring system. In: Sutton JR, Hanston CS, Coates G, eds. *Hypoxia and Molecular Medicine.* Burlington, VT: Queen City Press; 1993:272–274.
15. Imray CHE, Barnett NJ, Walsh S, et al. Near-infrared spectroscopy in the assessment of cerebral oxygenation at high altitude. *Wilderness Environ Med.* 1998;9:198–203.
16. Cohen L, Holliday M. *Statistics for Social Scientists.* London: Harper & Row; 1982.
17. Harvey T. Om Mani Padme Hum. *Lancet.* 1993;342:363.
18. Wright AD, Forster PJG, Cadigan P, Fletcher RF, Bradwell AR, and BMRES. Refinements of the Lake Louise self-reporting AMS questionnaire. In: Sutton JR, Houston CS, Coates G, eds. *Hypoxia and the Brain.* Burlington, VT: Queen City Press; 1995:No. 57:21.

19. Bayliss DA, Millhorn DE. Central neural mechanisms of progesterone action: application to the respiratory system. *J Appl Physiol.* 1992;73:393–404.
20. Hannhart B, Pickett C, Grindlay Moore L. Effects of oestrogen and progesterone on carotid body neural output responsiveness to hypoxia. *J Appl Physiol.* 1990;68:1909–1916.
21. Hellman L, Yoshida K, Zumoff B, Levin J, Kream J, Fukishima D. The effect of medroxyprogesterone acetate on the pituitary-adrenal axis. *J Clin Endocrinol Metab.* 1976; 42:912–917.
22. Johnson TS, Rock PB. Acute mountain sickness. *N Engl J Med.* 1988;319:841–845.
23. Harris CW, Shields JL, Hannon JP. Acute altitude sickness in females. *Aerospace Med.* 1966;37:1163–1167.
24. Hackett PH, Rennie D. The incidence, importance and prophylaxis of acute mountain sickness. *Lancet.* 1976;2: 1149–1155.
25. Honigman B, Theis MK, Koziol-McLain J, et al. Acute mountain sickness in a general tourist population at moderate altitudes. *Ann Intern Med.* 1993;118:587–591.

Effect of exercise on cerebral perfusion in humans at high altitude

C. H. E. Imray, S. D. Myers, K. T. S. Pattinson, A. R. Bradwell, C. W. Chan, S. Harris, P. Collins, A. D. Wright and the Birmingham Medical Research Expeditionary Society

Journal of Applied Physiology 99:699-706, 2005. First published May 26, 2005;
doi:10.1152/japplphysiol.00973.2004

J Appl Physiol 99: 699–706, 2005.
First published May 26, 2005; doi:10.1152/japplphysiol.00973.2004.

Effect of exercise on cerebral perfusion in humans at high altitude

C. H. E. Imray,[1] S. D. Myers,[2] K. T. S. Pattinson,[3] A. R. Bradwell,[4] C. W. Chan,[4] S. Harris,[2] P. Collins,[5] A. D. Wright,[4] and the Birmingham Medical Research Expeditionary Society[4]

[1]*Coventry and Warwickshire County Vascular Unit, University Hospitals Coventry and Warwickshire National Health Service Trust, Coventry;* [2]*QinetiQ, Farnborough;* [3]*Nuffield Department of Anesthetics, University of Oxford, John Radcliffe Hospital, Headley Way, Headington, Oxford;* [4]*The Medical School, University of Birmingham, Birmingham; and* [5]*ScanMed Medical Instruments, Moreton-in-the-Marsh, United Kingdom*

Submitted 3 September 2004; accepted in final form 1 April 2005

Imray, C. H. E., S. D. Myers, K. T. S. Pattinson, A. R. Bradwell, C. W. Chan, S. Harris, P. Collins, A. D. Wright, and the Birmingham Medical Research Expeditionary Society. Effect of exercise on cerebral perfusion in humans at high altitude. *J Appl Physiol* 99: 699–706, 2005. First published May 26, 2005; doi:10.1152/japplphysiol.00973.2004.—The effects of submaximal and maximal exercise on cerebral perfusion were assessed using a portable, recumbent cycle ergometer in nine unacclimatized subjects ascending to 5,260 m. At 150 m, mean (SD) cerebral oxygenation (rSo_2%) increased during submaximal exercise from 68.4 (SD 2.1) to 70.9 (SD 3.8) ($P < 0.0001$) and at maximal oxygen uptake ($\dot{V}o_{2\,max}$) to 69.8 (SD 3.1) ($P < 0.02$). In contrast, at each of the high altitudes studied, rSo_2 was reduced during submaximal exercise from 66.2 (SD 2.5) to 62.6 (SD 2.1) at 3,610 m ($P < 0.0001$), 63.0 (SD 2.1) to 58.9 (SD 2.1) at 4,750 m ($P < 0.0001$), and 62.4 (SD 3.6) to 61.2 (SD 3.9) at 5,260 m ($P < 0.01$), and at $\dot{V}o_{2\,max}$ to 61.2 (SD 3.3) at 3,610 m ($P < 0.0001$), to 59.4 (SD 2.6) at 4,750 m ($P < 0.0001$), and to 58.0 (SD 3.0) at 5,260 m ($P < 0.0001$). Cerebrovascular resistance tended to fall during submaximal exercise (P = not significant) and rise at $\dot{V}o_{2\,max}$, following the changes in arterial oxygen saturation and end-tidal CO_2. Cerebral oxygen delivery was maintained during submaximal exercise at 150 m with a nonsignificant fall at $\dot{V}o_{2\,max}$, but at high altitude peaked at 30% of $\dot{V}o_{2\,max}$ and then fell progressively at higher levels of exercise. The fall in rSo_2 and oxygen delivery during exercise may limit exercise at altitude and is likely to contribute to the problems of acute mountain sickness and high-altitude cerebral edema.

maximal oxygen uptake; cerebral oxygenation; cerebral blood flow; cerebrovascular resistance; cerebral oxygen delivery

ALTERED CEREBRAL FUNCTION on ascent to altitude was part of the first description of mountain sickness in 1913 (40), and acute mountain sickness (AMS) and high-altitude cerebral edema (HACE) have been shown to be potentially serious clinical conditions that may occur on acute exposure to altitudes above 2,500–3,000 m. Exercise at altitude causes further decreases in arterial oxygenation and so may exacerbate cerebral hypoxia. However, the fall in arterial saturation that occurs during exercise at high altitude (14) might not affect cerebral oxygenation to the same extent as it does in peripheral tissues due to a compensatory increase in cerebral blood flow (24). Nevertheless, avoidance of strenuous exercise during ascent, and on arrival at altitude, is standard advice for reducing the risk of AMS and HACE. Evidence from clinical studies is conflicting. Higher AMS symptom scores were found in subjects exercising four times a day for 30 min at 50% of their altitude-specific maximal oxygen consumption ($\dot{V}o_{2\,max}$), compared with no exercise, in a chamber study at simulated altitude of 4,800 m (41). Another study of mountaineers, however, showed that physical fitness and exercise intensity during ascent to 4,559 m were of minor importance for the development of AMS (3). It is also possible that other neurological conditions falling outside the usual definition of altitude sickness (2) could be related to exercise.

Near-infrared cerebral spectroscopy and transcranial Doppler measurement of middle cerebral artery (MCA) blood velocity offer continuous noninvasive assessments of cerebral perfusion. Cerebral spectroscopy has been shown to track changes in jugular venous bulb saturations in healthy volunteers under conditions of isocapnic hypoxia (12) and has also been validated by comparison with PET scanning, with ^{133}Xe washout methods and with internal carotid artery stump pressures (54). We have used this technique during dynamic studies of cerebral oxygenation at altitude and assessed the effects of hyperventilation, oxygen therapy, and CO_2 supplementation (19, 20) and during assessment of the effects of pressurization in a portable hyperbaric chamber (21). Assessments of cerebral blood flow and cerebral oxygenation during exercise and under field conditions have proven challenging. The standard, upright exercise cycle results in excessive head movement and use of arms, particularly as one approaches maximal exercise. To overcome these difficulties, we built a portable, recumbent exercise ergometer (Alticycle) for undertaking cerebral perfusion measurements in the field.

This study aimed to measure changes in cerebral perfusion at rest and during exercise up to $\dot{V}o_{2\,max}$ at altitudes from 150 to 5,260 m to gain further insight into the factors that limit exercise and alter cerebral function on acute exposure to high altitude.

MATERIALS AND METHODS

Subjects. Eleven healthy white Europeans (1 woman; ages 32–65 yr) were studied. All were nonsmokers, normotensive, on no medication, physically fit, living at 50–150 m, with no recent exposure to high altitude, and were familiar with cycle ergometer-based exercise tests. Measurements were recorded at Birmingham, UK (150 m) and during an expedition to Bolivia. The first measurement at high altitude was made 24–36 h after arrival at 3,610 m (La Paz). Two subjects were subsequently excluded from the study because of excessive rises of blood pressure during exercise at this altitude. The group then

Address for reprint requests and other correspondence: C. H. E. Imray, Coventry and Warwickshire County Vascular Unit, Univ. Hospitals Coventry and Warwickshire NHS Trust, Coventry, CV2 2DX, UK (E-mail: chrisimray@aol.com).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

traveled by road, and repeat measurements were made on the remaining nine subjects 24–36 h after arrival at 4,750 m (Refugio Potosi) and 5,260 m, (ski station, Chacaltaya). All measurements at high altitude were therefore completed within 9 days of arrival in Bolivia. Barometric pressure was obtained from the mean of four portable barometers (Suunto Observer, Helsinki, Finland).

Alticycle. The Alticycle cycle ergometer has four novel features (Fig. 1). First, the cycling position is fully supine. The body of the subject is held by shoulder straps and a waist belt to the alticycle frame. The head, resting freely in a stable position, is isolated from the main body of the alticycle, and the arms are free. Second, the exercise load is provided by a friction brake applied to a 2-kg flywheel linked through a series of gears that allows it to rotate between 4,000 and 5,000 revolutions/min. This combination provides good inertia for cycling but with minimal weight. Third, power output and cadence are measured via a strain-gauged crank set assessing torque and cadence (Schoberer Rad Meβtechnik, Jülich, Germany). Power is measured directly in Watts on a second-by-second basis. Fourth, it folds into a self-contained compact backpack-style unit (81× 37× 24 cm, weight 25 kg), allowing it to be carried by a single person.

Exercise tests. Subjects completed two tests at each altitude. A $\dot{V}o_{2\,max}$ test was undertaken first, followed by a submaximal test on the same day separated by a minimum interval of 4 h. Subjects rested for one-half hour before each test and then exercised gently for 5 min at 50 W to warm up. Subjects maintained a cadence rate of 55 pedal revolutions/min for each test. For the maximal test, starting loads for each subject were estimated to produce a test lasting ~10 min (53). The load was increased by 20-W increments per minute up to volitional exhaustion. In the submaximal test, subjects were required to complete 15 min of cycling comprising three 5-min, consecutive exercise periods at 30, 50, and 70% of the power of the altitude-specific $\dot{V}o_{2\,max}$, respectively.

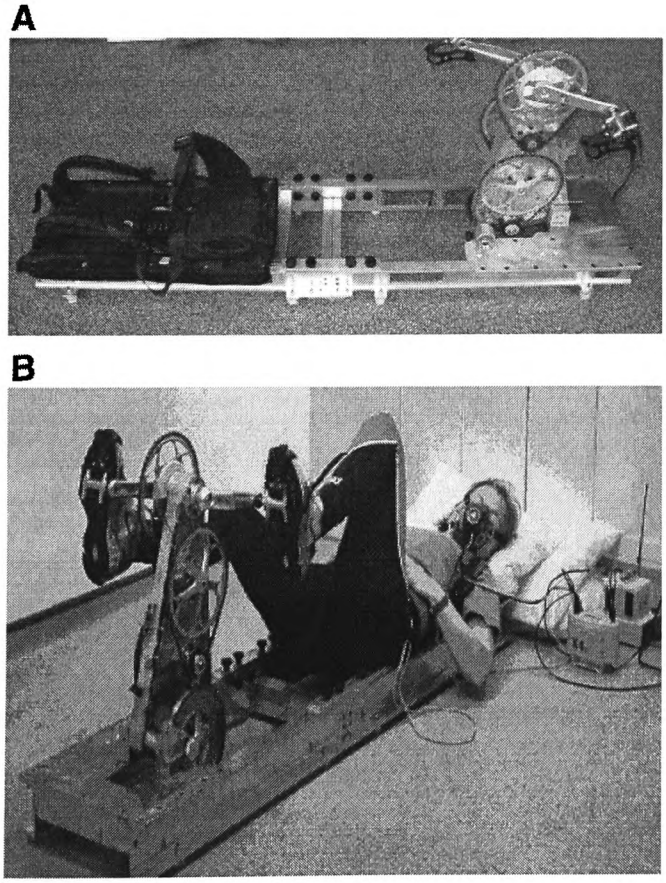


Fig. 1. *A*: Alticycle. *B*: Alticycle in use.

Expired gas was analyzed breath by breath using a Cosmed K4b[2] portable gas-exchange unit (Cosmed, Rome, Italy) for oxygen uptake ($\dot{V}o_2$; photometric gas analyzer), end-tidal CO_2 (infrared absorption), and minute volume (turbine flowmeter). The Cosmed K4b[2] was chosen for its portability and performance at high altitude (6), which has been confirmed subsequently by the authors (36). Gases were collected via a tight-fitting Cosmed-modified Hans Rudolph facemask. Finger-pulse oximetry (arterial oxygen saturation) was measured using an Ohmeda Biox 3740 Pulse Oximeter (Ohmeda). Continuous beat-to-beat blood pressure was measured using the radial artery tonometry technique with a COLIN CBM-7000 monitor (ScanMed Medical Instruments, Moreton-in-the-Marsh, UK), and mean blood pressure was calculated from the formula mean blood pressure = diastolic blood pressure + 1/3(systolic blood pressure − diastolic blood pressure). Predicted heart rates at $\dot{V}o_{2\,max}$ were calculated using the formula 220 − age (yr).

Cerebral hemodynamics. MCA blood velocity was measured using a 2-MHz, pulsed-wave, range-gated Doppler ultrasound (DWL Multi-Dop T1, DWL Elektronische Systeme, Singen, Germany). The MCA time-averaged mean velocity (cm/s) was recorded electronically. A single, experienced operator performed the measurements by insonating the right MCA through the temporal bone window with the subject at rest. The insonation depth was initially set at 50 mm and then gradually increased to identify the optimal signal. Once found, the position was fixed using a locking headband, which allowed the subject to cycle freely. Occasionally, it was necessary to optimize the signal manually during a test by adjusting the direction but not the depth of the beam.

Cerebral regional oxygenation (rSo_2) was measured by continuous, noninvasive, near-infrared cerebral spectroscopy. The Critikon 2020 (Johnson and Johnson Medical, Newport, UK) spectroscope is based on a two-channel sensor and a coupling compensation system. Infrared light is emitted at four wavelengths (776.5, 819.0, 871.4, and 908.7 nm) from a light-emitting diode, and two silicon photodiode detectors are set 10 and 37 mm from the light-emitting diode. The absolute concentrations of oxyhemoglobin (in μM) and deoxyhemoglobin (in μM) are calculated from a modified version of the Beer-Lambert law. The dual detector sensor position was standardized over the right frontoparietal region of the head with sensor margins 3 cm from the midline and 3 cm above the supraorbital crest, taking care to avoid the sagittal and frontal sinus areas (18). The measurement of rSo_2 was calculated from the equation rSo_2= (oxygenated hemoglobin/total hemoglobin) × 100.

Statistical analyses. Data was collected continuously by logging it to the DWL Multi-Dop T1. Offline analysis was subsequently undertaken. All data are reported as mean and standard deviation (SD) unless indicated otherwise. Resting measurements were taken immediately before the $\dot{V}o_{2\,max}$ test at each altitude. Heart rate, mean blood pressure, arterial saturation, end-tidal Pco_2, minute volume, $\dot{V}o_2$, MCA blood velocity, cerebral deoxygenation, cerebral oxygenation, total hemoglobin, and rSo_2 were taken from a mean of the three last readings (−20, −10, and 0 s) at each level of exercise. Cerebrovascular resistance (CVR_{est}) was calculated using the formula CVR_{est} = mean arterial blood pressure/MCA blood velocity (26, 44), and cerebral oxygen delivery using the formula cerebral oxygen delivery = arterial oxygen saturation × MCV blood velocity (33).

The significance of changes occurring in resting measurements during ascent and changes in measurements during submaximal exercise were assessed by repeated-measures ANOVA (StatView for Windows, Abacus Concepts, Berkley, CA) with difference located using Tukey's honestly significant different post hoc test. Resting and $\dot{V}o_{2\,max}$ data were compared using paired *t*-tests. *P* values of <0.05 were considered significant.

Table 1. *Environmental measurements and subject characteristics for each altitude*

	Altitude, m			
	150	3,610	4,750	5,260
Atmospheric pressure, mmHg	743	496	435	410
Ambient temperature, °C	23.6	24.9	14.6	14.3
Body mass, kg	81.1 (9.7)	81.6 (9.7)	82.5 (10.3)	82.5 (10.9)
Height, cm	181.1 (5.1)			
Body mass index, kg/m^2	25.4 (2.9)			

Data are means (SD); $n = 9$. Body mass did not alter significantly during ascent.

The Research and Ethics Committee of the South Birmingham Health Authority granted approval for the studies, and subjects gave their written, informed consent.

RESULTS

No technical difficulties were experienced with the pulse oximeter or the Alticycle. The signal from the Colin blood pressure monitor occasionally required optimization by adjusting the sensor position over the radial artery, and this was a particular problem with the recordings at 5,260 m. The K4b^2 needed to be carefully cleared of condensation before each test. When using an early version of the Alticycle, background rumble interfered with the transcranial Doppler recordings when subjects exercised close to $\dot{V}o_{2\,max}$. Interference was eliminated initially using a 100-MHz filter. Although this was satisfactory, the Alticycle was adapted for all experimental data reported in this paper with a rubber interface placed between the joints of the Alticycle and the subject's head being supported independently of the ergometer by a firm pillow, removing the need for the 100-MHz filter. Good signals from the cerebral spectroscopy probe were maintained by careful cleaning of the forehead and probe with ethanol. Mean (SD) heart rate recorded at $\dot{V}o_{2\,max}$ was 90% (SD 7) of predicted of 150 m at 3,610 m, 81% (SD 5) of predicted at 4,750 m, and 74% (SD 4) at 5,260 m.

Environmental measures and subject characteristics for each altitude are listed in Table 1. Body mass did not change significantly during the study. Resting and exercise cardiorespiratory data are shown in Table 2 and cerebral perfusion data in Table 3 and Figs. 2–5. With increasing altitude, resting heart rate, mean blood pressure, total hemoglobin, and oxyhemoglobin did not change (Table 2). Resting arterial oxygen saturation and end-tidal Pco_2 decreased at all altitudes compared with 150 m ($P < 0.0001$ for both) (Table 2). Resting $\dot{V}o_2$ increased at all altitudes compared with 150 m ($P < 0.05$). Resting ventilation also increased significantly at 4,750 m ($P < 0.05$) and 5,260 m ($P < 0.001$). Resting MCA blood velocity increased from 60.2 cm/s (SD 14.1) at 150 m to 73.4 cm/s (SD 20.4) at 5,260 m ($P < 0.05$), and resting rSo_2 decreased from 68.4% (SD 2.1) at 150 m to 62.4% (SD 3.6) at 5,260 m ($P < 0.0001$) (Table 3). There was no difference in resting CVR_{est} or cerebral oxygen delivery between the different altitudes (Fig. 2).

Exercise at 150 m (Tables 2 and 3). Mean arterial blood pressure did not change significantly during exercise. Oxygen saturation was unchanged during submaximal exercise but fell at $\dot{V}o_{2\,max}$ ($P < 0.0001$). End-tidal CO_2 was unchanged during submaximal exercise but was reduced from 36.3 Torr (SD 4.7) resting to 33.1 Torr (SD 5.3) at $\dot{V}o_{2\,max}$ ($P < 0.05$). Ventilation and $\dot{V}o_2$ rose progressively during both submaximal and $\dot{V}o_{2\,max}$ tests ($P < 0.0001$). MCA blood velocity rose initially but fell at the highest workloads with an increase from 60.2 cm/s (SD 4.1) at rest to 65.5 cm/s (SD 12.9) at 70% $\dot{V}o_{2\,max}$ ($P < 0.05$) and a reduction to 50.5 cm/s (SD 22.3) at $\dot{V}o_{2\,max}$

Table 2. *Cardiorespiratory data during exercise at different altitudes*

	150 m					3,610 m					4,750 m					5,260 m				
	Rest	30%	50%	70%	$\dot{V}o_{2max}$	Rest	30%	50%	70%	$\dot{V}o_{2max}$	Rest	30%	50%	70%	$\dot{V}o_{2max}$	Rest	30%	50%	70%	$\dot{V}o_{2max}$
Heart rate, beats/min	68 (14)	98 (9.3)[a]	119 (13.1)[a]	133 (13.4)[a]	164 (9)	78 (10)	124 (9)	132 (7)	148 (8)	142 (27)	78 (12)	108 (9)	121 (8)	134 (8)	135 (11)	72 (12)	92 (24)	107 (22)	118 (18)	130 (5)
Mean BP, mmHg	106 (12)	112 (9)	115 (12)	120 (11)	112 (18)	107 (20)	123 (12)	130 (14)	138 (17)	123 (19)	107 (13)	114 (13)	122 (17)	128 (15)[b]	122 (15)[c]	108 (14)	109 (8)	116 (9)	126 (12)[c]	107 (14)
Oxygen, saturation %	99.0 (0.8)[e]	98.6 (0.5)	98.1 (0.8)	97.1 (0.7)	94.9 (2.8)[e]	89.5 (4.7)[e]	83.7 (5.1)	81.9 (4.1)	80.6 (4.2)[e]	83.1 (11.5)[e]	82.3 (4.6)[e]	73.76 (8.5)	71.2 (8.5)	71.6 (6.1)	74.1 (9.3)	81.8 (4.7)[e]	68.9 (15.1)	69.9 (8.6)	72.1 (4.4)[e]	74.6 (5)[e]
End-tidal Pco_2, Torr	36.2 (4.7)	38.6 (3.7)	38.4 (3.8)	37.3 (4.6)	33.1 (5.3)[b]	25.0 (1.8)[d]	29.7 (12.2)	23.4 (2.2)	21.1 (2.4)[d]	19.3 (1.7)[e]	24.1 (1.8)[d]	24.1 (2.6)	22.3 (2.8)	20.9 (2.3)[e]	19.0 (2.7)[e]	21.5 (2.9)[d]	23.7 (2.1)	21.4 (1.8)	19.4 (1.9)[d]	14.9 (2)[e]
Ventilation, l/min	12.9 (2.2)	37.8 (4.9)	56.4 (8.1)	78.3 (9.9)	127 (25.4)	20.7[b] (6.1)	44.8 (9.9)	80.1 (21.5)	111 (18.5)	138 (24)	24.0[b] (5.3)	45.6 (9.6)	76.8 (18.5)	112.9 (22.4)	147 (35)	30.7[b] (5.6)	45.3 (13)	79.1 (13.1)	106.5 (16.6)	145 (26.8)
$\dot{V}o_2$, ml·min^{-1}·kg^{-1}	5.7 (1.5)	19.9 (1.4)	28.2 (3.3)	36.6 (4.1)	43 (7.7)	10.7 (6.1)	18.5 (4.2)	29.1 (7.3)	32.8 (9.5)	35.4 (6.3)	10.9 (5.4)[b]	17.1 (3.5)	25.4 (6.5)	31.7 (6.1)	36.4 (8.5)	11.0 (1.0)[d]	18.3 (8.5)	25.8 (6.9)	29.4 (6.7)	37.0 (7.8)

Data are means (SD) for the 9 subjects completing the study; [a]$n = 7$. Differences are reported between altitudes for resting values and for exercise at each altitude; 70% maximal oxygen uptake ($\dot{V}o_{2max}$) and $\dot{V}o_{2max}$ are compared with rest. BP, blood pressure; $\dot{V}o_2$, oxygen uptake. Significant differences: [b]$P < 0.05$; [c]$P < 0.01$; [d]$P < 0.001$; [e]$P < 0.0001$.

Table 3. *Cerebral perfusion data during exercise at different altitudes*

	150 m					3,610 m					4,750 m					5,260 m				
	Rest	30%	50%	70%	$\dot{V}O_{2max}$	Rest	30%	50%	70%	$\dot{V}O_{2max}$	Rest	30%	50%	70%	$\dot{V}O_{2max}$	Rest	30%	50%	70%	$\dot{V}O_{2max}$
MCA blood velocity, cm/s	60.2 (14.1)	66.1 (12.5)	69.4 (14.9)	65.5 (12.9)§	50.5 (22.3)*	64.5 (14.1)	76.1 (13.8)	71.7 (13.8)	66 (17.3)§	50.6 (21.7)§	66.6 (20.5)	87.2 (25.7)	83.4 (20.9)	78.7 (20.7)§	58.6 (19.4)§	73.4 (20.4)*	81 (28.6)	83.3 (24.7)	81 (19.6)	67.1 (16.3)§
Cerebral $HbDO_2$, μM	33.6 (6.2)	35 (5.4)	34.8 (4.9)	34.6 (3.3)	33.9 (6.6)	34.7 (5.2)	39.3 (4.4)	41.7 (4.6)	44.4 (5.4)	44.0 (6.8)	40.6 (4.5)	48.6 (6.6)	50.7 (6.1)	54.9 (6.9)	47.6 (6.4)	41.2 (3.9)	42 (4.9)	45.5 (3.9)	49.2 (8.6)	47.7 (5.8)
Cerebral HbO_2, μM	77 (12.4)	76.4 (19.3)	80.3 (21.7)	83.2 (22.6)	77.3 (15.8)	70.2 (14.6)	75.5 (10.1)	77.8 (10.7)	79.7 (10.5)	76.6 (18.3)	72.1 (17.1)	77.9 (13.2)	80 (13.6)	81.7 (16.4)	77.4 (23.6)	68.3 (11.9)	64.5 (13.3)	68.9 (8.8)	71.8 (7.9)	65.7 (10.7)
Cerebral total Hb, μM	104.7 (22.6)	109.4 (21.5)	111.9 (21)	114.6 (21.3)	108.2 (24.9)	107.6 (21.5)	114.6 (14.1)	118.2 (14.8)	122 (15.7)	112 (27)	11.0 (15.4)	126 (18.5)	131.5 (18.9)	134.6 (21.9)	114.7 (16.6)	110 (15.4)	103 (26)	110 (22.1)	113 (19.5)	116 (20.8)
Cerebral oxygenation, %	68.4 (2.1)	68.6 (2.6)	69.9 (3.4)	70.9 (3.8)§	69.8 (3.1)*	66.2 (2.5)	64.6 (2.5)	63.7 (1.8)	62.6 (2.1)§	61.2 (3.3)§	63 (2.1)	61.4 (2.2)	60.6 (2.0)	58.9 (2.1)§	59.4 (2.6)	62.4 (3.6)	57.9 (10.1)	60.1 (4.4)	61.2 (3.9)‡	58 (3.0)

Data are means (SD) for the 9 subjects completing the study. MCA, middle cerebral artery; $HbDO_2$, deoxyhemoglobin; HbO_2, oxyhemoglobin. Differences are reported between altitudes for resting values and for exercise at each altitude; 70% $\dot{V}O_{2max}$ and $\dot{V}O_{2max}$ are compared with rest. Significant differences: *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$; §$P < 0.0001$.

($P < 0.01$) (Fig. 2). rSo_2 increased from 68.4% (SD 2.1) at rest to 70.9% (SD 3.8) during submaximal exercise ($P < 0.0001$) and to 69.8% (SD 3.1) at $\dot{V}O_{2\,max}$ ($P < 0.05$) (Fig. 3). CVR_{est} and cerebral oxygen delivery were not significantly different between resting and $\dot{V}O_{2\,max}$ (Figs. 4 and 5).

Exercise at 3,610 m (Table 2 and 3). Mean arterial blood pressure did not change significantly during exercise. Arterial oxygen saturations were reduced at all levels of exercise compared with baseline ($P < 0.0001$). End-tidal CO_2 during submaximal exercise rose initially but was reduced from 24.9 Torr (SD 1.7) at rest to 21.1 Torr (SD 2.4) at 70% $\dot{V}O_{2\,max}$ ($P < 0.001$) and to 19.3 Torr (SD 1.7) at $\dot{V}O_{2\,max}$ ($P < 0.0001$). Ventilation and $\dot{V}O_2$ rose progressively during the tests ($P < 0.0001$). MCA blood velocity rose initially and fell with maximal exercise, with an increase from 64.5 cm/s (SD 14.1) at rest to 66.0 cm/s (SD 17.3) at 70% $\dot{V}O_{2\,max}$ ($P < 0.0001$) and a reduction to 50.6 cm/s (SD 21.7) at $\dot{V}O_{2\,max}$ ($P < 0.0001$) (Fig. 2). rSo_2 was reduced from 66.2% (SD 2.5) at rest to 62.6% (SD 2.1) during submaximal exercise ($P < 0.0001$) and to 61.2% (SD 3.3) at $\dot{V}O_{2\,max}$ ($P < 0.0001$) (Fig. 3). There was a rise in CVR_{est} from 1.7 (SD 0.41) at rest to 2.16 (SD 0.57) at $\dot{V}O_{2\,max}$ ($P < 0.05$) (Fig. 4) and a fall in cerebral oxygen delivery from 5,811 (SD 1,419) at rest to 4,665.6 (SD 1,324) at $\dot{V}O_{2\,max}$ ($P < 0.01$) (Fig. 5).

Exercise at 4,750 m (Tables 2 and 3). Mean arterial blood pressure increased from 107 mmHg (SD 13) to 128 mmHg (SD 15) during submaximal exercise ($P < 0.05$) and remained elevated at $\dot{V}O_{2\,max}$ compared with resting ($P < 0.001$). End-tidal CO_2 rose initially but was reduced from 23.7 mmHg (SD 2.0) at rest to 20.9 mmHg (SD 2.3) at 70% $\dot{V}O_{2\,max}$ ($P < 0.0001$) and to 19.0 mmHg (SD 2.7) at $\dot{V}O_{2\,max}$ ($P < 0.0001$). Ventilation and $\dot{V}O_2$ rose progressively during the tests ($P <$

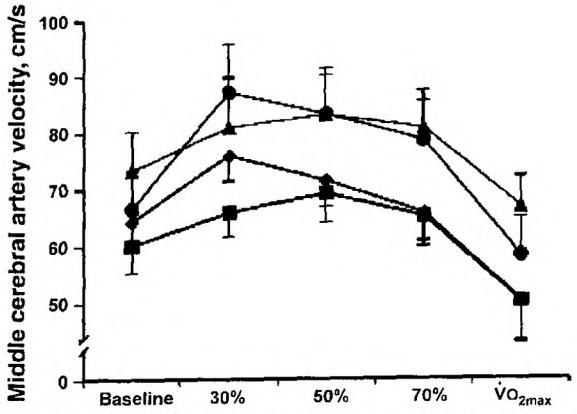


Fig. 2. Changes in middle cerebral artery blood velocity during exercise at different altitudes (■, 150 m; ◆, 3,610 m; ●, 4,750 m; ▲, 5,260 m). Values are means and SE. Velocity at rest increased with increasing altitude ($P < 0.05$). At all altitudes, velocity increased during submaximal exercise ($P < 0.05$–0.0001) but fell at maximal oxygen uptake ($\dot{V}O_{2\,max}$; $P < 0.01$–0.0001).

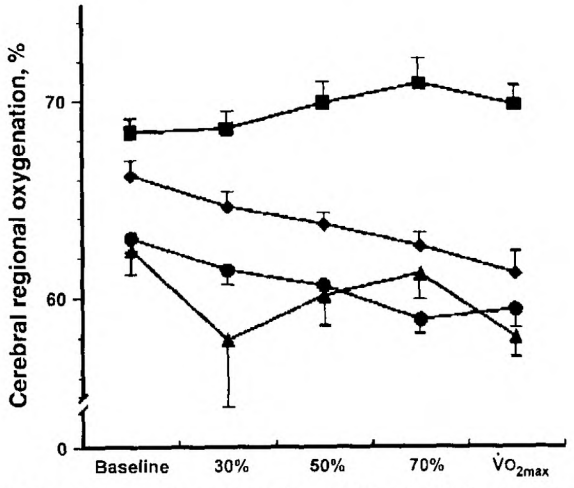


Fig. 3. Changes in cerebral oxygenation at different altitudes (■, 150 m; ◆, 3,610 m; ●, 4,750 m; ▲, 5,260 m). Values are means and SE. Resting oxygenation decreased with increasing altitude ($P < 0.0001$). At 150 m, oxygenation increased during submaximal exercise ($P < 0.0001$) and at $\dot{V}O_{2\,max}$ ($P < 0.05$). At higher altitudes, oxygenation was reduced during submaximal exercise and at $\dot{V}O_{2\,max}$ ($P < 0.01$–0.0001).

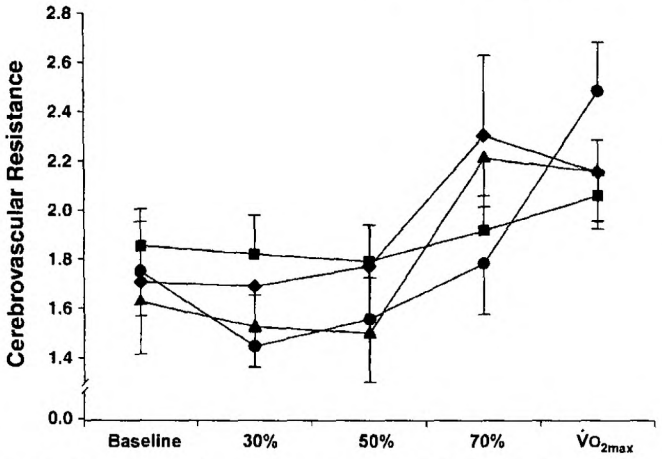


Fig. 4. Changes in cerebrovascular resistance at different altitudes (■, 150 m; ◆, 3,610 m; ●, 4,750 m; ▲, 5,260 m). Values are means and SE. Resting values did not change with increasing altitude. Resting and $\dot{V}o_{2\,max}$ values were not significantly different at 150 m but rose at 3,610 m ($P < 0.05$), 4,750 m (not significant), and 5,260 m ($P < 0.0001$).

0.0001). MCA blood velocity rose initially and fell at maximal workloads, with an increase from 66.6 cm/s (SD 20.5) at rest to 78.7 cm/s (SD 20.7) at 70% $\dot{V}o_{2\,max}$ ($P < 0.0001$) and a reduction to 58.6 cm/s (SD 19.4) at $\dot{V}o_{2\,max}$ ($P < 0.0001$) (Fig. 2). rSo_2 was reduced from 63.0% (SD 2.1) at rest to 58.9% (SD 2.1) during the submaximal exercise test ($P < 0.0001$) and was reduced to 59.4% (SD 2.6) at $\dot{V}o_{2\,max}$ ($P < 0.0001$) (Fig. 3). The rise in CVR_{est} from 1.75 (SD 0.61) at rest to 2.49 (SD 1.25) at $\dot{V}o_{2\,max}$ was not significant ($P = 0.057$; Fig. 4), but there was a fall in cerebral oxygen delivery from 5,487 (SD 1,688) at rest to 4,270 (SD 1,295) at $\dot{V}o_{2\,max}$ ($P < 0.01$; Fig. 5).

Exercise at 5,260 m (Tables 2 and 3). Mean arterial blood pressure increased from 108 mmHg (SD 14) at rest to 126 mmHg (SD 12) during submaximal exercise ($P < 0.001$) but was reduced to 107 mmHg (SD 14) at $\dot{V}o_{2\,max}$ compared with resting. Arterial oxygen saturations were reduced compared with resting ($P < 0.0001$). End-tidal CO_2 rose initially but then was reduced from 21.3 Torr (SD 2.9) at rest to 19.4 Torr (SD 1.9) at 70% $\dot{V}o_{2\,max}$ ($P < 0.001$) and to 14.9 Torr (SD 2.0) at $\dot{V}o_{2\,max}$ ($P < 0.0001$). Ventilation and $\dot{V}o_2$ rose progressively during the tests ($P < 0.0001$). MCA blood velocity rose initially and fell at maximal exercise, with an increase from 73.4 cm/s (SD 20.4) at rest to 81.0 cm/s (SD 19.6) at 70% $\dot{V}o_{2\,max}$ ($P < 0.001$) and a reduction to 67.1 cm/s (SD 16.3) at $\dot{V}o_{2\,max}$ ($P < 0.0001$) (Fig. 2). rSo_2 was reduced from 62.4% (SD 3.6) at rest to 61.2% (SD 3.9) during submaximal exercise ($P < 0.01$) and was reduced to 58.0% (SD 3.0) at $\dot{V}o_{2\,max}$ ($P < 0.0001$) (Fig. 3). There was a rise in CVR_{est} from 1.63 (SD 0.64) at rest to 2.16 (SD 0.7) at $\dot{V}o_{2\,max}$ ($P < 0.0001$) (Fig. 4) and a fall in cerebral oxygen delivery from 6,158 (SD 1,690) at rest to 5,049 (SD 1,264) at $\dot{V}o_{2\,max}$ ($P < 0.01$) (Fig. 5).

DISCUSSION

The cardiopulmonary effects of exercise at altitude have been studied extensively, but the effect of exercise on cerebral perfusion has received limited attention. No comparable studies of cerebral oxygenation at $\dot{V}o_{2\,max}$, or any combined measurements of cerebral oxygenation and MCA blood velocity at $\dot{V}o_{2\,max}$, at high altitude have been reported. Our results showed reductions in cerebral oxygenation and oxygen delivery during submaximal and maximal exercise at altitude.

The major determinants of cerebral blood flow are arterial Po_2 (Pa_{O_2}), arterial Pco_2 (Pa_{CO_2}) (1), and blood pressure, and each of these is altered by both exercise and altitude. Reductions in both Pa_{O_2} and Pa_{CO_2} on acute exposure to altitude, and during exercise at altitude, will have opposing effects on cerebral blood flow. Furthermore, the effects of these stimuli will be modified and vary with acclimatization. An important part of the respiratory acclimatization to altitude is the change in the hypercapnic ventilatory response, resulting in increased ventilatory sensitivity to CO_2 (26). It has been shown that both cerebral blood flow and cerebral oxidative metabolism returns toward baseline by 3 wk at 5,260 m (31). In the present study, the responses observed at 4,750 and 5,260 m probably reflected partial acclimatization since they were performed 4–7 days after arrival at 3,610 m.

Our finding that acute exposure to the three altitudes had no effect on resting mean systemic arterial blood pressure is consistent with other reported studies (50). The rise in mean blood pressure in response to submaximal exercise at each high altitude was similar to that found at 150 m but was only significantly increased at the two highest altitudes. The fall in blood pressure at $\dot{V}o_{2\,max}$ is consistent with other reports (50, 51). The changes in blood pressure we observed with exercise at altitude are well above the range at which autoregulation has been shown to occur. Autoregulation maintains a constant cerebral blood flow of 50–60 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ over arterial pressures ranging from 60 to 140 mmHg (16). Experience during carotid endarterectomy under loco-regional anesthesia suggests that cerebral blood flow during the cross-clamp phase can be increased with a fairly modest rise in blood pressure, avoiding the need for shunting. A rise in systolic blood pressure of 35–45 mmHg can reverse neurological deficits (46) and is also associated with improved regional cerebral oxygenation (22). The rise in blood pressure may maintain cerebral perfusion during submaximal exercise at altitude, but the fall in blood pressure at $\dot{V}o_{2\,max}$ could be a critical factor limiting exercise.

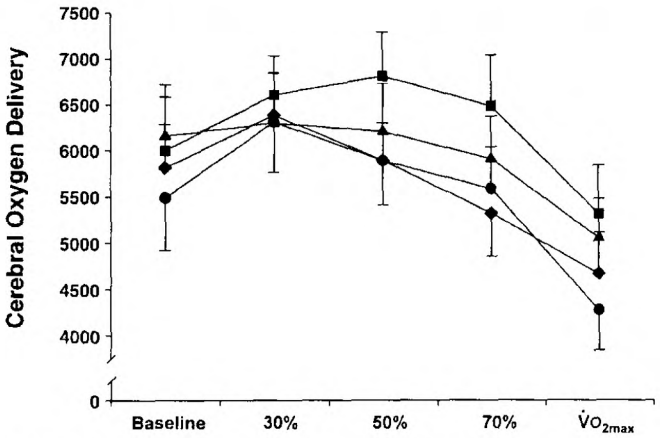


Fig. 5. Changes in cerebral oxygen delivery at different altitudes (■, 150 m; ◆, 3,610 m; ●, 4,750 m; ▲, 5,260 m). Values are means and SE. Resting values did not change with increasing altitude. Resting and $\dot{V}o_{2\,max}$ values were not significantly different at 150 m but fell at 3,610 m ($P < 0.01$), 4,750 m ($P < 0.01$), and 5,260 m ($P < 0.01$).

Near infrared cerebral spectroscopy measures changes in cerebral tissue oxygenation, which is dependent on blood flow, arterial oxygenation, cerebral metabolism, and arterial/venous partitioning (the relative proportion in either the arterial or venous vascular beds). The fall in arterial oxygen saturation at rest with increasing altitude was the most likely cause of the decrease in resting cerebral oxygenation and the increase in resting MCA blood velocity. Similar rises in MCA blood velocity have previously been reported and appear to be most marked on acute ascent, gradually returning toward normal over the following days to weeks (14, 23, 31). The small rise in cerebral oxygenation during submaximal exercise at 150 m could have occurred as a result of an increase in oxygen delivery induced by a gradual fall of cerebral vascular resistance and a matching increase in MCA velocity; but an alternative explanation for the observed rise in cerebral oxygenation could be decreased cerebral oxygen consumption. Similar changes in MCA blood velocity and cerebral oxygenation during submaximal exercise have been reported (17, 18, 34). At $\dot{V}o_{2\,max}$ at 150 m, there was a rise in CVR_{est} and an associated fall in MCA velocity. Despite this, near infrared cerebral oxygenation remained higher than the resting levels. This may be attributable to decreased $\dot{V}o_2$, which has been described previously during exhaustive exercise at sea level (9).

In contrast, at the high altitudes studied, cerebral oxygenation (rSo_2) fell progressively during submaximal exercise, with a further fall at maximal exercise. There was an increase in cerebral deoxygenated hemoglobin with both altitude and exercise. Saito and colleagues (42) showed similar changes in cerebral oxygenation at sea level and a fall at 2,700 and 3,700 m during submaximal exercise, which was equivalent to our level of 50% of $\dot{V}o_{2\,max}$. However, we found that although cerebral oxygen delivery was sustained to 70% $\dot{V}o_{2\,max}$ at sea level, at the high altitudes studied, oxygen delivery peaked at 30% $\dot{V}o_{2\,max}$ and thereafter fell. With partial acclimatization, there appeared to be a trend toward improved cerebral oxygen delivery as seen at 5,260 m. The increase in MCA blood velocity during submaximal exercise may have been due to several factors, the most important of which would appear to be increases in mean blood pressure, because there were only small changes in end-tidal CO_2. Our finding of a gradual fall of cerebral oxygenation during submaximal exercise and $\dot{V}o_{2\,max}$ at altitude may be attributed in part to the gradual fall in oxygen delivery, but an alternative explanation could be a decrease in cerebral oxygen consumption. We believe the slight differences in cerebral oxygenation during submaximal exercise at the two highest altitudes were due to the relatively small change in altitude and to some acclimatization between the two tests.

It has been shown that, during maximal exercise on a rowing machine in elite athletes (33), arterial oxygen saturation and regional cerebral oxygenation decrease but are maintained at resting levels with moderate hyperoxia (inspired oxygen fraction of 0.3). Exercise performance was also elevated without a change in muscle oxygenation, indicating that the cerebral hypoxia rather than muscle hypoxia appears to be a contributing factor for the limitation of exercise capacity. There was an observed reduction in arterial CO_2 at maximal exercise. In a second sea level study by the same group, cerebral perfusion was shown to increase in excess of the increases in the global cerebral metabolic activity during the brain activation associated with exercise and that lactate supplements glucose as energy fuel for the brain when the plasma lactate level is elevated. Furthermore, as evidenced by mean MCA velocity determined by transcranial Doppler, cerebral perfusion was enhanced and cerebral oxygenation determined by near-infrared spectroscopy suggested flow increased to a larger extent than the corresponding metabolic oxygen demand (17).

We found no difference in resting CVR_{est} between the different altitudes, although there was a nonsignificant reduction of resting CVR_{est} with increasing altitude. CVR_{est} appeared to change in two distinct phases with exercise. Up to 50% of $\dot{V}o_{2\,max}$, there was a tendency for a small reduction in CVR_{est}, which was associated with a fall in arterial oxygen saturation and a rise in end-tidal CO_2. These changes would tend to increase cerebral blood flow, and this was reflected in the rise in cerebral oxygen delivery observed at all altitudes at 30% submaximal exercise. There appeared to be a second phase between 70% $\dot{V}o_{2\,max}$ and $\dot{V}o_{2\,max}$. In this phase, there was a marked rise in CVR_{est} at all altitudes, and this is associated with falls in end-tidal CO_2 and small rises in arterial oxygen saturation. Both of these changes would tend to decrease cerebral perfusion, and again this was reflected in the reduction of cerebral oxygen delivery observed at all altitudes at $\dot{V}o_{2\,max}$. Somewhat surprisingly, we found no direct correlation between end-tidal CO_2 and CVR_{est}. However, CVR_{est} is a product of the complex dynamic interrelationship between all variables mentioned above as well as changes in hypoxic and hypercapnic ventilatory responses and cerebrovascular responsiveness to CO_2.

The factors limiting exercise at altitude may be different from those that limit exercise at sea level and may include diffusion limitation of $\dot{V}o_2$ in the alveolus, the work of ventilation, respiratory muscle fatigue, and the possible steal of blood from limb locomotor muscles to respiratory muscles (8, 10, 30). The perception of dyspnea is also increased during exercise at altitude (5), which may lead to the premature ending of exercise. At altitude, $\dot{V}o_2$ in the lung is diffusion limited (52), and this is further exacerbated by exercise. Our results do not support a diffusion limit of CO_2 at $\dot{V}o_{2\,max}$ at altitudes up to 5,260 m, but further studies are required with measurements of Pa_{CO_2}. Assessment of other vascular beds, such as exercising muscle, using near-infrared techniques could be used to determine whether there were significant steals of blood either to or from the cerebral circulation at $\dot{V}o_{2\,max}$. These techniques have been successfully used by Nielsen and colleagues at sea level (33).

Our findings of reduced cerebral oxygen delivery and increased CVR_{est} during exercise above 50% of maximum exercise at altitude may relate to the pathogenesis of AMS and HACE. Exercise is likely to exacerbate AMS through increased hypoxia and sodium retention (55), and our results confirm that the brain is subjected to increasing hypoxia during exercise. Our results may explain the deterioration seen in the accuracy of marksmanship caused by acute exposure to altitude and independent of exercise (47) as well as transient and focal neurological deficits occurring at altitude (2, 32). The large rises in blood pressure observed on exercising close to or at $\dot{V}o_{2\,max}$ could explain some of the focal and global transient and permanent neurological events observed at high altitude. Clinical examination at a later time point might miss the period

of profound hypertension. It is also of interest that the standard formula of 220 − age (yr) used to predict maximal heart rate provided a good estimate at 150 m but increasingly underestimated maximal heart rate at each of the high altitudes. This finding has implications for studies using this formula for predicting energy expenditure or work rate during exercise at altitude.

The reduction in cerebral oxygenation we demonstrated at submaximal exercise is relevant for normal climbing at $\dot{V}o_2$ of 50–75% $\dot{V}o_{2\,max}$ (39). The finding that mountaineers with a more vigorous ventilatory response to hypoxia have more residual neurobehavioral impairment may be a result of reduced cerebral oxygen delivery (13). The hypercapnic vasoconstriction and subsequent reduced cerebral oxygenation might be due to a hypocapnic-driven reduction in cerebral blood flow (13). Schoene and colleagues (44) showed that the fall in arterial saturation on exercise at altitude was actually greater in subjects with a low hypoxic ventilatory drive. The observed reduction of cerebral oxygen delivery during exercise may be more important than absolute altitude in determining the development of AMS. At any given altitude, arterial and cerebral oxygenations are a dynamic variable dependent on absolute altitude, oxygen delivery, and $\dot{V}o_2$. A resting individual at a higher altitude may have the same cerebral oxygenation as an exercising individual at a lower altitude. Both subjects are at the same "virtual" altitude. Assessing cumulative hypoxic insult (time at a virtual altitude) over a 24-h period might more accurately predict the hypoxic stress an individual has experienced.

The limitations of the near-infrared cerebral spectroscopy method have been reviewed (43, 37). The two-sensor technique eliminates the contribution from the scalp and skull, thereby giving a measurement of tissue oxygenation at a depth of 2.5–5.0 cm. Concerns over contamination of the intracerebral readings with scalp blood flow have been raised in the past. Providing the spacing between the scalp detectors is adequate, scalp flow makes no significant contribution. This was demonstrated using laser Doppler velocimetry and occlusion of scalp flow using a pneumatic tourniquet (35). Near-infrared spectroscopy provides a measure of the proportion of blood that is oxygenated. It does not distinguish how much is in the arterial or venous part of the vascular bed. The proportion of total blood in the brain has been estimated to be 28% arterial and 72% venous (29). In this study, we assumed that neither hypoxia nor exercise affects the arteriovenous partitioning. However, partitioning of the arterial and venous volumes in the brain under hypoxic conditions at rest has been modeled (56), and it is possible that further changes could occur with exercise.

The transcranial Doppler technique is operator dependent and requires careful focusing of the ultrasound probe on the MCA. We standardized this as far as possible by using one experienced operator (28). We cannot be certain whether arterial diameter remained constant during the exercise tests at altitude, but other studies at sea level found no changes with either decreases or increases in Pa_{CO_2} (45) or during hypocapnia alone (49). Jorgensen and colleagues (24) showed that the increase in regional cerebral perfusion during exercise at sea level occurred in the MCA territory, with increases in mean MCA blood velocities of 19–32%. However, it has been suggested that much of the increase in MCA blood velocity in response to exercise could arise as an artifact from the increase in amplitude and frequency of the arterial pressure waveform used in Doppler ultrasound studies (38). Nevertheless, cerebral blood flow measured by ^{133}Xe clearance increased by 31% during submaximal exercise at sea level (48). Our finding of a 15% increase in MCA blood velocity was similar to the 14% reported by Hellstroem and colleagues (11), who combined duplex ultrasonography and transcranial Doppler ultrasonography. Our results are also comparable to those reported by Huang and colleagues (15), who, on acute exposure to 4,300 m, recorded increases in internal carotid flow velocity of 15–33% on exercising at 45 and 72% $\dot{V}o_{2\,max}$. Hellstroem and colleagues (11) performed a study at sea level in which a reduction in MCA blood velocity was found at 80–90% of maximal exercise. This was associated with a reduction of Pa_{CO_2}, again similar to our findings at 150 m. When exercising at 96% $\dot{V}o_{2\,max}$ at high altitude, Huang and colleagues (15) noted a small fall in internal carotid flow velocity, but flow remained higher than resting levels in contrast to our study.

Our results are consistent with the hypothesis that cerebral blood flow provides an important signal to the central nervous system and may become a factor limiting exercise at altitude, rather than cardiorespiratory capacity and muscle fatigue (25). Our finding of considerable reductions in cerebral oxygen delivery and cerebral oxygenation during exercise at altitude suggest that these may provide the critical signals. The reduction of cerebral oxygenation during exercise, if it persists during altitude acclimatization, may explain why $\dot{V}o_{2\,max}$ is reduced despite normalization of arterial oxygen content (7). Reduction in cerebral oxygenation during exercise may exacerbate the neurological features of AMS and contribute to the development of HACE and other neurological deficits. Our results lend credence to the time-honored advice to avoid strenuous exercise on arrival at high altitude.

ACKNOWLEDGMENTS

We are grateful to QinetiQ staff for assistance in the design and construction of Alticycle. The pulse oximeter was loaned by Freelance Surgical, Bristol, UK, and the COLIN CBM-7000 monitor by ScanMed Medical Instruments, Moreton in the Marsh, UK. Margaret Richards provided invaluable secretarial assistance.

GRANTS

The work was supported by the Mount Everest Foundation.

REFERENCES

1. **Ainslie PN and Poulin MJ.** Ventilatory, cerebrovascular, and cardiovascular interactions in acute hypoxia: regulation by carbon dioxide. *J Appl Physiol* 97: 149–159, 2004.
2. **Basnyat B, Wu T, and Gertsch JH.** Neurological conditions at altitude that fall outside the usual definition of altitude sickness. *High Alt Med Biol* 5: 171–179, 2004.
3. **Bircher HP, Eichenberger U, Maggiorini M, Oelz O, and Bartsch P.** Relationship of mountain sickness to physical fitness and exercise intensity during ascent. *J Wilderness Med* 5: 302–311, 1994.
4. **Buchfurher MJ, Hansen JE, Robinson TE, Sue DY, Wasserman K, and Whipp BJ.** Optimizing the exercise protocol for cardiopulmonary assessment. *J Appl Physiol* 55: 1558–1564, 1983.
5. **Burki NK, McConnell JW, Ayub M, and Liles RM.** Effects of acute prolonged exposure to high-altitude hypoxia on exercise-induced breathlessness. *Clin Sci (Lond)* 96: 327–333, 1999.
6. **Burtscher M, Bachmann O, Hatzl T, Hotter B, Likar R, Philadelphy M, and Nachbauer W.** Cardiopulmonary and metabolic responses in healthy elderly humans during a 1-week hiking programme at high altitude. *Eur J Appl Physiol* 84: 379–386, 2001.

7. **Calbet JAL, Boushel R, Radegran G, Sondergaard H, Wagner PD, and Saltin B.** Why is $\dot{V}O_{2\,max}$ after altitude acclimatization still reduced despite normalization of arterial O_2 content? *Am J Physiol Regul Integr Comp Physiol* 284: R304–R316, 2003.
8. **Cibella F, Cuttita G, Romano S, Grassi B, Bonsignore G, and Milic-Emili J.** Respiratory energetics during exercise at high altitude. *J Appl Physiol* 86: 1785–1792, 1999.
9. **Dalsgaard MK, Ogoh S, Dawson EA, Yoshiga CC, Quistorff B, and Secher NH.** Cerebral carbohydrate cost of physical exertion in humans. *Am J Physiol Regul Integr Comp Physiol* 287: R534–R540, 2004.
10. **Gudjonsdottir M, Appendini L, Baderna P, Purro A, Patessio A, Villanis G, Pastorelli M, Sigurdsson SB, and Donner CF.** Diaphragm fatigue during exercise at high altitude: the role of hypoxia and workload. *Eur Respir J* 17: 674–680, 2001.
11. **Hellstroem G, Fischer-Colbrie W, Wahlgren NG, and Jogestrand T.** Carotid artery blood flow and middle cerebral artery blood flow velocity during physical exercise. *J Appl Physiol* 81: 413–418, 1996.
12. **Henson IC, Calalang C, Temp JA, and Ward DS.** Accuracy of a cerebral oximeter in healthy volunteers under conditions of isocapnic hypoxia. *Anesthesiology* 88: 58–65, 1998.
13. **Hornbein TF, Townes BD, Schoene RB, Sutton JR, and Houston CS.** The cost to the central nervous system of climbing to extremely high altitude. *N Engl J Med* 321: 1714–1719, 1989.
14. **Huang SY, Moore LG, McCullough RE, McCullough RG, Micco AJ, Fulco C, Cymerman A, Manco-Johnson M, Weil JV, and Reeves JT.** Internal carotid and vertebral arterial flow velocity in men at high altitude. *J Appl Physiol* 63: 395–400, 1987.
15. **Huang SY, Tawney KW, Bender PR, Groves BM, McCullough RE, McCullough RG, Micco AJ, Manco-Johnson M, Cymerman A, Greene ER, and Reeves JT.** Internal carotid flow velocity with exercise before and after acclimatisation to 4,300 m. *J Appl Physiol* 71: 1469–1476, 1991.
16. **Humphey PRD.** Clinical relevance of measurements of cerebral blood flow. *Br J Hosp Med* 26: 233–241, 1981.
17. **Ide K, Horn A, and Secher NH.** Cerebral metabolic response to submaximal exercise. *J Appl Physiol* 87: 1604–1608, 1999.
18. **Ide K and Secher NH.** Cerebral blood flow and metabolism during exercise. *Prog Neurobiol* 61: 397–414, 2000.
19. **Imray CH, Barnett NJ, Walsh S, Clarke T, Morgan J, Hale D, Hoar H, Mole D, Chesner I, and Wright AD.** Near-infrared spectroscopy in the assessment of cerebral oxygenation at high altitude. *Wilderness Environ Med* 9: 198–203, 1998.
20. **Imray CH, Brearey S, Clarke T, Hale D, Morgan J, Walsh S, and Wright AD.** Cerebral oxygenation at high altitude and the response to carbon dioxide, hyperventilation and oxygen. *Clin Sci (Colch)* 98: 159–164, 2000.
21. **Imray CH, Clarke T, Forster PJ, Harvey TC, Hoar H, Walsh S, and Wright AD.** Carbon dioxide contributes to the beneficial effect of pressurization in a portable hyperbaric chamber at high altitude. *Clin Sci (Colch)* 100: 151–157, 2001.
22. **Imray CH, Mead MK, Thacker AJ, and Dimitri WR.** Blood pressure manipulation during loco-regional anaesthetic carotid surgery. *Br J Anaesth* 88: 303–304, 2002.
23. **Jensen JB, Wright AD, Lassen NA, Harvey TC, Winterborn MH, Raichle ME, and Bradwell AR.** Cerebral blood flow in acute mountain sickness. *J Appl Physiol* 69: 430–433, 1990.
24. **Jorgensen LG, Perko G, and Secher NH.** Regional cerebral artery mean flow velocity and blood flow during dynamic exercise in humans. *J Appl Physiol* 73: 1825–1830, 1992.
25. **Kayser B.** Exercise starts and ends in the brain. *Eur J Appl Physiol* 90: 411–419, 2003.
26. **Kellogg RH.** The role of CO_2 in altitude acclimatization. In: *The Regulation of Human Respiration*, edited by Cunningham DJC and Lloyd BB. Oxford, UK: Blackwell Scientific Publications, 1963, p. 374–394.
27. **Lavi S, Egbarya R, Lavi R, and Jacob G.** Role of nitric oxide in the regulation of cerebral blood flow in humans: chemoregulation versus mechanoregulation. *Circulation* 107: 1901–1905, 2003.
28. **Lennard NS, Vijayasekar C, Tiivas C, Chan CWM, Higman DJ, and Imray CHE.** Control of emboli in patients with recurrent or crescendo transient ischaemic attacks using preoperative transcranial Doppler-directed Dextran therapy. *Br J Surg* 90: 166–170, 2003.
29. **McCormick PW, Stewart M, Goetting MG, and Balakrishnan G.** Regional cerebrovascular oxygen saturation measured by optical spectroscopy in humans. *Stroke* 22: 596–602, 1991.
30. **Mognini P, Saibene F, and Veicsteinas A.** Ventilatory work during exercise at high altitude. *Int J Sports Med* 3: 33–36, 1982.
31. **Moller K, Paulson OB, Hornbein TF, Colier WN, Paulson AS, Roach RC, Holm S, and Knudsen GM.** Unchanged cerebral blood flow and oxidative metabolism after acclimatization to high altitude. *J Cereb Blood Flow Metab* 22: 118–126, 2002.
32. **Murdoch DR.** Focal neurological deficits associated with high altitude. *Wilderness Environ Med* 7: 79–80, 1996.
33. **Nielsen HB, Boushel R, Madsen P, and Secher NH.** Cerebral desaturation during exercise reversed by O_2 supplementation. *Am J Physiol Heart Circ Physiol* 277: H1045–H1052, 1999.
34. **Nielsen HB, Boesen M, and Secher NH.** Near-infrared spectroscopy determined brain and muscle oxygenation during exercise with normal and resistive breathing. *Acta Physiol Scand* 171: 63–70, 2001.
35. **Owen-Reece H, Elwell CE, Wyatt JS, and Delpy DT.** The effect of scalp ischaemia on measurement of cerebral blood volume by near-infrared spectroscopy. *Physiol Meas* 17: 279–286, 1996.
36. **Pattinson K, Myers S, and Gardner-Thorpe C.** Problems with capnography at high altitude. *Anaesthesia* 59: 69–72, 2004.
37. **Pattinson K, Clutton-Brock T, and Imray C.** Validity of near-infrared cerebral spectroscopy. *Anaesthesia* 59: 507–508, 2004.
38. **Poulin MJ, Syed RJ, and Robbins PA.** Assessments of flow by transcranial Doppler ultrasound in the middle cerebral artery during exercise in humans. *J Appl Physiol* 86: 1632–1637, 1999.
39. **Pugh LGCE.** Muscular exercise on Mt. Everest. *J Physiol* 141: 233–261, 1958.
40. **Ravenhill TH.** Some experiences of mountain sickness in the Andes. *J Trop Med Hyg* 16: 313–320, 1913.
41. **Roach RC, Maes D, Sandoval D, Robergs RA, Icenogle M, Hinghofer-Szalkay H, Lium D, and Loeppky JA.** Exercise exacerbates acute mountain sickness at simulated high altitude. *J Appl Physiol* 88: 581–585, 2000.
42. **Saito S, Nishihara F, Takazawa T, Kanai M, Aso C, Shiga T, and Shimada H.** Exercise-induced cerebral deoxygenation among untrained trekkers at moderate altitudes. *Arch Environ Health* 54: 271–276, 1999.
43. **Schindler E, Zickmann B, Muller M, Boldt J, Knoll J, and Hernpelmann G.** Cerebral oximetry by infrared spectroscopy in comparison with continuous measurement of oxygen saturation of the jugular vein bulb in intervention of the internal carotid artery. *Vasa* 24: 168–175, 1995.
44. **Schoene RB, Lahiri S, Hackett PH, Peters RM, Milledge JS, Pizzo CJ, Sarnquist FH, Boyer SJ, Graber DJ, Maret KH, and West JB.** Relationship of hypoxic ventilatory response to exercise performance on Mount Everest. *J Appl Physiol* 56: 1478–1483, 1984.
45. **Serrador JM, Picot PA, Rutt BK, Shoemaker JK, and Bondar RL.** MRI measures of middle cerebral artery diameter in conscious humans during simulated orthostasis. *Stroke* 31: 1672–1678, 2000.
46. **Stoneham MD and Warner O.** Blood pressure manipulation during awake carotid surgery to reverse neurological deficit after carotid cross-clamping. *Br J Anaesth* 87: 641–644, 2001.
47. **Tharion WJ, Hoyt RW, Marlowe BE, and Cymerman A.** Effects of high altitude and exercise on marksmanship. *Aviat Space Environ Med* 63: 114–117, 1992.
48. **Thomas SN, Schroeder T, Secher NH, and Mitchell JH.** Cerebral blood flow during submaximal and maximal dynamic exercise in humans. *J Appl Physiol* 67: 744–748, 1989.
49. **Valdueza JM, Balzer JO, Villringer A, Vogl TJ, Kutter R, and Einhaupl KM.** Changes in blood flow velocity and diameter of the middle cerebral artery during hyperventilation: assessment with MR and transcranial Doppler sonography. *Am J Neuroradiol* 18: 1929–1934, 1997.
50. **Vogel JA and Harris CW.** Cardiopulmonary responses of resting man during early exposure to high altitude. *J Appl Physiol* 22: 1124–1128, 1967.
51. **Vogel JA, Hansen JE, and Harris CW.** Cardiovascular responses in man during exhaustive work at sea level and high altitude. *J Appl Physiol* 23: 531–539, 1967.
52. **West JB, Boyer SJ, Graber DJ, Hackett PH, Maret KH, Milledge JS, Peters RM, Pizzo CJ, Samaja M, Sarnquist FH, Schoene RB, and Winslow RM.** Maximal exercise at extreme altitudes on Mount Everest. *J Appl Physiol* 55: 688–698, 1983.
53. **Whipp BJ, Davis JA, Torres F, and Wasserman K.** A test to determine the parameters of aerobic function during exercise. *J Appl Physiol* 50: 217–221, 1981.
54. **Williams IM, Voha R, Farrel A, Picton AJ, Mortimer AJ, and McCollum CN.** Cerebral oxygen saturation, transcranial Doppler ultrasonography and stump pressure in carotid surgery. *Br J Surg* 81: 960–964, 1994.
55. **Withey WR, Milledge JS, Williams ES, Minty BD, Bryson EI, Luff NP, Older MW, and Beeley JM.** Fluid and electrolyte homeostasis during prolonged exercise at altitude. *J Appl Physiol* 55: 409–412, 1983.
56. **Wolff CB and Imray CHE.** Partitioning of arterial and venous volumes in the brain under hypoxic conditions. *Adv Exp Med Biol* 540: 19–23, 2003.

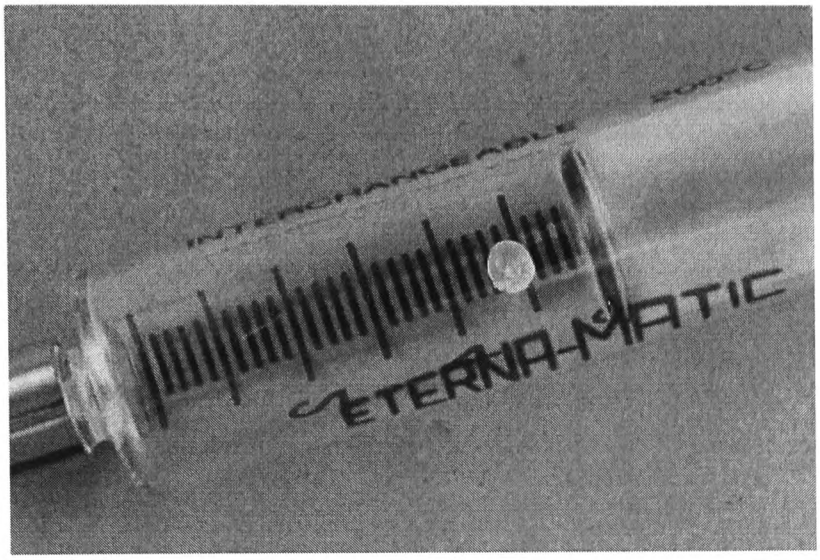


Figure 1

due to a failure on our part to completely remove packaging material used to prevent damage to the barrel prior to assembly. Since becoming aware of the potential for this type of incident we have reviewed and improved our packaging methods for this device to remove the potential for a recurrence of this type of incident.

We thank Dr Fawcett for bringing this matter to our attention.

T. Evans
Product Manager,
SIMS Portex Ltd,
Hythe, Kent CT21 6JL

Monitors of cerebral oxygenation

'The unacceptably high failure rate of the recently introduced Critikon 2020 will limit or prevent its clinical use' (*Anaesthesia* 1997; **52:** 136–40). Our experience of the Critikon 2020 does not reflect the authors. Satisfactory data collection has been achieved during 15 carotid endarterectomies. We have encountered problems with diathermy interference and the partial loss of a trace due to movement of the sensor (caused by the surgeon). The Critikon 2020 was also used to perform 130 field studies up to an altitude of 4670 m and in temperatures ranging from −11 °C to 85 °C. Power was obtained from a 2-kW Honda generator. Data collection was satisfactory (only one trace was unacceptable). On the same expedition we experienced equipment failures with the pulse oximeters, capnographs and the blood gas analyser.

Like McKeating *et al.* we experienced more data loss in young males, who appeared to have a combination of low hairlines and 'thickset' skulls. Signal loss was greatest during the hyperventilation studies and was related to movement of the subject's head. We found the Critikon 2020 disposable adhesive fixation pads unsatisfactory and used a blue-line tubifast bandage (Seton Healthcare Group plc, Tubiton House, Oldham OL1 3HS) to keep the sensor in place. All subjects were monitored in the lying position after a 5-min resting phase. Data from the monitor were logged continuously to a Toshiba Satellite 200CDS Computer. Data sampling was at intervals of 1 s, and the Interlock hold time was set at 120 s. We feel these settings may be important in improving data collection.

Our experience of the Critikon 2020 would suggest that it is at least as reliable as other standard clinical monitoring systems and we do not accept the authors conclusion regarding reliability.

C. Imray
C. Knickenberg
Walsgrave Hospital, Coventry

A dual technique for identification of the epidural space

Jacob and Tierney describe a novel and innovative method for teaching the skills required for the identification of the epidural space (*Anaesthesia* 1997; **52:** 141–3). Although we acknowledge the advantages of a method of involving both student and tutor in this difficult technique, we question the wisdom of encouraging the use of air to define the loss of resistance. The disadvantages of a 'loss of resistance to air' are well documented and include air embolism, cauda equina compression and an increased incidence of inadvertent dural puncture and incomplete block [1–5]. Although many anaesthetists regard these disadvantages as contentious it would seem sensible to teach inexperienced anaesthetists a technique which is as safe as possible. It could be argued that this new dual technique allows an inexperienced operator to develop a feel for entering the dural space which can then be applied to a saline-based method but this then negates the benefit of such close supervision when this changeover is made. If the advantages of saline are not stressed, an increasing number of anaesthetists will be encouraged to perpetuate an inferior technique.

R. J. H. Baylis
J. E. Cropp
Salisbury District Hospital,
Salisbury,
Wiltshire SP2 8BJ

References

1 Sethna NF, Berde CB. Venous air embolism during identification of the epidural space in children. *Anesthesia and Analgesia* 1993; **76:** 925–7.
2 Nay PG, Milaszkiewicz R, Jothilingam S. Extradural air as a cause of paraplegia following lumbar analgesia. *Anaesthesia* 1993; **48:** 402–4.

contralateral lesions leading to velocity enhancement but no filling defect. All were asymptomatic. Twenty-four patients had abnormal intraoperative scans. Thirteen patients had visible kinking of the ICA or reperfusion hyperaemia; 12 of these patients had normal 6-week scans and one had a mild residual kink but no symptoms. Eleven patients had visible colour-filling defects and significant velocity enhancement. Nine of these were reopened and refashioned. Subsequent duplex imaging was satisfactory in all cases and 6-week scans were normal. One patient had an occluded ICA at operation and developed a dense stroke after operation. Another had residual raised velocities distally which remained at 6 weeks. This patient had no symptoms.

Conclusion: Intraoperative velocity measurements alone cannot be relied upon as an indication for reoperation. Significant velocity enhancement combined with a visible filling defect appears to represent a satisfactory criterion for reoperation. There were no complications as a result of reoperation. There was no early restenosis in the whole group and there were no neurological sequelae in any patient with a satisfactory scan using the above criteria.

Transcranial Doppler-directed dextran therapy in the prevention of postoperative carotid thrombosis

P. Hayes, N. Lennard, J. Smith, R. Abbott, D. Evans, N. London, P. Bell and A. R. Naylor
Royal Infirmary, Leicester, UK

Background: Evidence suggests that embolization precedes carotid thrombosis, a previously unpredictable event complicating 2–3 per cent of all carotid endarterectomies. It was hypothesized that dextran 40 therapy might prevent progression to complete thrombosis in high-risk patients.

Methods: Between October 1995 and July 1998, 400 consecutive patients were monitored following carotid endarterectomy using transcranial Doppler ultrasonography. Those with sustained embolization (more than 25 in 10 min) or those with emboli that distorted the middle cerebral artery waveform were commenced on an incremental dextran 40 infusion.

Results: Two hundred and sixteen patients (54 per cent) had one or more emboli detected (96 per cent within 2 h of flow restoration) but only 15 (4 per cent) required dextran therapy. Embolization ceased in each case although the dextran dose had to be adjusted in four. In one of the latter patients, embolization recurred on day 5 but was again controlled with high-dose dextran. Overall, the death and any stroke rate was 2 per cent and no patient suffered a stroke due to carotid thrombosis.

Conclusion: A few patients develop sustained embolization following carotid endarterectomy which, in previous studies, has been shown to be highly predictive of carotid thrombosis. The authors' experience to date suggests that dextran can stop this phase of embolization and prevent progression to complete carotid thrombosis. However, the dose of dextran has to be adjusted in 25 per cent of patients (i.e. blind administration of dextran may not be effective) and, very rarely, embolization may recur later.

Near-infrared spectroscopic monitoring of patients undergoing carotid endarterectomy under locoregional anaesthesia

D. J. Williams, P. Laws, C. Imray, A. W. Lambert and M. Horrocks
Walsgrave Hospital, Coventry and Royal United Hospital, Bath, UK

Background: The level of cerebral desaturation, which is associated with a change in level of consciousness during carotid endarterectomy, was measured by near-infrared spectroscopy.

Methods: Patients were recruited in two centres over 24 months. Surgery was performed under deep and superficial cervical block using 0·5 per cent bupivacaine, with temazepam as a premedication. Cerebral oxygenation was measured by Critikon 2020 near-infrared spectrophotometers (Johnson and Johnson Medical, Newport, UK).

Results: Forty-nine procedures were performed on 45 patients (39 men; age range 52–84 (mean 68) years). Recordings were made from the ipsilateral frontal site in 38 patients, from the ipsilateral temporal site in 23 and bifrontally in eight patients. Monitoring failed in three subjects. Percentage changes in regional cerebral oxygen saturation are detailed below.

	Change in saturation (%)	
Site	Symptomatic (n = 8)	Asymptomatic (n = 41)
Frontal (ipsilateral)	6·4 (2·5–14)*	2·4 (0–8)*
Temporal	3·8 (2–8)*	1·5 (0–8)
Frontal (contralateral)	2 (0–4)	0·2 (0–0·5)

Values are mean (range). *$P < 0·01$

Conclusion: Significantly different levels of cerebral desaturation occur in patients with neurological compromise during carotid endarterectomy compared with those who are unaffected.

Transcranial Doppler ultrasonography as a predictor of haemodynamically significant carotid stenosis

S. Byrd, J. Wolfe, A. Nicolaides, G. Stansby, N. Cheshire, D. Thomas and A. Mansfield
St Mary's Hospital, London, UK

Background: Transcranial Doppler (TCD) ultrasonography can detect evidence of collateral flow across the anterior communicating artery and/or the posterior communicating artery, which occurs when there is significant alteration of 'inflow' to the brain. The aim of the study was to determine the blood flow velocity produced by a carotid stenosis which produces this haemodynamic effect on the cerebral circulation and evokes collateral circulation.

Methods: Forty-eight patients with varying degrees of carotid stenosis (10 per cent to occlusion) who underwent both carotid duplex and TCD examination were reviewed. An ATL HDI 3000 ultrasound system was used for the carotid and TCD studies. The carotid examination recorded peak-systolic velocity (PSV) and end-diastolic velocity (EDV) in the carotid systems bilaterally. TCD recorded Doppler spectra from the bilateral

the paper (i.e. the time without accurate infusion to the patient), and will considerably affect its clinical recommendations. However, especially in infants, when several drugs are needed, any increase of the infusion rate is limited. Therefore, if one is concerned about this problem, the clinical practice should be changed to using low compliant syringes, that is small volume syringes, and using low compliant–low volume infusion lines as are common in neonatal practices. Special care must be taken that the syringes are filled carefully without air bubbles.

H. Wissing
Frankfurt am Main
Germany

1 Kern H, Kuring A, Redlich U, *et al.* Downward movement of syringe pumps reduces syringe output. *Br J Anaesth* 2001; 86: 828–31

Editor—We read with interest Wissing's letter commenting on our article.

Indeed, Wissing correctly identified a conversion error. This occurred while transforming the infusion rate of the syringe pumps for the compliance measurements from $ml\,h^{-1}$ into $\mu l\,s^{-1}$. The reported compliances therefore have been divided by 60. The corrected results for the compliance of the different systems resulted in identical values for the Injectomat-C and the Perfusor fm of $1.4\,\mu l\,mm\,Hg^{-1}$. The compliance of the IVAC 770 system was greater, at $1.7\,\mu l\,mm\,Hg^{-1}$. There was a statistically significant positive correlation ($r^2=0.863$, $P<0.05$) between time without infusion and the compliance of the system. This correlation has been tested again and remained unchanged. We apologize for this error and thank Wissing for pointing it out.

However, the main results of our work are not affected by this mistake. We measured the volume shift ($\Delta v/\Delta p$) correctly in our experiments. Compliance is a calculated value as indicated in the Methods section. However, we would like to emphasize that our model used a fixed pressure of 8 mm Hg working against the infusion, which is comparable to central venous pressures encountered in daily clinical practice. This is in contrast to previous investigations which used syringes working against ambient air pressure. We took great care to avoid the occurence of any air bubbles while filling the syringes and lines in our experimental setting. Before starting to take measurements, the equipment was visually checked for gas bubbles.

The main goal was to investigate systematically the daily clinical observation of haemodynamic instability and sometimes even backward flow in the infusion lines while lowering the height of the syringe pumps towards the end of paediatric cardiac surgery. This question was investigated with the equipment used in daily clinical practice. Obviously, there is equipment available with better elastic properties (compliance). However, we consider the other tubing, which is made for neonatal intensive care purposes, to be too short for daily use in the operating room. We do not think that a broad discussion of all possible elastic and non-elastic components of the infusion systems would increase the clinically relevant information. As we stated, we did not endorse any particular manufacturer or model of infusion device.

Our main conclusion was that, whenever possible, the height of the syringe pumps should not be changed during transport. If changes in the position of the syringe pumps are inevitable, we proposed a drug dilution achieving a flow rate of at least $5\,ml\,h^{-1}$. Obviously, this recommendation has to be balanced against possible deleterious effects caused by fluid overload, particularly in paediatric patients.

H. Kern
Berlin
Germany

Blood pressure manipulation during loco-regional anaesthetic carotid surgery

Editor—We read with interest the three case reports regarding blood pressure manipulation during local anaesthetic carotid surgery.[1] Our experience with over 200 local anaesthetic carotid endarterectomy (CEA) patients, approximately 35% of whom subsequently underwent urgent coronary artery bypass graft (CABG) surgery, is very similar. However, we feel that there are a number of additional points that should be considered.

In patients requiring CABG and CEA, it is our strategy to perform local anaesthetic CEA(s) followed at a later date by the cardiac surgery. In a few high risk patients we found coronary angioplasty and/or stenting of target lesions to be beneficial prior to the staged CEA/CABG.

Cross-clamping usually results in a moderate rise in arterial blood pressure. Whilst the carotid artery is clamped, a subsequent fall in arterial pressure can result in the development of a neurological deficit. Like the authors, we feel pharmacological augmentation of the blood pressure is useful and sometimes reverses the deficit. However, this augmentation clearly increases cardiac work and oxygen consumption, and we have seen angina, and occasionally myocardial infarction and pulmonary oedema, as a direct result of this manipulation.

Angina occurring during the cross-clamp phase will often respond to coronary artery vasodilators. However, an exaggerated fall in blood pressure can then occur and this can be associated with neurological deterioration. We have encountered two patients who were already on high doses of i.v. glyceryl trinitrate who developed angina when cross-clamped. In these two patients, we found insertion of a carotid artery shunt led to immediate relief of their angina, as the arterial pressure returned to pre-clamp levels.

Our practice is to use near infrared spectroscopy to measure cerebral oxygenation during awake carotid surgery. Cross-clamping usually results in a fall in cerebral oxygenation, and this fall is partially reversed by raising the blood pressure, which adds further support to blood pressure augmentation during the cross-clamp phase.

We believe that local anaesthetic carotid surgery allows optimal and integrated treatment of both the neurological and cardiac aspects of these patients. Close cooperation between the vascular anaesthetist, the vascular surgeon, the cardiologist, the cardiac-surgeon and the patient is clearly vital in this challenging group.

C.H.E. [illegible]
M.K.Mead
A.J. Thacker
W.R. Dimitri
Coventry
UK

1 Stoneham MD, Warner O. Blood pressure manipulation during awake carotid surgery to reverse neurological deficit after carotid cross-clamping. *Br J Anaesth* 2001; 87: 641–4

Editor—Thank you for the opportunity to reply to the letter from Imray and colleagues, which appears to be generally supportive of regional carotid surgery. I agree with them and, indeed, discussed in the case report the fact that angina may be precipitated perioperatively in this high-risk group of patients. However, I am curious as to whether the two patients they described, who developed angina following carotid cross-clamping, also developed neurological dysfunction, as shunting is not a conventional therapy for angina and is certainly not without risk itself.[1]

Imray and his anaesthetic colleagues have also rasied a different issue—namely the treatment of patients with combined carotid

and coronary arterial disease. In Oxford, our cardiac surgeons also request that patients with symptomatic carotids and coronaries have endarterectomy performed under regional anaesthesia before they have their coronary artery surgery. This has proved very successful in 20 or so patients, thus far. However, this is not the only solution and there are certainly centres in which patients with those two conditions are operated on synchronously under general anaesthesia.[2]

Finally, the authors do not say what information they gain from using near infrared spectroscopy in addition to that which the conscious patient provides.

M. Stoneham
Oxford
UK

1 Jacobowitz GR, Rockman CB, Lamparello PJ, *et al.* Causes of perioperative stroke after carotid endarterectomy: special considerations in symptomatic patients. *Ann Vasc Surg* 2001; 15: 19–24
2 Farooq MM, Reif TD, Gelabert HA, *et al.* Combined carotid endarterectomy and coronary bypass: a decade of experience at UCLA. *Cardiovasc Surg* 2001; 9: 339–44

Sedative and analgesic practice in the intensive care unit

Editor—I read with interest Soliman, Melot and Vincent's European survey of sedative and analgesic practice in the intensive care unit.[1] This article demonstrated considerable international differences in the use of drugs for this purpose.

However, one factor that was not investigated in the survey or discussed in the accompanying editorial was the use of physical restraints. Whilst restraints are very rarely used in the UK, they are more common in the USA,[2] Canada,[3] Australasia and continental Europe.

Because of the recognized dangers of chemical oversedation, it is tempting to realize the use of physical restraints in UK units. However, this may not be straightforward. Notwithstanding the moral and ethical complexities, physical restraints are associated with a number of disadvantages. They have not been shown to decrease the incidence of self-extubation,[4] and they are associated with certain types of physical injuries.[5] More worryingly, physical restraints have also been associated with sudden death.[6]

In all probability, there are many other reasons why sedation practice varies in Europe and the rest of the world, but the use of physical restraints should be considered with investigating these differences.

A. MacKillop
Manchester
UK

1 Soliman HM, Merlot C, Vincent JL. Sedative and analgesic practice in the intensive care unit: the results of a European survey. *Br J Anaesth* 2001; 87: 186–92
2 Wilson E. Physical restraint of elderly patients in critical care. *Crit Care Nurs Clin North Am* 1996; 8: 65
3 Leith BA. Canadian critical care nurses and physical restraints. *Off J Can Assoc Crit Care Nurs* 1999; 10: 6
4 Freza EE, Carleton GL, Valenziano CP. A quality improvement and risk management initiative for surgical ICU patients. *Am J Med Qual* 2000; 15: 221–5
5 Neufield RR, Libow LS, Foley WJ, *et al.* Restraint reduction reduces serious injuries among nursing home residents. *J Am Geriatr Soc* 1999; 47: 1202–7
6 Miles S. A case of death by physical restraint. *J Am Geriatr Soc* 1996; 44: 291–2

Editor—Dr MacKillop raises an interesting subject when referring to the use of physical restraints. This issue was not addressed in our study, largely because the survey focused on differences in drug selection, rather than the use of sedation *per se*.

In addition, the definition of 'physical restraint' is broad and subjective, and it would have been difficult in a short questionnaire of this type to retrieve valuable information from a simple yes/no question. If asked whether physical restraints were used in their ICU, the vast majority of, if not all, physicians would have to reply 'sometimes'. Further questions would then be needed to define how often and in which patients. Moreover, individual physicians will have different theories as to what constitutes physical restraint, founded on previous experience and background, local practice, and cultural, religious and moral beliefs.

Furthermore, while Dr MacKillop suggests that the use of physical restraints may be used in place of, or to limit, sedation, it is equally possible that some restrained patients may need more sedation due to their agitation at being restrained. There is, in fact, very little published data regarding the use of physical restraints in adult intensive care unit patients—a quick Medline search drew only 10 related publications in the last decade[1–10]—and this interesting topic certainly warrants further study.

J.-L. Vincent
C. Melot
H. Soliman
Brussels
Belgium

1 Happ MB, Kagan SH, Strumpf NE, Evans LK, Sullivan-Marx E. Elderly patient reports of physical restraint experiences in intensive care units. *Am J Crit Care* 2001; 10:168–71
2 Frezza EE, Carleton GL, Valenziano CP. A quality improvement and risk management initiative for surgical ICU patients: a study of the effects of physical restraints and sedation on the incidence of self-extubation. *Am J Med Qual* 2000; 15: 221–5
3 Happ MB. Preventing treatment interference: the nurse's role in maintaining technologic devices. *Heart Lung* 2000; 29: 60–9
4 Bower F, McCullough C. Restraint use in acute care settings: Can it be reduced? *J Nurs Adm* 2000; 30: 592–8
5 Chevron V, Menard JF, Richard JC, Girault C, Leroy J, Bonmarchand G. Unplanned extubation: risk factors of development and predictive criteria for reintubation. *Crit Care Med* 1998; 26: 1049–53
6 Minnick A, Mion L, Leipzig R, Lamb K, Palmer RM. Prevalence and patterns of physical restraint use in the acute care setting. *J Nurs Adm* 1998; 28: 19–24
7 Kanski GW, Janelli LM, Jones HM, Kenneoy MC. Family reactions to restraints in an acute care setting. *J Gerontol Nurs* 1996; 22: 17–22
8 Tominage GT, Ruczwick H, Scannell G, Waxman K. Decreasing unplanned extubations in the surgical intensive care unit. *Am J Surg* 1995; 170: 586–9
9 Scherer YK, Janelli LM, Wu YW, Kuhn MM. Restrained patients: an important issue for critical care nursing. *Heart Lung* 1993; 22: 77–83
10 Hall M, Marr JA. Patient restraint: a new philosophy. *Leadersh Health Serv* 1993; 2: 22–6

Allergy to chlorhexidine-coated central venous catheters revisited

Editor—We read the case report by Stephens and colleagues[1] with interest as the scenario they describe parellels our own recent experiences of the same phenomenon.

A 51-year-old male presented for corpectomy of the 4th cervical vertebra, for relief of severe intractable cervical

Original article

Control of emboli in patients with recurrent or crescendo transient ischaemic attacks using preoperative transcranial Doppler-directed Dextran therapy

N. S. Lennard, C. Vijayasekar, C. Tiivas, C. W. M. Chan, D. J. Higman and C. H. E. Imray

Coventry and Warwickshire County Vascular Unit, Coventry and Warwickshire University Hospitals, Walsgrave Hospital, Clifford Bridge Road, Walsgrave, Coventry CV2 2DX, UK
Correspondence to: Mr C. H. E. Imray (e-mail: chrisimray@aol.com)

Background: Transcranial Doppler (TCD)-directed Dextran 40 treatment after carotid endarterectomy reduces the rate of early postoperative thrombosis. This study assessed the efficacy of intravenous Dextran 40 at controlling symptoms and emboli before elective carotid endarterectomy in patients with recurrent or crescendo transient ischaemic attacks (TIAs).

Methods: In a prospective study, patients with more than 70 per cent internal carotid artery stenosis who had two or more symptomatic episodes within 30 days and TCD-detected microemboli were studied. Dextran 40 was commenced at 20 ml/h and TCD was repeated to reassess the rate of embolization. The infusion was increased in 20-ml/h increments until symptoms and emboli were controlled. The patient then had carotid surgery on the next elective list.

Results: Nineteen patients with internal carotid stenosis greater than 70 per cent, recurrent symptoms and TCD-detected emboli were studied. All patients had symptoms and emboli controlled with Dextran 40. One patient with both unstable angina (awaiting urgent operation) and crescendo TIAs died from a myocardial infarct before undergoing operation. Of the 18 patients who had an operation, one suffered a non-disabling stroke on the third postoperative day.

Conclusion: TCD-directed Dextran 40 offers a safe approach to high-risk patients before elective carotid endarterectomy, and warrants further study.

The presentation based on this paper won the Sol Cohen Prize at the meeting of the Vascular Surgical Society of Great Britain and Ireland, Brighton, UK, November 2001

Paper accepted 15 September 2002

Published online in Wiley InterScience (www.bjs.co.uk). DOI: 10.1002/bjs.4030

Introduction

Stroke is a major cause of morbidity and mortality; it is the third commonest cause of death in the Western world. There were an estimated 133 800 strokes in England and Wales in 1999[1] and carotid artery disease is thought to be responsible for up to 25 per cent of strokes[2]. Of these, approximately 15 per cent will have a warning transient ischaemic attack (TIA). Carotid endarterectomy, combined with maximal medical therapy in selected symptomatic patients, has been shown to be superior to maximal medical therapy in two large prospective randomized trials[3,4].

The risk of stroke is highest after the first TIA; 4–8 per cent of strokes occur in the first month and 12 per cent in the first year[5,6]. The optimal treatment of patients with recurrent or crescendo TIAs is uncertain. Based on the poor outcome of patients with crescendo TIAs with medical treatment alone, an aggressive approach with urgent carotid endarterectomy has been advocated[7]. However, the published results of emergency carotid surgery are variable, with complication rates ranging from no deficit in 12 patients, to an operative mortality rate as high as 20 per cent and neurological deficit in up to 40 per cent of patients in other series[8–14].

The aim of this study was to assess whether preoperative transcranial Doppler-directed intravenous Dextran therapy might control symptoms and emboli prior to elective carotid endarterectomy.

Patients and methods

Between November 1998 and July 2001, 19 patients were recruited into this prospective pilot study. Patients were seen in an open-access carotid duplex clinic, having been referred either by their general practitioner or by a hospital consultant. The vascular unit serves a population of 950 000.

Duplex imaging of both carotid arteries was performed by one of three vascular technologists. An internal carotid artery peak systolic velocity of 200 cm/s was used to define patients with more than 70 per cent stenosis, in accordance with the criteria of the European Carotid Surgery Trialists' Collaborative Group.

Patients who had two or more episodes of transient cerebral or retinal ischaemia within the previous month underwent transcranial Doppler (TCD) ultrasonography of the symptomatic middle cerebral artery using a PC Dop 842 (SciMed, Fishponds, Bristol, UK) with a 2-MHz probe focused on the middle cerebral artery at 4·5–5·5 cm using a sample volume length of 1·1 cm for 1 h. One of three experienced vascular technicians observed the TCD signals for embolic signals by listening for their characteristic sound and spectral appearance, using published identification criteria[15]. All patients had been on antiplatelet therapy at the time they experienced the symptoms.

Patients with internal carotid artery stenosis greater than 70 per cent, ipsilateral middle cerebral artery embolization, and a history of two or more TIAs within the previous month in the appropriate carotid territory were included in the trial.

Patients were admitted to the vascular ward and commenced on an intravenous infusion of Gentran 40® (Dextran 40 intravenous infusion BP, 10 per cent w/v, in glucose intravenous infusion BP, 5 per cent w/v; Baxter Healthcare, Thetford, UK). An initial 20-ml bolus was given, and the infusion was then run at 20 ml/h. Once the Dextran 40 had been running for at least 2 h, TCD scanning was repeated to reassess the rate of embolization. If the patient continued to have emboli, or had further symptoms of cerebral or retinal ischaemia, the rate of the Dextran 40 infusion was increased at increments of 20 ml/h until the symptoms and emboli were controlled. All patients were treated with either aspirin 75–150 mg or clopidogrel 75 mg daily, and with enoxaparin 20 mg daily.

These patients proceeded to carotid endarterectomy on the next available elective list, allowing time for routine surgical work-up. The Dextran 40 infusion was stopped 2 h before operation.

Results

Nineteen patients (13 men) were included in the study; their ages ranged between 38 and 86 years. Fourteen patients had recurrent hemisensory or hemimotor symptoms, and five had recurrent amaurosis fugax. Eight patients had coexisting ischaemic heart disease and two were awaiting coronary artery bypass surgery. One patient was an insulin-dependent diabetic. The number of symptomatic episodes suffered by each patient ranged from two episodes within 10 days to four episodes within 24 h. The number of emboli detected by TCD ultrasonography before institution of the Dextran 40 infusion ranged from two to nine per h. No patient had any recurrent neurological symptoms, and all had their emboli controlled while on the Dextran 40 infusion. Sixteen patients required Dextran 40 at a rate of 20 ml/h, two needed a rate of 40 ml/h and one needed 100 ml/h to abolish the emboli.

Carotid endarterectomy

The time from commencement of the Dextran infusion to carotid endarterectomy ranged from 1 to 10 days. The majority had the operation within 5 days, although one patient with recurrent right hand weakness and coexisting headache required investigation with computed tomography and magnetic resonance angiography, which prolonged the wait before operation. The Dextran was infused continuously until the day of operation in all patients.

All but one of the carotid endarterectomy procedures were performed under locoregional anaesthesia. In these patients, shunting was determined by awake-testing and near-infrared cerebral spectroscopy. In the patient who had general anaesthesia, the need for shunting was determined using standard TCD criteria. All patients were monitored in the immediate postoperative period with TCD ultrasonography, and four patients required a Dextran 40 infusion after operation to control continued embolization.

One patient died before operation. This 79-year-old woman was on the coronary care unit, requiring intravenous nitrates for angina and awaiting urgent coronary artery bypass grafting. She also experienced recurrent episodes of cerebral ischaemia. She was commenced on a Dextran 40 infusion at 20 ml/h, which controlled her symptoms and emboli; however, she developed congestive cardiac failure and suffered a fatal myocardial infarction.

Of 18 patients who underwent carotid endarterectomy, one suffered a non-disabling stroke on the third postoperative day (early carotid occlusion based on duplex imaging). The stroke resolved fully at 6 weeks. Seventeen patients recovered without either neurological or cardiac complications. Four patients developed a minor wound haematoma after operation, but none required surgical intervention. One patient developed moderate renal impairment following preoperative Dextran therapy; however, this resolved fully on conservative management before discharge.

Discussion

TCD monitoring allows continuous non-invasive assessments of middle cerebral artery velocity, which is closely related to cerebral blood flow. It is also possible to measure transient microemboli signals or high-intensity transient signals. Microemboli are a common phenomenon in patients with acute stroke and may continue for some days after the acute event[16]. The presence of microemboli is a significant independent predictor of early recurrence in patients with stroke or TIA of arterial origin[17].

In asymptomatic patients with a critical internal carotid artery stenosis[18] when the microemboli rate was greater than two per hour in the ipsilateral middle cerebral artery, there was an increased risk of developing ischaemia (odds ratio 31 (95 per cent confidence interval (c.i.) 3 to 302); $P = 0{\cdot}005$). In a study[20] of both symptomatic and asymptomatic patients with carotid stenosis greater than 60 per cent, the presence of embolic signals gave an adjusted odds ratio for future TIA or stroke of 8·1 (95 per cent c.i. 1·6 to 41·6); $P = 0{\cdot}01$). The presence of high-intensity transient signals may therefore define a subgroup of patients with a critical stenosis who may be at greater risk of stroke[19].

TCD sensitivity to the presence of particulate emboli can help to guide surgical dissection during carotid endarterectomy, allowing changes in surgical technique or strategy (such as early carotid clamping)[21]. A microemboli signal count greater than 50–100 per h in the early postoperative phase after carotid endarterectomy is also predictive of the development of ipsilateral focal ischaemia[22,23].

Postoperative TCD-detected high-intensity transient signals are almost always platelet aggregates generated by a partially denuded, highly thrombogenic, vascular endothelium. Unchecked, these aggregates may mature into occlusive thromboemboli, resulting in infarcts in succeeding hours or days. Lennard *et al.*[24] found that signs of persistent embolization, characterized by more than 25 high-intensity transient signals in 10 min, consistently preceded injury[24]. Embolization was completely prevented by incremental infusion of Dextran 40. The same workers have now audited 600 consecutive procedures, following the introduction of TCD-directed Dextran therapy, and the rate of thrombotic stroke after carotid endarterectomy fell from 2·7 per cent to zero (eight strokes prevented)[25,26]. Six hours of postoperative TCD monitoring is impractical outside a research programme; however, the technique appears to work in 3 h, and there is evidence that 30 min of monitoring may be adequate[27].

The rheological improvement caused by Dextran 40, together with its effect of decreased platelet adhesiveness and reduced factor VIII activity, is well recognized[28]. It has been further postulated that there is a coating effect on the denuded artery, which decreases electronegativity and increases clot lysability, both of which might make this agent a useful adjunct in preventing graft or endarterectomy-associated thrombosis. It should be noted that Dextran may interfere with cross-matching blood, cause bleeding, renal failure or occasionally acute allergic reaction. In addition, it can precipitate cardiac failure, as happened in the only patient to die in this series.

The study suggested a possible role for TCD in the preoperative management of symptomatic carotid stenosis. It also showed that it is possible to treat recurrent or crescendo TIAs with a combination of aggressive medical therapy and elective surgery. In this study, when emboli were controlled, neurological symptoms stopped. While a single embolus does not cause a TIA, a high embolic load indicates that an individual is at greater risk of further neurological events. As Dextran 40 has no known effect on cholesterol emboli, it could be speculated that the recurrent symptoms controlled by the antiplatelet agent must have been caused by platelet emboli.

The efficacy of medical treatment could be assessed with TCD. Although most of the emboli were controlled with a low dose of Dextran 40, a small number of patients (three of 18) required considerably higher doses. Failure to control either emboli or symptoms with TCD-directed Dextran and adjuvant medical therapy could be an indication for urgent carotid endarterectomy. Patients with symptoms but without emboli, and patients with emboli and no symptoms, were excluded from this study.

If the results of this study are confirmed, there may be important implications regarding the management of recurrent TIAs. All patients would require duplex scanning to determine the state of the ipsilateral internal carotid artery. The presence of a critical internal

carotid artery stenosis would necessitate a TCD study to interrogate the middle cerebral artery for high-intensity transient signals. Medical therapy could then be instigated, and the efficacy of various pharmacological interventions assessed by confirming the control of symptoms and high-intensity transient signals. Elective surgery could then be considered if appropriate. Further study is warranted, in particular to examine how this control might influence the timing of carotid surgery.

References

1 Office for National Statistics. News release. *Health Statistic Quarterly* 2001; **12**: 3–4.

2 Timsit SG, Sacco RL, Mohr JP, Foulkes MA, Tatemichi TK, Wolf PA *et al.* Early clinical differentiation of cerebral infarction from severe atherosclerotic stenosis and cardioembolism. *Stroke* 1992; **23**: 486–491.

3 North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991; **325**: 445–453.

4 European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or mild (0–29%) carotid artery stenosis. *Lancet* 1991; **337**: 1235–1243.

5 Dennis M, Bamford J, Sandercock P, Warlow C. Prognosis of transient ischemic attacks in the Oxfordshire Community Stroke Project. *Stroke* 1990; **21**: 848–853.

6 Heyman A, Wilkinson WE, Hurwitz BJ, Haynes CS, Utley CM, Rosati RA *et al.* Risk of ischemic heart disease in patients with TIA. *Neurology* 1984; **34**: 626–630.

7 Wilson SE, Mayberg MR, Yatsu F, Weiss DG. Crescendo transient ischemic attacks: a surgical imperative. Veterans Affairs Trialists. *J Vasc Surg* 1993; **17**: 249–255.

8 Nehler MR, Moneta GL, McConnell DB, Edwards JM, Taylor LM Jr, Yeager RA *et al.* Anticoagulation followed by elective carotid surgery in patients with repetitive transient ischemic attacks and high-grade stenosis. *Arch Surg* 1993; **128**: 1117–1121.

9 Goldstone J, Moore WS. Emergency carotid artery surgery in neurologically unstable patients. *Arch Surg* 1976; **111**: 1284–1291.

10 Schneider C, Johansen K, Konigstein R, Metzner C, Oettinger W. Emergency carotid thromboendarterectomy: safe and effective. *World J Surg* 1999; **23**: 1163–1167.

11 Brandl R, Brauer RB, Maurer PC. Urgent carotid endarterectomy for stroke in evolution. *Vasa* 2001; **30**: 115–121.

12 Greenhalgh RM, Cuming R, Perkin GD, McCollum CN. Urgent carotid surgery for high-risk patients. *Eur J Vasc Surg* 1993; **7**(Suppl A): 25–32.

13 Mayberg MR, Wilson SE, Yatsu F, Weiss DG, Messina L, Hershey LA *et al.* Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Cooperative Studies Program 309 Trialist Group. *JAMA* 1991; **266**: 3289–3294.

14 Gertler JP, Blankensteijn JD, Brewster DC, Moncure AC, Cambria RP, LaMuraglia GM *et al.* Carotid endarterectomy for unstable and compelling neurologic conditions: do the results justify an aggressive approach? *J Vasc Surg* 1994; **19**: 32–40.

15 Consensus Committee of the Ninth International Cerebral Hemodynamic Symposium. Basic identification criteria of Doppler microembolic signals. *Stroke* 1995; **26**: 1123.

16 Sliwka U, Lingnau A, Stohlmann WD, Schmidt P, Mull M, Diehl RR *et al.* Prevalence and time course of microembolic signals in patients with acute stroke. A prospective study. *Stroke* 1997; **28**: 358–363.

17 Valton L, Larrue V, le Traon AP, Massabuau P, Geraud G. Microembolic signals and risk of early recurrence in patients with stroke or transient ischemic attack. *Stroke* 1998; **29**: 2125–2128.

18 Siebler M, Nachtmann A, Sitzer M, Rose G, Kleinschmidt A, Rademacher J *et al.* Cerebral microembolism and the risk of ischemia in asymtomatic high-grade internal carotid artery stenosis. *Stroke* 1995; **26**: 2184–2186.

19 Babikian VL, Wijman CAC, Hyde C, Cantelmo NL, Winter MR, Baker E *et al.* Cerebral microembolism and early recurrent cerebral or retinal ischemic events. *Stroke* 1997; **28**: 1314–1318.

20 Molloy J, Markus HS. Asymptomatic embolization predicts stroke and TIA risk in patients with carotid artery stenosis. *Stroke* 1999; **30**: 1440–1443.

21 Jansen C, Ramos LMP, van Heeswijk JPM, Moll FL, van Gijn J, Ackerstaff RG. Impact of microembolism and hemodynamic changes in the brain during carotid endarterectomy. *Stroke* 1994; **25**: 992–997.

22 Levi CR, Roberts AK, Fell G, Hoare MC, Royle JP, Chan A *et al.* Transcranial Doppler microembolus detection in the identification of patients at high risk of perioperative stroke. *Eur J Vasc Endovasc Surg* 1997; **14**: 170–176.

23 Levi CR, O'Malley HM, Fell G, Roberts AK, Hoare MC, Royle JP *et al.* Transcranial Doppler detected cerebral microembolism following carotid endarterectomy. High microembolic signal loads predict postoperative cerebral ischaemia. *Brain* 1997; **120**: 621–629.

24 Lennard N, Smith J, Dumville J, Abbott R, Evans DH, London NJ *et al.* Prevention of postoperative thrombotic stroke after carotid endarterectomy: the role of transcranial Doppler ultrasound. *J Vasc Surg* 1997; **26**: 579–584.

25 Hayes PD, Lloyd AJ, Lennard N, Wolstenholme JL, London NJ, Bell PR *et al.* Transcranial Doppler-directed Dextran-40 therapy is a cost-effective method of preventing carotid thrombosis after carotid endarterectomy. *Eur J Vasc Endovasc Surg* 2000; **19**: 56–61.

26 Naylor AR, Hayes PD, Allroggen H, Lennard N, Gaunt ME, Thompson MM *et al.* Reducing the risk of carotid surgery: a 7-year audit of the role of monitoring and quality control assessment. *J Vasc Surg* 2000; **32**: 750–759.
27 Chan CWM, Tiivas C, Pritchard G, Higman CJ, Imray CHE. Postoperative transcranial Doppler monitoring – an early warning device? *Int Angiol* 2000; **19**(Suppl 1): 128.
28 Aberg M, Hedner U, Bergentz SE. Effect of Dextran on factor VIII (antihemophilic factor) and platelet function. *Ann Surg* 1979; **189**: 243–247.

The important thing about promoting safe cycling and walking is that the environment, transport, and urban planning sectors are essential partners. Since 1999 when European Member States adopted the WHO Charter on Transport, Environment and Health, health policymakers have worked alongside colleagues from other sectors to place health and environmental considerations firmly on the agenda of transport and land-use policy-makers. There is no time to lose. Physical inactivity has become one of the leading risk factors for the health of Europeans. Across the WHO European Region, the proportion of deaths attributable to physical inactivity is estimated at 5–10% of the total number of deaths[1]—ie, about 600 000 deaths per year.

Children's health is of immediate concern. In countries where figures are available, the levels of physical activity among children have declined greatly in the past 15 years. The prevalence of overweight and obesity has increased in parallel.

World Health Day was dedicated to "Move for Health" in 2002 and since then a World Day on physical activity takes place annually on May 10. Also in May, 2004, the WHO Global Strategy on Diet and Physical Activity will be discussed at the World Health Assembly. In the European Region, we have emphasised safe walking and cycling, not only to achieve higher levels of physical activity but also better quality of urban life through reduced air pollution, noise, traffic, and congestion.[2] The joint UNECE-WHO Transport, Health and Environment Pan-European Programme (THE PEP) established in 2002 is pushing the agenda forward in the European Region, and at WHO's Fourth Ministerial Conference on Environment and Health, to be held in Budapest, Hungary, in June, 2004, the emphasis will be on children and how to protect their health from environmental hazards. Inactivity is a hazard. It also costs society dear. Work is also underway to develop guidelines for health impact assessment and cost-benefit analysis of transport-related policies and interventions that might have implications for levels of physical activity through walking and cycling.

*Francesca Racioppi, Roberto Bertollini, Vivienne Taylor Gee

*Accidents, Transport and Health (FR) and Division of Technical Support "Health Determinants" (RB), WHO Regional Office for Europe, European Centre for Environment and Health, Via Francesco Crispi 10, 00187 Rome, Italy; and WHO Regional Office for Europe, Copenhagen, Denmark (VTG)
(e-mail: frr@who.it)

1 The Lancet. The catastrophic failures of public health. *Lancet* 2004; 363: 745.
2 Andersen LB, Schnohr P, Schroll M, Hein HO. All-cause mortality associated with physical activity during leisure time, work, sports, and cycling to work. *Arch Intern Med* 2000; 160: 1621–28.
3 Rowland D, DiGuiseppi C, Gross M, Afolabi E, Roberts I. Randomized controlled trial of site specific advice on school travel patterns. *Arch Dis Child* 2003; 88: 8–11.
4 WHO. World Health Report 2002: reducing risks, promoting healthy life. Geneva: World Health Organization, 2002. http://www.who.int/whr/2002/en/ (accessed Mar 6, 2004).
5 Racioppi F, Dora C, Krech R, von Ehrenstein O. A physically active life through everyday transport: with a special focus on children and older people and examples and approaches from Europe. Copenhagen: WHO Regional Office for Europe, 2002. http://www.euro.who.int/document/e75662.pdf (accessed Feb 1, 2004).

Sir—In your Editorial,[1] you point out the failures of public health in the developed world, particularly in relation to chronic diseases. But what of the state of public health in the developing world?

The developing world's limited resources bear a much higher burden of communicable diseases and an almost equal burden of non-communicable diseases.[2] Addressing the root cause of poverty would do more good to the health of people than any number of specific interventions. The need for health research is also imperative in the generation of the good quality data governments need to formulate national policies. Decision frameworks must be evidence-based and take into account disease burden, prevention effectiveness, cost-effectiveness, and affordability.[3]

Pakistan faces an ever increasing double burden of disease: the infant mortality rate is 80 per 1000—the highest in south Asia—and cardiovascular diseases account for more than 100 000 deaths per year. The development of public health faces serious challenges in Pakistan. As the country undergoes epidemiological transition, the new realities in the health sector point towards a wide range of health issues that are faced with a lack of capacity to respond. This discrepancy between need and capacity underscores the importance of health research to identify priority areas.[4]

More than a third of Pakistan's population lives below the poverty line. Pakistan spends only 0·7% of its gross national product on health. Pakistan's spending on preventive health care and education is about 10 times less than Nepal and Bhutan, its poorer and smaller neighbours.[5] Effective interventions require a functioning health system, which must be able to use and effectively promulgate research-based knowledge. Low-cost interventions such as health education in schools and effective media campaigns carry a lot of promise if implemented sincerely. We agree that by targeting the youth (more than 40% of Pakistan's population is younger than 15 years), a lot can be gained.

Public health needs the support of poverty reduction, higher literacy, good governance, and accountability if it is to begin making its much needed impact on the lives of more than 150 million citizens of Pakistan.

*Fawad Aslam, Muhammad Ahad Qayyum

*Aga Khan University Medical College, Stadium Road, Karachi 74800, Pakistan (FA); and Punjab Medical College, Faisalabad, Pakistan (MAQ)
(e-mail: fawadaslam2@hotmail.com)

1 The Lancet. The catastrophic failures of public health. *Lancet* 2004; 363: 745.
2 Global Forum for Health Research. The 10/90 Report on Health Research 2000. Geneva: GFHR, 2000.
3 White F. Developing effective and affordable models for non-communicable disease prevention and control. *Int J Epidemiol* 2001; 30: 1494–95.
4 Hyder AA. Health research investments: a challenge for national public health associations. *J Pak Med Assoc* 2002; 52: 276–77.
5 Wallerstein C. Pakistan lags behind in reproductive health. *BMJ* 1998; 317: 1546.

Timing of surgery for symptomatic carotid stenosis

Sir—P M Rothwell and colleagues (Mar 20, p 915)[1] present an important study. If the optimum timing of surgery for symptomatic carotid stenosis is 2 weeks after the patient's last symptoms, the implications for health-care provision are enormous. To be able to offer the highest-risk patients early surgery, an attempt to stratify the risk of waiting needs to be made.

Transcranial doppler can be used to assess middle cerebral artery velocity and platelet microemboli. Immediately after a carotid-territory transient ischaemic attack (TIA) or stroke, there is a rise in microemboli in the middle cerebral artery, and patients who continue to embolise are at a greater risk of a further neurological event.[2] A high microembolic load after carotid endarterectomy is associated with early carotid thrombosis. Control of this load by means of intravenous transcranial doppler-directed antiplatelet agents reduces the risk of early postoperative

stroke[3]. It is possible to influence the timing of carotid surgery in patients with recurrent or crescendo TIAs. Control of both emboli and symptoms with transcranial doppler-directed dextran allows these high-risk patients to undergo carotid surgery safely on the next elective list.[4]

Microemboli seem to be surrogate markers for future embolic events (TIAs or strokes) and the pharmacological efficacy of any therapeutic intervention can now rapidly and non-invasively be assessed. Transcranial doppler emboli detection could offer an approach to the management of patients both medically and surgically.

*Chris Imray, Dan Higman, Carl Tiivas

Coventry and Warwickshire County Vascular Unit, Coventry CV2 2DX, UK.
(e-mail: chrisimrey@aol.com)

1 Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJM, for the Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 2004; 363: 915–24.

2 Goertler M, Blaser T, Krueger S, Lutze G, Wallesch CW. Acetylsalicylic acid and microembolic events detected by transcranial Doppler in symptomatic arterial stenoses. *Cerebrovasc Dis* 2001; 11: 324–29.

3 Lennard N, Smith J, Dunville J, et al. Prevention of postoperative thrombotic stroke after carotid endarterectomy: the role of transcranial Doppler ultrasound. *J Vasc Surg* 1997; 26: 579–84.

4 Lennard NS, Vijayasekar C, Tiivas C, Chan CWM, Higman DJ, Imrey CH. Control of emboli in patients with recurrent or crescendo transient ischaemic attacks using preoperative transcranial Doppler-directed Dextran therapy. *Br J Surg* 2003; 90: 166–70.

A network of excellence

Sir—Nathan Clumeck and Christine Katlama's ambitious proposal of a network of centres of excellence in clinical research across Europe (Mar 13, p 901)[1] is to be welcomed. They identify the threat posed to non-commercial academic research, which is especially difficult in oncology because surgery and radiotherapy attract little commercial support.

Optimum delivery of radiotherapy can make substantial contributions to improving local control. Currently, about 90% of all cancers are cured by local treatment with surgery and radiotherapy. Kogelnik and Lukas have estimated that, if a 100% local control rate could be achieved, cancer survival rates would rise from 45% to 60%.[2] At present, there are many opportunities to improve local control—eg, advances in radiation planning and delivery such as intensity-modulated radiotherapy, and integration of structural (CT, MRI) and functional (positron emission tomography) scans into the radiotherapy planning process. In addition, positron emission tomography imaging could provide valuable information on response to multimodal therapy—eg, with radiotherapy and inhibitors of tumour angiogenesis.

There are rising clinical and laboratory needs to obtain cellular and molecular information in vivo.[3] Developments in molecular imaging could allow us to identify the optimum time in the cell cycle for radiotherapy and chemotherapy to be delivered for individual tumours.

Ring-fenced European Union research funding for biological and clinical aspects of combined modality therapy for cancer would help redress the current imbalance in the provision of funding. Networks of excellence would facilitate the collaboration needed to deliver these research priorities.

Ian Kunkler

University Department of Clinical Oncology, Western General Hospital, University of Edinburgh, Crewe Road, Edinburgh EH2 2XU, UK.
(e-mail: I.Kunkler@ec.ac.uk)

1 Clumeck N, Katlama C. Call for network of centres of excellence in clinical research in Europe. *Lancet* 2004; 363: 901–02.

2 Kogelnik HD, Lukas P, Sedlmayer F. Foreword. In: Kogelnik HD, Lukas P, Sedlmayer F, eds. Progress in radio-oncology, VII. Bologna: Monduzzi Editore, 2002.

3 Sullivan DC. Challenges and opportunities for in vivo imaging in oncology. *Technol Cancer Res Treat* 2003; 6: 419–22.

Sir—In their Correspondence letter (Mar 13, p 901),[1] Nathan Clumeck and Christine Katlama put forward the intriguing idea that clinical research in Europe should be done only by networks of centres of excellence appointed by research specialists and selected from European agencies. Centres of excellence in basic research already exist since their establishment represents a priority for the recently launched European Commission Framework Project 6. However, the negative consequences of the establishment of such clinical networks should be carefully considered and weighed against the advantages pointed out by Clumeck and Katlama.

The criteria by which clinical centres across Europe will get the status of "excellence" might not be easy to identify. Should clinical centres be drawn up on the basis of the number of patients referring to them, the availability of high-tech equipment, or compliance with the national standards of care? Any of these criteria will influence the applicability of the results of clinical trials to the general population. Clumeck and Katlama correctly state that there are great differences in quality of clinical investigation and in standards of care across Europe. But are we sure that results obtained in top-level clinical centres can be easily applied to less than optimum clinical settings? As an example, if high-tech centres are included in the networks of excellence, then large areas of Europe will not benefit from the results. Conversely, if clinical trials are done in small and less-equipped centres, results might not represent the best available treatment for any given disease. Similar arguments have been used to criticise evidence-based medicine.[2]

Networks of centres of clinical excellence will be of limited usefulness for individual patients across Europe, and their research priorities will not match the needs of patients and the health-care system.[3] In this light, I do not think that the establishment of such networks will generate data which in turn will determine standards of care across Europe. Rather, the minimum standards of care should be set first; only then will clinical trials done in any European country yield results applicable to the general European population.

Finally, I agree with Clumeck and Katlama in their criticism of the procedure by which the European Commission financially supports scientific proposals, since it is burdened with unnecessary bureaucratic difficulties. These limitations are known by the Commission, which is working to improve its procedures. However, I would not say that it "claims to support investigative centres of excellence, but in practice the political will is not apparent". To my knowledge, any decision on a proposal's scientific accuracy and adequacy of budget is not taken by "Eurobureaucrats" but by independent international peer-reviewers with expertise in the field.

Alessandro Laviano

Department of Clinical Medicine, University La Sapienza, Viale dell'Università 37, 00185 Rome, Italy
(e-mail: alessandro.laviano@uniroma1.it)

1 Clumeck N, Katlama C. Call for network of Centres of Excellence in clinical research in Europe. *Lancet* 2004; 363: 901–02.

2 Cohen AM, Stavri PZ, Hersh WR. A categorization and analysis of the criticisms of Evidence-Based Medicine. *Int J Med Inf* 2004; 73: 35–43.

3 Tallon D, Chard J, Dieppe P. Relation between agendas of the research community and the research consumer. *Lancet* 2000; 355: 2037–40.

Reference

1 Williamson JA, Webb RK, Szekely S, Gillies ER, Dreosti AV. The Australian Incident Monitoring Study. Difficult intubation: an analysis of 2000 incident reports. *Anaesthesia and Intensive Care* 1993; 21: 602–7.

A reply

Thank you for giving us an opportunity to respond to the comments raised by Drs Tighe, Staber, Hardman and Henderson and by Drs Merron and Lim regarding the conclusions drawn from our study of four cricothyroidotomy sets performed on a human patient simulator. Dr Tighe *et al.* may be correct in their assertion that surgical cricothyroidotomy, using a cuffed tube, performed appropriately and in a timely fashion by a practitioner experienced and dextrous in this technique allows maximal oxygenation in a patient in whom conventional anaesthetic management has failed to establish an airway. Unfortunately, as the correspondents point out this is not a technique that is familiar to most anaesthetists. Our primary intention when designing the study was to assess the efficacy of the available kits using a method of insertion familiar to anaesthetists in everyday practice who might not necessarily possess surgical skills or experience. This study clearly demonstrated that all the anaesthetists who participated were able to establish an airway by cannula over needle cricothyroidotomy despite unfamiliarity with the sets provided.

Two particular points were questioned in our methodology:

1. Degree of obstruction of the simulated airway: the presence of a swollen 'tongue' and 'pharyngeal' swelling on the manikin reduces the calibre of the pharyngeal airway but does not produce marked obstruction to gas flow. The 'lungs' were preset at normal compliance with full neuromuscular blockade such that any increase in lung oxygen concentration was a result of the flow of oxygen achieved via the airway device and by the efforts of the anaesthetist. The assertion that a cuffed tube is essential to provide adequate oxygenation of the lungs in clinical practice is questionable. Should oxygen escape upwards out of the trachea with an uncuffed tube to such a degree that one cannot achieve adequate alveolar ventilation it may be necessary to close the patient's mouth and pinch the nose or block the backflow with a throat pack, although for the purposes of standardisation, this was not permitted during our study.

2. Degree of hypoxaemia simulated: the choice of 80% arterial oxygen saturation before intervention was not critical to the outcome of the study and was artificially created by shunt modelling to stimulate a degree of urgency. Moreover, a standard physiological model suffers severe arrhythmias with saturations at around 50%, making it difficult to carry out the experiment altogether because of the potential distracting need to undertake ALS manoeuvres. We recorded changes in oxygen tension in the lungs as an outcome measure not arterial saturation and were particularly interested in demonstrating a reversal in the downward trend of deoxygenation as defined by a rise in arterial oxygen content above 13.3 kPa.

Successful outcome in a 'can't intubate, can't ventilate' situation will depend upon the ability to recognise that conventional means of ventilation have failed, and successfully administering oxygen to the lungs via an alternative route before the patient suffers permanent hypoxic damage. In practice, as rightly pointed out by Drs Merron and Lim, both these steps may be difficult to achieve in a timely and effective fashion. Whilst an expert may be able to perform a surgical airway adeptly when arterial saturations have already fallen to 50%, this may leave insufficient time for the less experienced to react. Moreover, neither junior nor senior anaesthetists practice insertion of cricothyroidotomy cannulae routinely. Although the Quiktrach device does not use the Seldinger technique, it was found easiest to use by all our candidates. However, if one is more comfortable using Melkers inserted via a Seldinger approach it makes sense to use the more familiar kit. The results and complications with both the sets were comparable. We have demonstrated that success using one technique in a simulated emergency is dependent upon the design of the equipment both in terms of time taken and ability to oxygenate, whilst documenting the number and nature of potential complications that occurred.

Surgical tracheotomy may be the 'gold standard', but only in expert hands. This technique, however, is associated with more complications, compared with cricothyroidotomy. Whether or not to opt entirely for surgical cricothyoidotomy is beyond the scope of this study as it was deliberately excluded. As mentioned in our paper, it is impossible to replicate real-time scenarios. We have attempted to duplicate the urgency as best as we could, taking into consideration the limitations associated with the use of a simulator. This situation gives us a better environment than trying to use cadavers for such an experiment. The validity of extrapolation of the findings to live humans may be questionable, but must be viewed in the context that such studies in live subjects are ethically impossible to perform. The aim of our study was to compare the use and effectiveness of the available cricothyroidotomy kits using the end-points we selected. There is no doubt that more work is needed in this field and we thank the correspondents for their suggestions.

E. Wadeana
Northern General Hospital,
Sheffield S5 7AU, UK
E-mail: bvaddaria@aol.com
S. Gandy
Tameside General Hospital,
Ashton-under-Lyne, UK
A. McIndoe
Bristol Royal Infirmry,
Bristol, UK

Validity of near-infrared cerebral spectroscopy

Since its introduction in 1977, [1] near-infrared cerebral spectroscopy (NIRS) has been used in various applications as a research tool [2,3]. It has failed,

however, to become a widely used clinical monitor. NIRS has been shown to track changes in arterial [4] and jugular venous [5] saturations in individuals, but the relationship is variable and inconsistent between subjects. In addition a number of methodological problems have been identified with NIRS including attenuation of the infrared signal by extracerebral tissues [6], and variability between devices [7]. One study even showed that some dead subjects had higher cerebral saturations than live subjects [8].

In their recent paper, Shaaban Ali and colleagues (*Anaesthesia* 2004; **59**: 20–6) used NIRS and serum S100β to compare warm and cold cardiopulmonary bypass (CPB) in children undergoing cardiac surgery. They showed no significant difference in S100β levels between the two groups, and no difference in cerebral oximetry during CPB, except during rewarming. Based on these findings and specifically the improved cerebral oxygenation levels recorded during warm CPB, they concluded that warm CPB may be a useful alternative to cold CPB. Unfortunately, no data was provided about arterial oxygen saturations, which may account for the difference in cerebral oxygenation. There were no recorded neurological sequelae in either group. Since the validity of NIRS is still questioned, we do not believe it is possible to draw meaningful conclusions from the data presented. Warm CPB does appear to be an alternative to cold CPB, a view most strongly supported in this study by both groups having normal neurological outcomes.

K. Pattinson
T. Clutton-Brock
Queen Elizabeth Hospital,
Birmingham B15 2TH, UK
E-mail: kyletsp@postmaster.co.uk
C. Imray
Coventry and Warwickshire University Hospital,
Coventry CV2 2DX, UK

References

1 Jobsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science* 1977; **198**: 1264–7.

2 Imray CH, Breary S, Clarke T *et al*. Cerebral oxygenation at high altitude and the response to carbon dioxide, hyperventilation and oxygen. *Clinical Science* 2000; **98**: 159–64.

3 Nicklin SE, Hassan IA, Wickramsinghe YA, Spencer SA. The light still shines, but not that brightly? The current status of perinatal near infrared spectroscopy. *Archive of Diseases in Childhood Fetal and Neonatal Edition* 2003; **88**: F263–8.

4 Pollard V, Prough DS, DeMelo AE, Deyo DJ, Uchida T, Stoddart HF. Validation in volunteers of a near-infrared spectroscope for monitoring brain oxygenation in vivo. *Anesthesia and Analgesia* 1996; **82**: 269–77.

5 Henson LC, Calalang C, Temp JA, Ward DS. Accuracy of a cerebral oximeter in healthy volunteers under conditions of isocapnic hypoxia. *Anesthesiology* 1998; **88**: 58–65.

6 Young AER, Germon TJ, Barnett NJ, Manara AR, Nelson RJ. Behaviour of near-infrared light in the adult human head: implications for clinical near-infrared spectroscopy. *British Journal of Anaesthesia* 2000; **84**: 38–42.

7 Yoshitani K, Kawaguchi M, Tatsumi K, Kitaguchi K, Furuya H. A comparison of the INVOS 4100 and the NIRO 300 near-infrared spectrophotometers. *Anesthesia and Analgesia* 2002; **94**: 586–90.

8 Schwarz G, Litscher G, Kleinert R, Jobstmann R. Cerebral oximetry in dead subjects. *Journal of Neurosurgical Anesthesiology* 1996; **8**: 189–93.

A reply

We welcome the opportunity to respond to the letter of Pattinson, Clutton-Brock and Imray. The NIRO 300 is a promising non-invasive cerebral oxygenation monitor with the advantages of being non-invasive, and providing continuous real-time monitoring of changes in cerebral rather than extracerebral oxygenation [1]. However, it does have obvious limitations [2–4]; it detects regional cerebral oxygenation (small area under the optodes), the optical path length is difficult to quantify, and arterial and venous changes are not distinguished.

The previous limitations were very clear in adult studies [2,4,5]. Indeed, our group [5] reported a significant bias with wide limits of agreement between jugular bulb oxygen saturation and tissue oxygen index monitored by NIRO 300 in adult patients undergoing coronary bypass surgery. However, change in cerebral oxygenation may be monitored in adults [1] and in children and this may be useful in assessing the advantages and disadvantages of changes in surgical, anaesthetic and cardiopulmonary bypass (CPB) techniques without the necessity for waiting for long-term follow up. We agree that studies comparing such an intermediate end-point with neurological outcome will be essential, but this type of approach might help to prevent the unforeseen consequences of a change in practice undertaken on theoretical grounds, such as the increase in choreoathetosis after the change from pH-stat to α-stat during the 1980s [6].

In addition to the evidence suggesting that change in oxygenation provides a potentially useful trend in brain metabolic status, the CytOx signal appears to predict impaired neuropsychological outcome in patients undergoing cardiac surgery [7]. Furthermore, in animals a reduction in CytOx correlates with decreased brain energy state and predicts histologic brain injury after deep hypothermic circulatory arrest (DHCA) with a high sensitivity [7,8]. Also, in our pilot study (as we do not have enough funds to complete it) the lowest value of CytOx during CPB was the one variable to be significantly (inversely) associated with peak S100β protein levels after CPB (high S100β associated with low cellular oxygenation) [9]. These data suggest that the level of CytOx could be a very important predictor of brain damage [7–9]. Data on CytOx [10] formed part of the evidence base suggesting that deep hypothermic arrest had a detrimental effect on the child's brain, which led to the expensive but currently definitive randomised controlled trial with late neurological endpoints [11].

Despite the limitations of NIRS, it has produced interpretable data in the hands of critical researchers and may have a place in the near future for

Effect of fluoxetine and placebo on various end points

Intervention	Change in children's depression rating scale	Change in adolescent depression scale	Change in suicidal ideation questionnaire	Clinical global impressions improvement of 1 or 2 (%)
Fluoxetine	22.6	16.4	7.4	60.6
Placebo	19.4	14.6	9.2	34.8
Proportion of fluoxetine effect seen in placebo group	0.86	0.89	1.24	N/A

N/A=not applicable, categorical measure.

point, the children's depression rating scale (CDRS-R; $P=0.10$), but this was not mentioned in the abstract. This and the small or absent advantages of fluoxetine on other end points (table) and in other studies[2] shows that fluoxetine, like all other antidepressants, is of doubtful clinical importance for children.

Adverse events and suicidal behaviour may be greater than the TADS paper says. Despite small numbers, more subjects leaving the study than reporting adverse effects, and the splitting of adverse events into multiple groups, significantly more psychiatric adverse events occurred in the fluoxetine group than the placebo group (χ^2 test (1 df), $P=0.047$). Despite small numbers and the exclusion of known suicidal behaviour, TADS found a trend to more suicidal behaviour (six attempts in the fluoxetine groups and one attempt in the non-fluoxetine groups), consistent with other trials of selective serotonin reuptake inhibitors (SSRIs). We are less reassured than the authors by the fact that no attempt was fatal. Suicide is a rare event so that a study the size of TADS should be expected to miss a significantly increased risk.

The data do not support the TADS authors' optimistic conclusions. The balance between benefit and harm of SSRI treatment for depression in childhood and adolescence has yet to be shown to be favourable.

Jon Jureidini *head*
Department of Psychological Medicine, Women's and Children's Hospital North, Adelaide 5006, Australia
jureidini@wch.sa.gov.au

Anne Tonkin *associate professor, department of clinical and experimental pharmacology*
Peter R Mansfield *research fellow, department of general practice*
University of Adelaide, Adelaide 5005, Australia

Additional authors are Peter Parry, child psychiatrist, Women's and Children's Hospital, North Adelaide; David B Menkes, professor of psychological medicine, University of Wales Academic Unit, Wrexham; and Chris Doecke, associate professor of pharmacy practice, Quality Use of Medicines and Pharmacy Research Centre, University of South Australia, Adelaide.

Competing interests: None declared.

1 Lenzer J. Journalists on Prozac. *BMJ* 2004;329:748, 25 September.
2 Treatment for Adolescents with Depression Study Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: treatment for adolescents with depression study (TADS) randomized controlled trial. *JAMA* 2004;292:807–20.
3 Jureidini J, Doecke C, Mansfield P, Haby M, Menkes D, Tonkin A. Efficacy and safety of antidepressants for children and adolescents. *BMJ* 2004;328:879–83.

Surgery for carotid artery stenosis

Patients with critical stenoses should be admitted to stroke prevention units

EDITOR—While shopping in Florida, a man found a booth offering carotid duplex scans for a modest fee. He had a family history of cerebrovascular disease, so he decided to be scanned for peace of mind. Unfortunately, a critical internal carotid stenosis was found.

He returned to his hotel somewhat perturbed, only to be phoned by a vascular surgeon recommending urgent carotid endarterectomy before he flew home to the United Kingdom. He declined the offer, but underwent successful surgery some months later.

Screening is not without drawbacks. The asymptomatic carotid surgery trial confirms that carefully selected patients benefit from surgery when operated upon by skilled teams.[1] The logic which Toole finds compelling[2] is that carotid screening should be considered.

Transcranial Doppler ultrasound can detect microemboli, which allows the efficacy of therapeutic interventions to be rapidly and non-invasively assessed. Controlling the rate of embolisation reduces the risk of an early postoperative stroke.[3] Controlling emboli and symptoms in patients with recurrent or crescendo transient ischaemic attacks by using Doppler directed drug therapy allows these high risk patients to undergo elective carotid surgery safely.[4]

Patients with focal neurological events need assessment within 24-48 hours. Those with critical carotid stenoses, symptoms and emboli should be admitted to a stroke prevention unit (similar to a coronary care unit). It would be jointly managed by vascular surgeons and stroke doctors, with high ratio of staff to patients. Rapid control of microemboli could be achieved, and since microemboli seem to be surrogate markers for future embolic events, some strokes will be prevented.

Chris Imray *consultant vascular surgeon*
Coventry and Warwickshire County Vascular Unit, Coventry CV2 2DX
chrisimray@aol.com

Kyle Pattinson *clinical lecturer in anaesthesia*
John Radcliffe Hospital, Oxford OX3 9DU

Competing interests: None declared.

1 MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004;363:1491–502.
2 Toole JF. Surgery for carotid artery stenosis. *BMJ* 2004;329:695–6. (25 September.)
3 Leunard N, Smith J, Abbott R, Evans DH, London NJ, Bell PR, et al. Prevention of postoperative thrombotic stroke after carotid endarterectomy: the role of transcranial Doppler ultrasound. *J Vasc Surg* 1997;26:579–84.
4 Lennard NS, Vijayasekar C, Tivas, Chan CWM, Higman DJ, Imray CHE. Control of emboli in patients with recurrent or crescendo transient ischaemic attacks using preoperative transcranial Doppler-directed dextran therapy. *Br J Surg* 2003;90:166–70.

Cut-off point is problematic in selecting patients for carotid surgery

EDITOR—Toole's voice is important in the controversial debate on carotid surgery.[1] However, in determining a cut-off point for selecting patients for endarterectomy, the different methods of measurement (local versus distal degree of stenosis) used by European and American surgery trials must be considered.[2]

A cut-off point of 60% stenosis refers to the asymptomatic carotid artery stenosis study (ACAS) and uses the American method of stenosis measurement[3]: that degree of stenosis corresponds to a 75% stenosis according to European criteria.[4] Therefore, to define a cut-off point of 60% stenosis in a European journal is misleading.

I agree with Toole that other indicators for selecting patients for carotid surgery should be considered; however, apart from the degree of stenosis, there are no evidence based criteria that allow medical or surgical treatment to be decided. So the degree of stenosis remains the main criterion; measurement should be performed by means of Doppler and duplex ultrasound evaluation.

Christian Arning *head*
Department of Neurology, Wandsbek Hospital, Alphonsstr. 14, D-22043 Hamburg, Germany
Christian.Arning@t-online.de

Competing interests: None declared.

1 Toole JF. Surgery for carotid artery stenosis. *BMJ* 2004;329:695–6. (25 September.)
2 Rothwell PM, Gibson RJ, Slattery J, Sellar RJ, Warlow CP. Equivalence of measurements of carotid stenosis. A comparison of three methods on 1001 angiograms. European Carotid Surgery Trialists' Collaborative Group. *Stroke* 1994;25:2435–9.
3 The Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995;273:1421–8.
4 Arning C, Hammer F, Korunmaz H, Habib H, Muller-Jensen A, Lackenmawer L. Quantifying stenosis of the internal carotid artery: which ultrasound criteria are relevant? *Ultraschall Med* 2003;24:238–8.

Author's reply

EDITOR—I am pleased that my editorial has evoked responses about the looming epidemic of stroke, often the result of carotid artery disease. We hope that all risk factors will be reduced by careful attention to good health habits including diet, smoking, blood pressure control, etc, and in selected cases, platelet anti-aggregants and statins.[1] For

Are some strokes preventable? The potential role of transcranial doppler in transient ischaemic attacks of carotid origin

Christopher H E Imray, Carl A S Tiivas

Lancet Neurol 2005; 4: 580–86

Coventry and Warwickshire County Vascular Unit (C H E Imray FRCS), Clinical Physics and Biomedical Engineering Department (C A S Tiivas MSc), University Hospital Coventry and Warwickshire NHS Trust, Coventry, UK

Correspondence to: Dr Christopher H E Imray, Coventry and Warwickshire County Vascular Unit, University Hospitals Coventry and Warwickshire NHS Trust, Coventry CV2 2DX, UK
chrisimray@aol.com

Transient ischaemic attacks (TIA) are more than just ministrokes. The high frequency of early stroke following TIA has resulted in the recent publication of guidelines in the UK. The guidelines recommend that patients attend a neurovascular clinic within 7 days of the index event to expedite investigation and treatment and so reduce the risk of a subsequent (potentially more serious) neurological event. After a TIA or stroke caused by carotid-artery disease, there is an increase in cerebral microemboli detectable by transcranial doppler (TCD). High microembolic loads appear to be surrogate markers for future neurological events, and the pharmacological efficacy of therapeutic interventions can now be rapidly and non-invasively assessed in the clinic or at the bedside. Medical treatments can now be optimised, avoiding the need for urgent or emergency carotid surgery and therefore allowing patients to undergo safer elective surgery when appropriate.

Introduction

The risk of stroke after a hemispheric transient ischaemic attack (TIA) is greatest within the first 72 h, and event rates as high as 20% within the first month have been reported.[1] The Royal College of Physicians' National Clinical Guidelines for Stroke (2004) recommend that patients who have a TIA or minor stroke should be seen in a specialist neurovascular clinic within 7 days, and those with more than one TIA in a week should be admitted and investigated immediately.[2] The type, frequency, duration, and severity of a TIA are predictors of subsequent risk and severity of future strokes. All patients with a history of clear focal neurological deficit merit investigation, but those with motor or speech deficits have a more serious prognosis than those patients with sensory or short-lived deficits. There is also evidence that after an anterior-circulation TIA (resulting from a carotid stenosis) there is a high risk of early stroke.[1,4,5]

What should the next step be? Duplex ultrasonographic examination may confirm a critical internal-carotid-artery stenosis, and CT or magnetic resonance angiography (MRA) will exclude haemorrhagic stroke in most cases. If cardiac-rhythm or valvular problems are found, they can be addressed. Antiplatelet agents can be introduced or adjusted; and blood pressure, glycaemic, and lipid profiles can be modified. However, is this enough? If the patient continues to have further focal events, or a neurological deficit persists, should anything more be done? How can the efficacy of various treatments be assessed, and when is it safest to proceed with surgery?

Transcranial doppler and transient microembolic signals

Transcranial doppler (TCD) is a non-invasive ultrasound-based technique used to measure blood velocity within the large vessels of the cerebral arterial circulation. The middle cerebral artery is insonated with a 2 MHz pulsed signal transmitted through the temporal bone to a depth of 4·5–6·0 cm. The signal is reflected by solid components of blood (mostly red blood cells) and distorted according to the doppler-shift principle. The reflected waveform gives information about systolic, diastolic, and mean blood-flow velocity.

Gaseous or solid microemboli within the middle cerebral artery can be detected with TCD as high-intensity transient signals, also known as cerebral microembolic signals. Microemboli are defined as having a duration of less than 300 ms and an amplitude that is 3 dB higher than the background blood-flow signal.[6] Such signals are unidirectional and occur randomly within the cardiac cycle. Furthermore, most microemboli are easily recognised since they produce a characteristic sound (chirp). An individual microembolic signal does not cause neurological symptoms but may represent an early warning sign that an individual is at a greater risk of a neurological event in the near future.

Potential role for TCD in management of TIA of carotid origin

Patients with crescendo or recurrent TIAs seem to be at particularly high risk of subsequent stroke. The findings of a large, multicentre, non-selected, observational study emphasises the "not so benign" prognosis for all TIA patients.[7] The reported frequency of stroke after an index TIA is higher than was originally thought and the prevalence ranges from 5% within the first 2 days and 20% within the first month[1] to 10·5% within 90 days.[1] Perhaps the greatest justification for early investigation and treatment of symptomatic carotid-artery disease comes from the analysis of the pooled data from the ECST and NASCET trials. The benefit from surgery was greatest for patients undergoing surgery within 2 weeks of their last ischaemic event.[8]

Natural course of microemboli and TIA

TCD-detected transient microembolic signals are common for some days after an acute stroke.[9]

Microemboli are an important independent predictor of early ischaemic recurrence in patients with stroke or TIA of arterial origin.[10] In a study of 69 patients with symptomatic carotid stenoses,[11] microemboli were detected more frequently when the patients were examined soon after symptoms of cerebral ischaemia. Several other studies have shown a link between persistent cerebral microembolisation and the risk of future TIA or stroke.[12–14] In symptom-free patients with a critical internal-carotid-artery stenosis, when the microembolic signal rate was greater than two per hour in the ipsilateral middle cerebral artery, there was an associated increased risk of developing ischaemia (odds ratio 31 [95% CI 3–302], p=0·005).[11] The presence of microemboli may define a sub-group of patients with critical stenoses who might be at greater risk of having a stroke.[15]

Effect of antiplatelet agents on microemboli

Goertler and colleagues[16] have assessed the efficacy of intravenous aspirin in controlling microemboli. Nine patients with recent symptoms arising from a critical internal-carotid-artery stenosis underwent TCD monitoring for 1 h; they were then given intravenous aspirin (500 mg), and the TCD measurements were repeated. In most patients, there was a reduction in the number of microemboli within 30 min; however, one patient showed no sustained decrease in the number of microemboli and later had an ischaemic event. In a further study by the same group,[17] 74 patients with symptomatic critical internal-carotid-artery stenosis underwent 1 h of bilateral TCD monitoring within a month of their symptoms. 38 (51%) patients had detectable emboli. Among 48 receiving aspirin 19 (40%) had microembolic signals and among 26 not receiving aspirin 18 (70%) had detectable microemboli. TCD-detected emboli were controlled in about half of the patients on maximum medical therapy, whereas in the others persistent embolisation was an independent predictor of recurrent TIA or stroke (adjusted odds ratio 37·0 [95% CI 3·5–333], p<0·003).

Junghans and Siebler[18] described rapid control of microemboli with the glycoprotein IIb/IIIa inhibitor (Tirofiban) in 24 patients with recent cerebral or retinal embolism of arterial origin. With Tirofiban, the microembolic signal rate dropped from a median of 38 per hour (range 9–324) to zero in all patients. After the infusion was stopped the inhibitory effect of Tirofiban was found to be reversible, with a significant increase in microembolic signals (median 13·5 [range 0–35], n=16; p<0·001). Six patients received overlapping oral antiplatelet agents and no microemboli were detected. Junghans and Siebler concluded that cerebral microemboli of arterial origin have the properties of solid emboli—with platelet-fibrinogen units as predominant constituent parts—and that glycoprotein IIb/IIIa inhibitors might have the potential to reduce the risk of a subsequent ischaemic event in patients with unstable carotid disease. Tirofiban can also inhibit the extension of microthrombosis, which might occur after arterial occlusion by emboli.

In the CARESS trial,[19] 230 patients with at least 50% carotid stenosis and ipsilateral carotid-territory symptoms were screened with TCD for microemboli. Of the 110 patients with microemboli, 107 were randomly assigned to either the dual antiplatelet therapy of aspirin and clopidogrel, or aspirin alone. On day 7, the dual-therapy group (n=51) had more effective control of microembolic signals than the group assigned single antiplatelet therapy (n=56). There were four recurrent strokes and seven TIAs in the single-therapy group, and four TIAs in the dual-therapy group over 7 days.

Practicalities of TCD emboli detection

An ambulatory TCD system has been developed; it works by using an autosearch algorithm to restore vessel insonation if the quality of signals decreases.[20] Patients can now be monitored continuously for up to 5 h, and in view of the likely temporal variability in embolisation, the technique is likely to improve the predictive value of microemboli detection. However, Blaser and colleagues[21] found that monitoring periods shorter than 1 h did not pick up less clinically relevant information when signal frequency was already either high or low. Cerebral perfusion has been assessed in individuals undergoing a maximum exercise test at an altitude of 5260 m,[22] showing that TCD monitoring is a simple and robust investigation. As such, there is no reason why the technique should not be more widely available within a general hospital setting, and it should not be seen as an investigation that is only available within specialist units.

Surgery for symptomatic carotid-artery disease

Several prospective randomised trials in patients with sympotomatic critical internal-carotid-artery stenosis have shown that carotid endarterectomy combined with medical therapy is better than medical therapy alone (>70%).[23–25] However, in patients with multiple, recurrent, or crescendo TIA, there is little information on optimum management. The treatment options generally adopted are intravenous heparin and urgent surgery. Mentzer and colleagues described 12 patients with crescendo TIA.[26] Seven patients underwent emergency carotid endarterectomy, and none had major complications; but of the five patients who did not have surgery, three patients had strokes and one died of cerebral infarction. In the Veterans Affairs trialists study,[27] patients with recent TIA or minor stroke were randomly assigned to either surgery or best medical therapy. At 1 year the proportion of patients with subsequent stroke or crescendo TIA was significantly lower among the 91 who received carotid

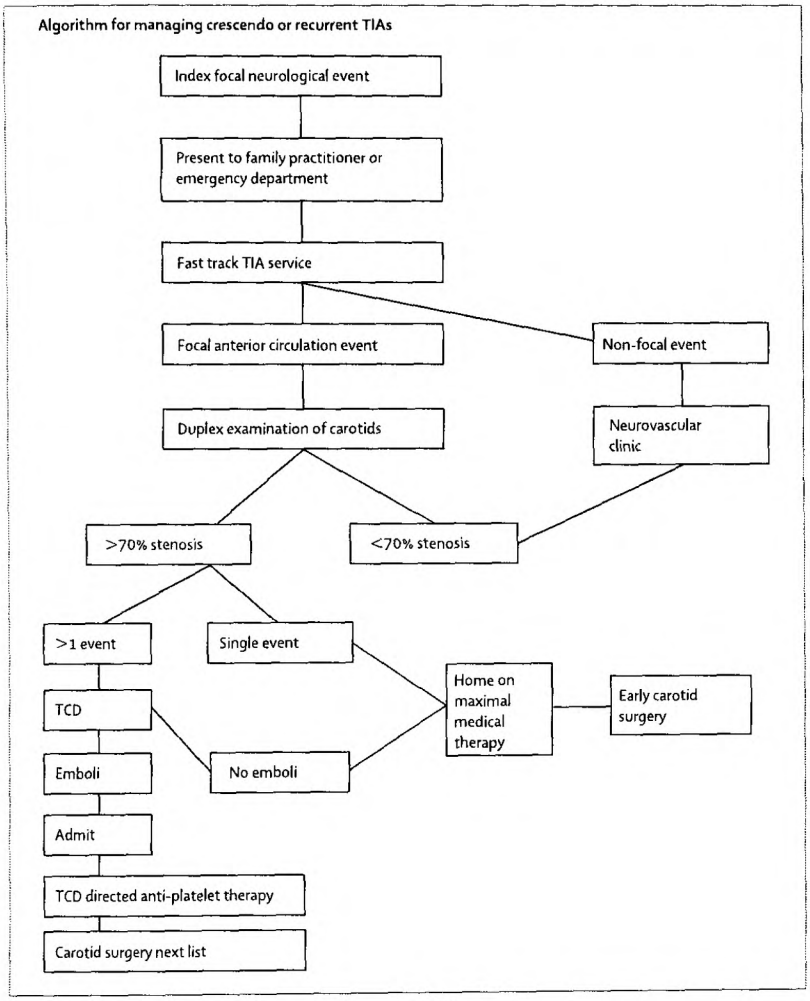


Figure 1: **Algorithm for managing crescendo or recurrent TIA**[28]

endarterectomy than among the 98 patients who did not undergo surgery (8% *vs* 19%; p=0·011). Of the 98 patients initially treated medically, 12 subsequently developed crescendo TIA, four had minor strokes, and three had major strokes. All 12 patients with crescendo TIA then underwent uncomplicated urgent carotid endarterectomy. In another study 29 patients with repeated TIAs were treated with heparin until elective carotid surgery was undertaken.[28] There was a mean wait of 5 days for surgery, and during heparin treatment there were two carotid occlusions and 13 patients continued to have further TIAs. Postoperatively there was one stroke and one death due to myocardial infarction. On the basis of the poor outcome in patients treated with drugs only,[27] a more aggressive approach with urgent surgical intervention has been advocated. However, the published results of urgent carotid surgery are variable,[27,29–34] with complication rates ranging from no deficits in 12 patients to operative mortalities as high as 20% and neurological deficits in up to 40% in some other series. A systematic review[35] of the risks of carotid endarterectomy in relation to both the clinical indication for and timing of surgery showed that urgent carotid surgery for evolving symptoms results in a much higher risk of stroke or death (19·2% [95% CI 10·7–27·8]) than surgery for stable symptoms (odds ratio 3·9 [95% CI 2·7–5·7], p<0·001; 13 studies). In view of the fact that both medical treatment and emergency carotid surgery have substantial complication rates, is there an alternative approach?

Preoperative TCD

The role of TCD before surgery has been explored in small trials in specialised centres but currently there is no level 1 evidence to support its use. Patients who recently had TIA or stroke associated with high-grade carotid stenosis and ipsilateral haemodynamic compromise with exhausted reactivity to carbon dioxide on TCD had a greater risk of early stroke before surgery than those with normal haemodynamics.[36]

Embolisation detected by TCD after recent neurological symptoms in carotid stenosis predicts the short-term ipsilateral stroke risk. TCD has been used to identify patients who are at high risk of a further event; Markus and MacKinnon[37] have argued that these patients should undergo urgent endarterectomy.

The timing of carotid surgery in patients with recurrent or crescendo TIA can be safely altered;[38] 19 patients were treated with a combination of TCD-directed medical therapy and elective surgery. After a TIA, patients were assessed as outpatients in the vascular laboratory, and each patient was questioned about any focal neurological symptoms in the previous 4 weeks (hemisensory, hemimotor, dysphasia, or amaurosis fugax). All patients then underwent a routine carotid duplex, and those with more than one focal event and an appropriate-sided critical internal-carotid stenosis underwent 1 h of TCD monitoring of the symptomatic middle cerebral artery. Patients with more than one focal event and microembolic signals were admitted to hospital. Maximum oral medical therapy was started, and a TCD-directed intravenous infusion of the antiplatlet agent dextran 40 was started. The infusion was increased incrementally until there were no microembolic signals. Sustained embolisation seemed to be associated with the development of neurological events since no patient had symptoms once the emboli were controlled. A single embolus does not cause a TIA or stroke, but a high embolic load seems to indicate that the individual is at greater risk of further focal neurological events. Patients underwent further TCD examinations to confirm that embolisation had ceased, and carotid endarterectomy was undertaken on the next elective operating list up to 10 days later (figure 1). This delay has the advantage of moving high-risk surgery out of the emergency setting and into

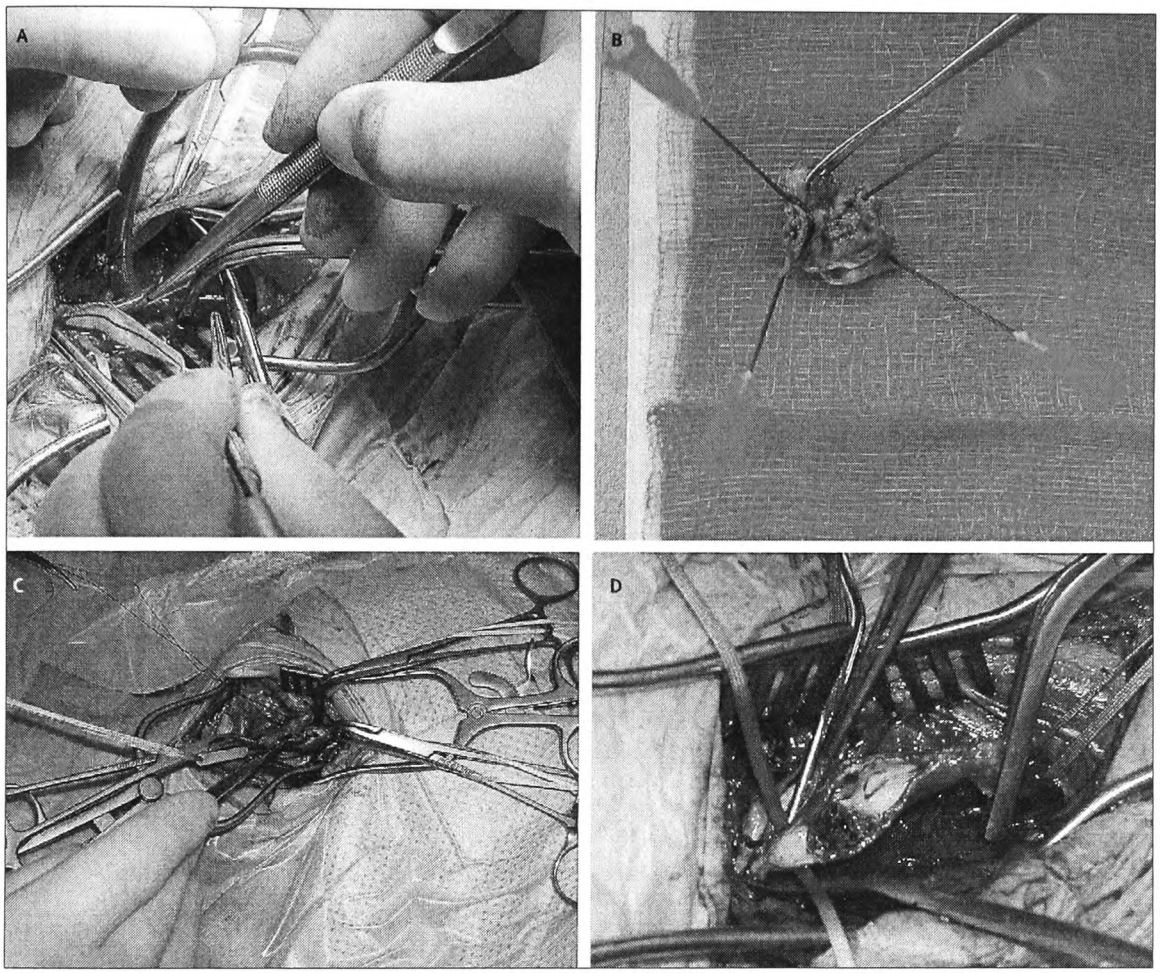


Figure 2: **Surgical technique and carotid plaque appearance**
A: right carotid endarterectomy with shunt in situ. B: carotid plaque with platelet frond from a symptomatic patient. C and D: intraoperative photographs of a symptomatic carotid plaque.

elective hours with independently demonstrated lower complication rates.[45] Therefore, safe interhospital transfer could be considered.

Intraoperative TCD

Historically, TCD was first used during carotid surgery to help assess the need for shunting during the cross clamp phase.[39] Among 1058 patients, a large decrease in velocity (greater than 90%) in the middle cerebral artery was associated with operative stroke (odds ratio 3·3, [1·3–8·3]).[40] Subsequently, TCD has also been used to measure the intraoperative microembolic load.[41,42] TCD sensitivity to the presence of particulate emboli can help guide surgical dissection of the carotid artery before endarterectomy. Jansen and colleagues[43] found that a high microembolic load was significantly related to new ischaemic lesions. Intraoperatively, detection of emboli by TCD has been used to modify surgical techniques or strategies; for example, early clamping of the internal carotid artery when there is a high embolic load (figure 2).[44,45]

Postoperative TCD

The reported rate of early postoperative carotid thrombosis is 2–3%.[46,47] After carotid endarterectomy, TCD-detected microemboli are thought to be platelet aggregates generated by a partly denuded and highly thrombogenic vascular endothelium. Unchecked, these aggregates can mature into occlusive thromboemboli, resulting in infarcts in the succeeding hours or days. In the early postoperative phase (after carotid endarterectomy) if micrembolic counts are greater than 50 per hour, this can help predict the development of ipsilateral focal ischaemia.[48,49] Lennard and colleagues[50] eliminated all postoperative strokes with the aid of a 3 h TCD monitoring session. They found that signs of persistent embolisation of at least 25 microemboli signals

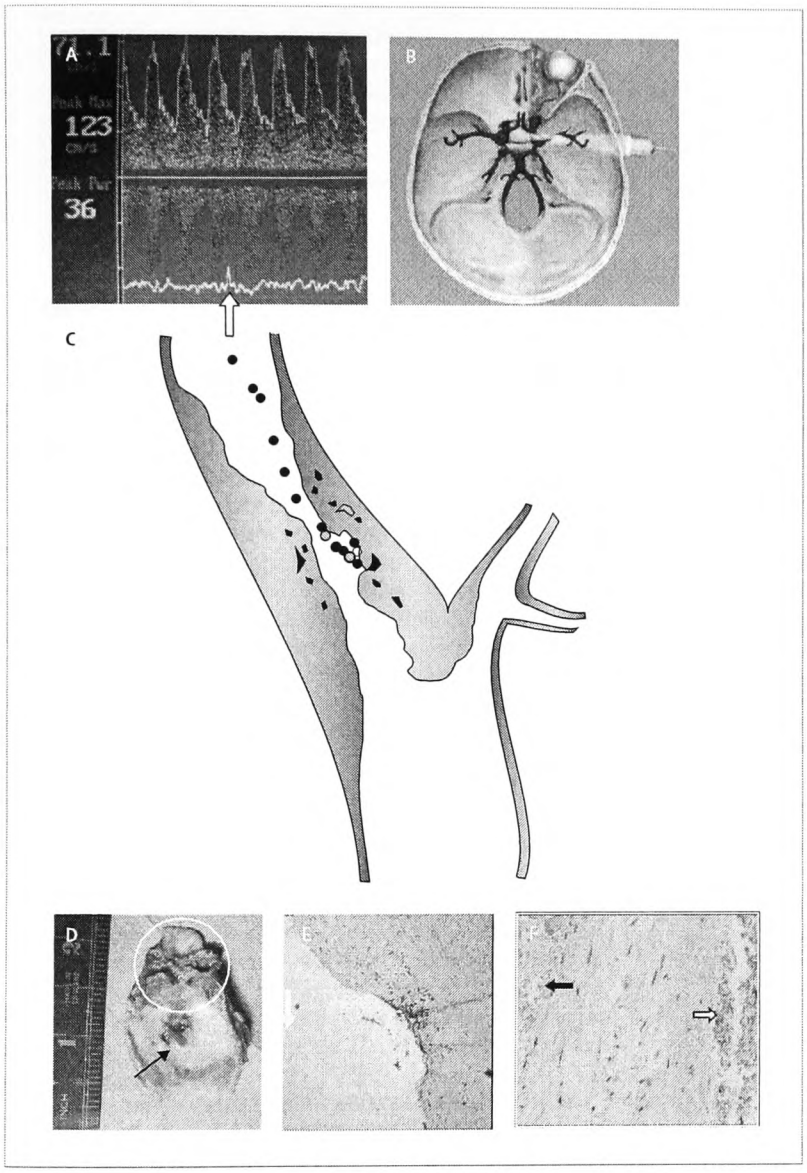


Figure 3: **Composite schematic of symptomatic carotid-artery stenosis**
High intensity transient signal (A, arrow) detected on transcranial doppler insonation of the middle cerebral artery via a temporal window using a 2 MHz probe (B). Carotid bifurcation with artherosclerotic plaque (C) causing >70% stenosis. Emboli originating from surface ulcer or plaque rupture shower the cerebral circulation. Carotid plaque showing surface ulceration (C, right; D, arrow) and disruption of media with intraplaque haemorrhage (D, circle). Microscopy of unstable plaque with subendothelial macrophage accumulation (E; CD68 stain light microscopy, ×100); and intraplaque haemorrhage (F, black arrow) and ulcerated surface with overlying erythrocytes (F, white arrow; haematoxylin and eosin light microscopy, ×200).

in 10 min consistently preceded injury. Embolisation was completely abolished with incremental infusion of the antiplatelet agent (dextran 40). The same group has now audited 600 consecutive carotid endarterectomies, after the introduction of TCD-directed dextran therapy and found that the rate of postoperative thrombotic strokes fell from 2·7% to 0%.[46,47] There is evidence that 30 min of postoperative TCD monitoring is adequate.[51]

Possible mechanisms of cerebral microemboli generation

In patients with symptomatic critical internal-carotid-artery stenoses, there is likely to be an acute rupture of an atherosclerotic internal carotid plaque with superimposed thrombosis—not dissimilar to the acute coronary syndrome. A period of instability and increased activity within the carotid plaque is indicated by an increase in cerebral microemboli signals that can be detected in the middle cerebral artery. Microemboli appear to be primarily solid platelet aggregates, since they have been controlled with various antiplatelet agents including intravenous aspirin,[16,17] dextran 40,[46–51] Tirofiban,[18] and S-nitrosoglutathione.[52] In 100 patients, use of clopidogrel (75 mg) preoperatively resulted in a large reduction in the relative risk of having 20 or more emboli in the postoperative period (odds ratio 10·23 [1·3–83·3]; p=0·01).[53] Plaque stabilisation with aspirin and glycoprotein IIb/IIIa inhibitors are established therapies for the acute coronary syndrome (figure 3).

Efficacy of pharmacological therapy

Cerebral microemboli seem to be surrogate markers for future ischaemic events. If they persist despite medical therapy, the risk of further neurological events is about 40 times higher than if they do not.[17] The CARESS trial[19] showed that dual therapy with clopidogrel and aspirin controls both microemboli and symptoms more effectively than single therapy. However, even in the dual-therapy group, some patients had continued embolisation and remained at risk of further events.

Identification of high-risk patients and timing of subsequent surgery

A case could be made for the use of TCD emboli detection in all carotid-based TIA, but at present this approach is not practicable. Some researchers believe that patients with continued embolisation should be offered urgent surgery.[17] However, cessation of both microemboli and symptoms in patients with recurrent or crescendo TIA has been described with use of TCD-directed intravenous antiplatelet agents.[18] Consequently, patients can undergo carotid endarterectomy safely on the next elective list, avoiding the risks associated with urgent or emergency surgery[15] or the risks associated with delay when microemboli persist despite oral antiplatelet therapy.[9,19]

Conclusion

Until further studies are undertaken, in our opinion all patients presenting with TIA or minor stroke should undergo rapid clinical assessment and duplex examination to assess the state of the internal carotid arteries (ideally within 24–48 h). A patient with a critical internal carotid stenosis and more than one TIA should have a TCD study to look for microemboli in the

Search strategy and selection criteria

References for this review were identified by searches of PubMed from 1980 until June 2005 with the terms TIA, microemboli, transcranial Doppler, TCD, crescendo TIA, recurrent TIA. Articles were also identified through searches of authors' own files. Only papers published in English were reviewed.

appropriate middle cerebral artery. Those with critical internal carotid stenosis, symptoms, and emboli should be admitted to stroke prevention and care units. These units would be similar to coronary-care units and jointly managed by stroke physicians, neurologists, and vascular surgeons. With a high ratio of staff to patients, frequent corrections of cardiovascular, metabolic, and haematological factors could be achieved, the aim being to prevent strokes from occurring.[54,55] Elective surgery is likely to have better outcomes than either the conventional treatments of medical therapy alone or urgent surgery. Failure to control either microemboli or symptoms from a critical internal-carotid stenosis remains an indication for urgent surgery. Although intravenous heparin decreases cerebral microemboli after a focal event,[9] the widely adopted approach of intravenous heparin and early surgery is unsatisfactory.[28]

Converging lines of evidence suggest that TCD can assist in identifying the patients at high risk of a subsequent neurological event, and the pharmacological efficacy of therapeutic interventions can now be assessed rapidly and non-invasively. TCD detection of cerebral microemboli offers an important advance in multidisciplinary team working which enables the physician to optimally integrate medical therapies and the surgeon to determine the safest timing of surgery for a patient who has had a recent TIA or stroke.

Acknowledgments

D J Higman, C Marshall, A J Sinclair, and N Balcombe (UHCW NHS Trust, Coventry, UK), K Pattinson (John Radcliffe Hospital, Oxford, UK), and C W M Chan (Queen Elizabeth Hospital, Birmingham, UK).

Authors' contributions

CI did the literature search, devised figures, and wrote the review. CT did an additional literature search and helped review and amend the paper.

Conflicts of interest

We have no conflicts of interest.

Role of the funding source

No funding source was involved in the preparation of this paper.

References

1 Coull A, Lovett J, Rothwell P. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public organisation of services. *BMJ* 2004; **328**: 326–28.

2 Royal College of Physicians. National clinical guidelines for stoke, 2nd edn. Sudbury, Suffolk: Laverham Press, 2004: 31.

3 Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA* 2000; **284**: 2901–06.

4 Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ. Endartectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 2004; **363**: 915–24.

5 Rothwell PM, Warlow CP. Timing of TIAs preceding stroke: time window for prevention is very short. *Neurology* 2005; **64**: 817–20.

6 Consensus Committee of the Ninth International Cerebral Hemodynamic Symposium. Basic identification criteria of Doppler microembolic signals. *Stroke* 1995; **26**: 1123.

7 Daffertshofer M, Mielke O, Pullwitt A, Felsenstein M, Hennerici M. Transient ischaemic attacks are more than "ministrokes". *Stroke* 2004; **35**: 2453–58.

8 Rothwell PM, Eliasziw, Gutnikov SA, Warlow CP, Barnett HJM. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 2004; **363**: 915–24.

9 Sliwka U, Lingnau L, Stohlmann WD, et al. Prevalence and time course of microembolic signals in patients with acute stroke. *Stroke* 1997; **28**: 358–63.

10 Valton L, Larrue V, Pavy le Traon A, Massabuau P, Geraud G. Microembolic signals and risk of early recurrence in patients with stroke or transient ischaemic attack. *Stroke* 1998; **29**: 2125–28.

11 Forteza AM, Babikian VL, Hyde C, Winter M, Pochay V. Effect of time and cerebrovascular symptoms on the prevalence of microembolic signals in patients with cervical carotid stenosis. *Stroke* 1996; **27**: 687–90.

12 Babikian VL, Hyde C, Winter MR. Cerebral microembolism and early recurrent cerebral or retinal ischemic events. *Stroke* 1997; **28**: 1314–18.

13 Molloy J, Markus HS. Asymptomatic embolization predicts stroke and TIA risk in patients with carotid artery stenosis. *Stroke* 1999; **30**: 1440–43.

14 Gao S, Wong KS, Hansberg T, Lam WW, Droste DW, Ringelstein EB. Microembolic signal predicts recurrent cerebral ischaemic events in acute stroke patients with middle cerebral artery stenosis. *Stroke* 2004; **35**: 2832–36.

15 Siebler M, Nachtmann A, Sitzer M, et al. Cerebral microembolism and the risk of ischemia in asymptomatic high-grade internal artery stenosis. *Stroke* 1995; **26**: 2184–86.

16 Goertler M, Baeumer M, Kross R, et al. Rapid decline of cerebral microemboli of arterial origin after intravenous acetylsalicylic acid. *Stroke* 1999; **30**: 66–69.

17 Goertler M, Blaser T, Krueger S, Hofmann K, Baeumer M, Wallesch C-W. Cessation of embolic signals after antithrombotic prevention is related to reduced risk of recurrent arterioembolic transient ischaemic attack and stroke. *J Neurol Neurosurg Psychiatry* 2002; **72**: 338–42.

18 Junghans U, Siebler M. Cerebral microembolism is blocked by tirofiban, a selective non-peptide platelet glycoprotein IIb/IIIa receptor antagonist. *Circulation* 2003; **107**: 2717–21.

19 Markus HS, Droste DW, Kaps M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic signal detection. *Circulation* 2005; **111**: 2233–40.

20 Mackinnon AD, Aaslid R, Markus HS. Long-term ambulatory monitoring for cerebral emboli using transcranial Doppler ultrasound. *Stroke* 2004; **35**: 73–78.

21 Blaser T, Glanz W, Krueger S, Wallesch CW, Kropf S, Goertler M. Time period of monitoring for transcranial Doppler of embolic signals to predict recurrent risk of embolic transient ischaemic attack and stroke from arterial stenosis. *Stroke* 2004; **35**: 2155–59.

22 Imray CHE, Myers SD, Pattinson KTS, et al. Effect of exercise on cerebral perfusion in humans at high altitude. *J Appl Physiol* 2005; **99**: 699–706.

23 North American Symptomatic Carotid Endarterectomy Trial Collaborators: Beneficial effect of carotid endarterectomy in patients with high-grade carotid stenosis. *N Engl J Med* 1991; **325**: 445–53.

24 European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: Interim results for symptomatic patients with severe (70–99%) or mild (0–29%) carotid stenosis. *Lancet* 1991; **337**: 1235–43.

25 Mayberg MR, Wilson, SE, Yatsu F, et al. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis: Veterans Affairs Co-operative Studies Program 309 Trialist Group. *JAMA* 1991; **266**: 3332–33.

26 Mentzer RM, Finkelmeier BA, Crosby IK, Wellons HA. Emergency carotid endarterectomy for fluctuating neurologic deficits. *Surgery* 1981; **89**: 60–66.

27 Wilson SE, Mayberg MR, Yatsu F, Weiss DG. Crescendo transient ischemic attacks: a surgical imperative. *J Vasc Surg* 1993; **17**: 249–55.

28 Nehler MR, Moneta GL, McConnell DB, et al. Anticoagulation followed by elective carotid surgery in patients with repetitive transient ischemic attacks and high-grade stenosis. *Arch Surg* 1993; **128**: 1117–21.

29 Goldstone J, Moore WS. Emergency carotid artery surgery in neurologically unstable patients. *Arch Surg* 1976; **111**: 1284–91

30 Schneider C, Johansen K, Konigstein R, Metzner C, Oettinger W. Emergency carotid thromboendarterectomy: safe and effective. *World J Surg* 1999; **23**: 1163–67.

31 Brandl R, Brauer RB, Maurer PC. Urgent carotid endarterectomy for stroke in evolution. *Vasa* 2001; **30**: 115–21.

32 Greenhalgh RM, Cuming R, Perkin GD, McCollum CN. Urgent carotid surgery for high-risk patients. *Eur J Vasc Surg* 1993; (suppl A): 25–32.

33 Eckstein HH, Schumacher H, Klemm K, et al. Emergency carotid endarterectomy. *Cerebrovasc Dis* 1999; **9**: 270–81.

34 Gertler JP, Blankenstein JD, Brewster DC, et al. Carotid endarterectomy for unstable and compelling neurologic conditions: do the results justify an aggressive approach? *J Vasc Surg* 1994; **19**: 42–40.

35 Bond R, Rerkasem K, Rothwell PM. Systematic review of the risks of carotid endarterectomy in relation to the clinical indication for and timing of surgery. *Stroke* 2003; **34**: 2302–03.

36 Blaser T, Hofmann, Buerger T, Effenberger O, Wallesch C-W, Goertler M. Risk of stroke, transient ischaemic attack, and vessel occlusion before endarterectomy in patients with symptomatic severe carotid stenosis. *Stroke* 2002; **33**: 1057–62.

37 Markus HS, MacKinnon A. Asymptomatic embolization detected by Doppler ultrasound predicts stroke risk in symptomatic carotid artery stenosis. *Stroke*. 2005; **36**: 971–75.

38 Lennard NS, Vijayasekar C, Tiivas C, Chan CWM, Higman DJ, Imray CHE. Control of emboli in patients with recurrent or crescendo transient ischaemic attacks using preoperative transcranial Doppler-directed Dextran therapy. *Br J Surg* 2003; **90**: 166–70.

39 Jansen C, Vriens EM, Eikelboom BC, Vermeulen FEE, van Ginj J, Ackerstaff RGA. Carotid endarterectomy with transcranial Doppler and electroencephalographic monitoring: a prospective study in 130 operations. *Stroke* 1993; **24**: 665–69.

40 Ackerstaff RG, Moons KG, van de Vlasakker, et al. Asscociation of intraoperative transcranial Doppler monitoring variables with stroke from carotid endarterectomy. *Stroke* 2000; **31**: 1817–23.

41 Smith JL, Evans DH, Fan L, et al. Interpretation of embolic phenomena during carotid endarterectomy. *Stroke* 1995; **26**: 2281–84.

42 Gaunt ME, Martin PL, Smith JL, et al. Clinical relevance of introperative embolization detection by transcranial Doppler ultrasonography during carotid endarterectomy: a prospective study of 100 patients. *Br J Surg* 1994; **81**: 1435–39.

43 Jansen C, Ramos LMP, van Heeswijk JPM, Moll FL, van Gijn J, Ackerstaff RG. Impact of microembolism and hemodynamic changes in the brain during carotid endarterectomy. *Stroke* 1994; **25**: 992–97.

44 Jansen C, Moll FL, Vermeulen FE, van Haelst, Ackerstaff RG. Continuous transcranial Doppler ultrasonography and electroencephalography during carotid endarterectomy: a multimodal monitoring system to detect intraoperative ischemia. *Ann Vasc Surg* 1993; **7**: 95–101.

45 Jansen C, Vriens EM, Eikelboom BC, Vermeulen FE, van Gijn J, Ackerstaff RG. Carotid endarterectomy with transcranial Doppler and electroecephalographic monitoring: a prospective study in 130 operations. *Stroke* 1993; **24**: 665–69.

46 Hayes PD, Lloyd AJ, Lennard N, et al. Transcranial Doppler-directed Dextran-40 therapy is a cost-effective method of preventing carotid thrombosis after carotid endarterectomy. *Eur J Vasc Endovasc Surg* 2000; **19**: 56–61.

47 Naylor AR, Hayes PD, Allroggen H, et al. Reducing the risk of carotid surgery: a 7-year audit of the role of monitoring and quality control assessment. *J Vasc Surg* 2000; **32**: 750–59.

48 Levi CR, Roberts AK, Fell G, et al. Transcranial Doppler microembolus detection in the identification of patients at high risk of perioperative stroke. *Eur J Vasc Endovasc Surg* 1997; **14**: 170–76.

49 Levi CR, O'Malley H, Fell G, et al. Transcranial Doppler detected cerebral microembolism following carotid endarterectomy: high microembolic signal loads predict postoperative cerebral ischaemia. *Brain* 1997; **120**: 621–29.

50 Lennard N, Smith J, Dumville J, et al. Prevention of postoperative thrombotic stroke after carotid endarterectomy: the role of transcranial Doppler ultrasound. *J Vasc Surg* 1997; **26**: 579–84

51 Chan CWM, Tiivas C, Pritchard G, Higman DJ, Imray CHE. Post operative transcranial Doppler monitoring: an early warning device? *Int Angiol* 2000; **19** (suppl 1): 128.

52 Kaposzta Z, Martin J, Markus HS. Switching off embolization from symptomatic carotid plaque using S-nitrosoglutathione. *Circulation* 2002; **105**; 1480–84.

53 Payne DA, Jones CI, Hayes PD, et al. Beneficial effects of clopidogrel combined with aspirin in reducing cerebral emboli in patients undergoing carotid endarterectomy. *Circulation* 2004; **109**: 1476–81.

54 Imray C, Higman D, Tiivas C. Timing of surgery in symptomatic carotid disease. *Lancet* 2004; **363**: 1553–54.

55 Imray CHE, Pattinson K. Surgery for carotid artery stenosis: patients with critical stenoses should be admitted to stroke prevention units. *BMJ* 2004; **329**: 1344.

9) Appendix 3

a) Recent altitude related publications

G Johnson, J Simmons, AD Wright, P Hillenbrand, MF Beazley, I Sutton, **CHE Imray**
Ataxia at altitude measued on a wobble board.
Wilderness and Environmental Medicine 2005; **16**: 42-46

BG Johnson, AD Wright, , MF Beazley, TC Harvey, P Hillenbrand, **CHE Imray**
The sharpened Romberg test for assessing ataxia in mild acute mountain sickness.
Wilderness and Environmental Medicine 2005; **16(2)**: 62-66

CWM Chan, H Hoar, K Pattinson, AR Bradwell, AD Wright, **CHE Imray** & Birmingham Medical Research Expeditionary Society.
The Effect of sildenafil (Viagra) and acclimatization on cerebral oxygenation at altitude
Clinical Science. 2005; **119**: 319-324

Imray CHE, Kennedy CH, Pattinson K, Brearey S, Wright A & Birmingham Medical Research Expeditionary Society.
Acute mountain sickness in adolescents: A pilot study.
Wilderness and Environmental Medicine, 2004; **15(3)**: 202-206

Wolff CB, Richardson N, Kemp O, **Imray CHE**. Near infra-red spectroscopy and arterial oxygen extraction at altitude. In the press. Advances in Experimental Medicine and Biology, 2005.

b) Recent carotid surgery related publications

K Pattinson, **CHE Imray**
Another double tails-up capnography trace.
Anaesthesia 2005; **65**: 97-98

Joseph T, Kandiyil N, Beale D, Tiivas C, **Imray CHE**
A novel treatment for symptomatic carotid dissection.
Postgraduate Medical Journal 2005; **81(958)** : e6.

K Pattinson, Wynne Jones, **CHE Imray**
Monitoring of intracranial pressure, cerebral perfusion and metabolism.
Continuing Education in Anaesthesia, Critical Care and Pain. 2005; **5(4)**: 130-133

K Pattinson, **CHE Imray,** AD Wright.
What does cerebral oximetry measure.
British Journal of Anaesthesia 2005; **94(6)**: 863-4
Imray CHE, A Thacker, M Mead.

Oxygen administration can reverse neurological deficit following carotid cross-clamp.
British Journal of Anaesthesia 2005; **95(2)**: 274-5

Imray CHE, Higman DJ, Marshall C. Transcranial Doppler monitoring and the CARESS Trial.
In the press Circulation 2005.

Pattinson KT and **Imray CHE**. Transcranial Doppler and carotid artery disease strokes: more than just risk stratification.
Stroke. 2005; **36 (11)**: 2340-1.

Wilderness and Environmental Medicine, **16**, 42–46 (2005)

BRIEF REPORT

Ataxia at Altitude Measured on a Wobble Board

Brian G. Johnson, MB; John Simmons, MB; Alexander D. Wright, MB; Peter Hillenbrand, MB; Margaret F. Beazley, MB; Ian Sutton, MB; Christopher H.E. Imray, MB; and the Birmingham Medical Research Expeditionary Society

From the Chirk Surgery, 1-2 Castle Road, Chirk, Wrexham, UK (Dr Johnson); Tools of Coventry, Coventry, UK (Dr Simmons); Walsall Manor Hospital, Walsall, UK (Dr Wright); Good Hope Hospital, Sutton Coldfield, UK (Dr Hillenbrand); Laurie Pike Health Centre, Birmingham, UK (Dr Beazley); Garvin Institute of Medical Research, Sydney, Australia (Dr Sutton); Walsgrave Hospital, Coventry, UK (Dr Imray); and Birmingham Medical Research Expeditionary Society, The Medical School, Edgbaston, Birmingham, UK (BMRES).

Objective.—To establish a simple measure of ataxia for use at high altitude.

Methods.—Twenty healthy subjects took part in a trek to 5005 m. At 5 different altitudes on the route, they undertook a balance test using a wobble board. The primary objectives were to investigate disturbances of ataxia at altitude and to correlate any observed disturbances with acute mountain sickness (AMS) scores. Secondary outcomes were correlations with cerebral regional oxygenation, pulse oximetry, and age.

Results.—After a short learning curve, the wobble board test was found to be reproducible. Subjects over 31 years of age were significantly less steady than younger subjects. Subjects suffering acute mountain sickness scored significantly worse on the wobble board test, although scores did not correlate with a specific question on unsteadiness. A positive test defined as equal to or more than 2.5 contacts over 2 minutes gave a predictive value for acute mountain sickness of 66.7% at 4650 m and 100% at 5005 m. Cerebral regional oxygenation in 9 subjects at 5005 m correlated with the wobble board test ($r = 0.72$; $p < .05$), whereas pulse oximetry did not.

Conclusions.—The wobble board may be a useful adjunct in quantitating ataxia in the field. A positive result may indicate the presence of AMS and may be a useful clinical measure of cerebral hypoxia but should be correlated with other clinical features.

Key words: altitude, ataxia, cerebral regional oxygenation, HACE, wobble board

Introduction

Ataxia refers to a disturbance in the smooth performance of voluntary motor acts and may affect the limbs, the trunk, or the gait. Ataxia or imbalance describes the inability to maintain an upright position while stationary or during movement. Ataxia is an important clinical feature of acute mountain sickness (AMS), not only increasing the risk of having accidents but also providing an indication that the common, relatively benign form of AMS is progressing to potentially fatal high-altitude cerebral edema (HACE).[1] Symptoms of ataxia were noted in 25 of 42 (60%) subjects suffering from HACE and were noted as a physical sign in a similar percentage.[2] The Lake Louise self-assessment questionnaire for AMS does not specifically address the issue of ataxia, and we have previously suggested appropriate amendments.[3] Our observations in studies of AMS are that the symptom of unsteadiness is commonly reported before any disturbance of the heel-to-toe walking test. The only question that may have some relevance to ataxia relates to the presence or absence of dizziness/light-headedness, but such symptoms are nonspecific. A question on coordination was included in the cerebral AMS (AMS-C) part of the environmental symptoms questionnaire, and on factor analysis, incoordination was rated higher than dizziness.[4] Although ataxia is partly assessed by the heel-to-toe walking test portion of the Lake Louise clinical assessment protocol,[5] this is a relatively insensitive measure of ataxia and, there is no clinical assessment that satisfactorily grades the severity of impaired balance. We therefore attempted to develop a more sensitive objective test of ataxia that might be useful in identifying patients at risk of progressing from AMS to more serious HACE.

Corresponding author: Brian G. Johnson, Chirk Surgery, 1-2 Castle Road, Chirk, Wrexham LL14 5BS, UK (e-mail: brian.johnson@gp-w91024.wales.nhs.uk).

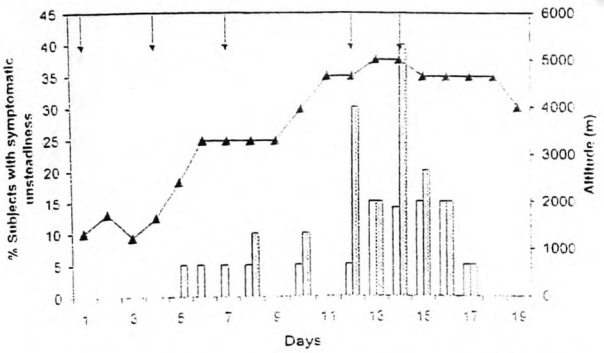


Figure 1. Altitude profile is shown in black triangles over the 19 days of the trek. The days of wobble board tests are indicated by arrows. The proportion of subjects with self-reported symptomatic unsteadiness is shown in the vertical columns, with the morning questionnaire as white bars and the evening questionnaire as stippled bars.

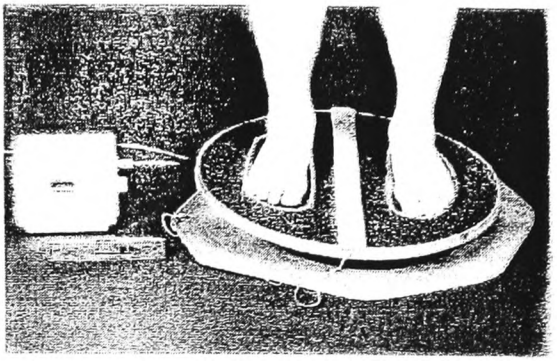


Figure 2. Wobble board equipment in use.

The objective of this study was to investigate disturbances of ataxia that occur at altitude and to correlate any observed disturbances with AMS and with symptoms of dizziness/light-headedness. Secondary endpoints of the study were to assess whether age was a factor in impaired balance arising at altitude, and whether there were any correlations with cerebral regional oxygenation and pulse oximetry studies. We designed an experimental protocol using a wobble board as a way of investigating balance.

Methods

Six healthy subjects (3 males and 3 females) aged 25–46 years undertook a reproducibility study of results between tests at sea level on four separate occasions, 2–3 days apart. Twenty different healthy subjects (16 males, 4 females) aged 21–61 years (median 33 years) who took part in a trekking expedition to an altitude of 5005 m in the Kanchenjunga region of Nepal (route profile: Figure 1) were recruited for this study. The subjects were all members of the Birmingham Medical Research Expeditionary Society (BMRES), traveling to altitude as part of a research expedition. No subject was excluded for any reasons. Initial recruitment was at sea level. A medical questionnaire pretrek revealed no subjects with known coordination problems. At altitudes below 3300 m, subjects were free of any symptoms of unsteadiness. Throughout the trek no prophylactic drugs against AMS were taken. Five subjects, however, were given acetazolamide to treat AMS between 4650 m and 5005 m. The drug was taken 12–18 hours before the wobble board test at 5005 m. No alcohol was allowed in the 12 hours before a test, and subjects were warm and well hydrated during testing.

All subjects completed Lake Louise questionnaires every morning and evening. Subjects were considered to be suffering from AMS at any given altitude if the questionnaire score was 3 or more before the wobble board test was done at that altitude. At the same time, a separate BMRES questionnaire assessing 23 different symptoms was completed, and question 3 ("I have been unsteady on my feet") was scored (0, not at all; 1, slight; 2, moderate; 3, quite a lot; or 4, extreme).

WOBBLE BOARD

A wobble board consisting of a flat board (diameter 53 cm) with a half sphere (diameter 15 cm) glued to the center of the undersurface was modified by attaching a metal strip to the inferior surface of the circumference. The board was placed on a flat metal plate checked for horizontal position with a spirit level. The combined weight of board and plate was 6 kg. The metal strip and plate were connected by a single electrical circuit to a battery-powered recording box (weight 1 kg) that recorded the duration of contact of the metal strip with the metal plate to the nearest 0.1 second (Figure 2). Each contact was marked by a buzzer sound so that the person supervising the test could record the number of contacts. The equipment was used in a covered area (mountain hut or tent) in which one could stand, so that environmental distractions of coldness, noise, sunlight, and distracting movement could be kept to a minimum.

Subjects removed footwear and stood on the board with their feet astride the central point. Foot outlines were drawn on the board to ensure a standard position 25 cm apart. Subjects kept their eyes open and were encouraged to fix visually on a distant point. When balance had been achieved, observations were then made for three separate 1-minute periods, separated by ap-

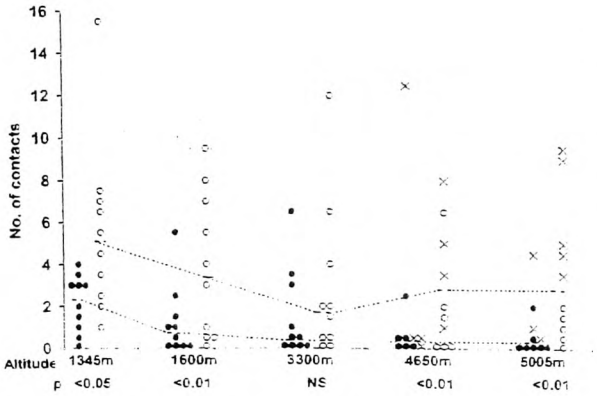


Figure 3. Wobble board (number of contacts) results at different altitudes. At each altitude, the p values refer to the difference between the younger (31 years of age or less, closed circles) compared with older (over 31 years of age, open circles) subjects. The crosses refer to subjects with AMS at 4650 m and 5005 m.

proximately 1 minute of rest. Subjects were asked to keep the board horizontal and were allowed to use their arms to maintain balance to simulate normal walking conditions. Subjects were familiarized with the test at sea level before departure and were assessed on five occasions during the trek: at 1345, 1660, 3300, 4650, and 5005 m (Figure 3). Because of difficulties in familiarizing and testing all subjects at the same time at sea level, 1345 m was used as the first assessment point and was considered still low enough not to play any part in symptoms or signs of AMS.

OXYGENATION

Measurements of peripheral oxygen saturation (Ohmeda oximeter) and cerebral regional oxygenation[6] were undertaken on 9 randomly chosen subjects from the group at 5005 m. All measurements were made under cover of tent or mountain hut. Reflected near-infrared cerebral spectroscopy (NIRS) uses light in the NIR spectrum (650–1100 m) and, similar to pulse oximeters and mixed venous oximeters, uses the principles of light transmission and absorption to measure concentrations of oxygenated (HbO_2) and deoxygenated ($HbDO_2$) hemoglobin and total hemoglobin (Total Hb) in cerebral tissue. The cerebral regional oxygen saturation (rSO_2) was derived from HbO_2/Total Hb × 100. Continuous noninvasive NIRS was performed using a Critikon 2020 monitor (Johnson and Johnson Medical, Newport, UK), with the sensor positioned over a standard point in the frontoparietal region and held in place with a pressure bandage around the forehead to ensure good waveforms throughout the measurements.

STATISTICS

Within-subject comparisons were made using paired t-tests, and between-subject comparisons were made using the Wilcoxon rank sum test.

Results

Duration and Number of Contacts

The duration of contact and the number of contacts in any given test were highly correlated ($r = 0.92$; $p < .0001$). The number of contacts has therefore been used when relating wobble board results to other measurements.

REPRODUCIBILITY

The first of the three readings of all tests at sea level and at altitude was significantly higher than the second and third readings; for example, during the altitude study, the mean number of contacts (SD) was 5.0 (5.9) at the first reading, which was higher than 2.6 (3.6) at the second reading and 2.7 (3.4) at the third reading ($p < .001$). The second and third readings were not significantly different, and for further analysis the mean of these two readings was used. The mean number of contacts (SD) on repeated testing on alternate days at sea level fell from 4.4 (2.4), to 2.1 (1.4), to 1.8 (1.6), to 0.5 (0.6). The number of contacts was less than 1.5 in all subjects by the fourth successive test.

EFFECT OF AGE

The number of contacts increased with increasing age ($r = 0.48$; $p < .05$). Subjects over 31 years of age were significantly unsteadier on the wobble board (mean number of contacts, 3.79; SD, 3.5) than those aged 31 years or under (mean, 1.52; SD, 2.2) ($p < .001$). Older subjects were unsteadier at each altitude except at 3300 m (Figure 3).

EFFECT OF ALTITUDE

Wobble board results improved, comparing results at 1345 and 1660 m (mean number of contacts 3.77 [SD 3.4] vs. 2.58 [SD 2.97]; $p < .05$, paired t-test), but thereafter, mean results were not affected by ascent to higher altitude (3300 m, 2.23 [SD 3.1]; 4650 m, 2.26 [SD 3.34]; and 5005 m, 2.25 [SD 2.89]).

Predictive values for acute mountain sickness (AMS)

No. of contacts		*4650 m*		*5005 m*	
+Test	*−Test*	*Positive (%)*	*Negative (%)*	*Positive (%)*	*Negative (%)*
>0.5	0	53.8	85.7	57.1	100.0
≥1.0	≥0.5	55.5	72.7	63.6	88.8
≥1.5	≥1.0	50.0	72.7	75.0	83.3
≥2.0	≥1.5	57.1	69.2	75.0	83.3
≥2.5	≥2.0	66.7	71.4	100.0	85.7
≥3.0	≥2.5	80.0	73.3	100.0	85.7
≥7.01	<7.01	100.0	66.7	100.7	66.7

CLINICAL QUESTIONNAIRES AND EXAMINATION AT ALTITUDE

The Lake Louise question on dizziness/lightheadedness was scored positive by 4 subjects at 4650 m (number of contacts 12.5, 6.5, 0.5, 0.5), compared with 16 subjects scoring negative (mean number of contacts, 1.95 [SD 2.7]) and was scored positive by 2 subjects at 5005 m (number of contacts, 4.5 and 0.5).

Five subjects scoring positive to the specific question on unsteadiness in the BMRES questionnaire at 4650 m did not perform differently (number of contacts: mean, 4.62 ± 5.1 SD) than those with no unsteadiness (mean, 1.41 ± 2.3) ($p > .05$, Wilcoxon rank sum test). Similarly, the 6 subjects scoring positive on the question at 5005 m did not perform differently (number of contacts, 3.77 ± 3.3 SD) than those with no unsteadiness (mean, 1.57 ± SD 2.5 $p > .05$). No subjects were unsteady using the heel-to-toe test at 4650 m, and only 2 subjects (number of contacts 9.0 and 4.5) were unsteady on heel-to-toe testing at 5005 m.

EFFECT OF AMS

At 4650 m, the 8 subjects with AMS had a greater number of contacts on the wobble board (4.3 ± SD 4.63) compared with those with no AMS (1.09 ± SD 1.82) ($p < .01$, Wilcoxon rank sum test). At 5005 m, the 8 subjects with AMS had a greater number of contacts on the wobble board (4.50 ± SD 3.29), compared with those with no AMS (1.98 ± SD 3.3) ($p < .01$ Wilcoxon rank sum test). The predictive value of the wobble board test for AMS is shown in Table 1.

RELATIONSHIP TO CEREBRAL OXYGENATION

Cerebral regional oxygenation measured in 9 subjects at 5005 m correlated with the number of contacts on the wobble board ($r = 0.73$; $p < .05$), but peripheral oxygenation did not correlate with the wobble board test result.

Discussion

Active balance, as defined by maintaining equilibrium while moving,[7] is essential to trekkers and climbers in mountainous terrain. Normal balance function is reliant on complex central mechanisms that result in coordinated neurologic and musculoskeletal interactions. Different inputs are received via the vestibular, visual, and somatosensory systems, and normal posture is maintained through the vestibulo-spinal and vestibulo-ocular motor reflexes that are integrated by the cerebellum, pons, and midbrain. Higher cortical functions, notably attention, volition, and memory are also necessary to maintain balance. We attempted to devise a test of ataxia that was largely independent of higher cortical function and learning effects.

It has been shown that static balance deteriorates with hypobaric hypoxic conditions as low as 2438 ft,[8] and the importance of ataxia is recognized by the inclusion of the heel-to-toe test in the clinical assessment of AMS.[5] However, the results in our study show that the heel-to-toe test is relatively insensitive, and a simple quantitative test of ataxia applicable to field conditions is required. The wobble board proved easy to use at high altitude, with the equipment being simple and reliable in use. This included the battery, which was in a protective box to protect against coldness. The improvement in results we observed early in the trek probably reflected a learning effect. We were not able to determine in this small group whether older subjects took longer to learn the technique, but repeated testing in subjects taken from a wide age range showed complete mastery by the fourth test, and results at the four altitudes above 1345 m were stable.

No subjects undertaking the wobble board test were taking regular medications that would affect balance. It is particularly important to note that acetazolamide was not used prophylactically for AMS but had been given to five subjects for management of AMS at 5005 m. Acetazolamide is known to improve intermittent episodes of ataxia that occur in individuals with defined ion-channel mutations.[9,10] Furthermore, magnetic resonance spectroscopy in untreated individuals with episodic ataxia type 2 shows an increased pH in the cerebellum and cerebrum that is normalized following acetazolamide therapy.[11]

Older subjects would be expected to have greater subclinical ataxia at sea level than younger subjects, because aging is associated with hair cell loss and selective neu-

ronal loss that particularly affects the Purkinje cells of the cerebellar vermis,[12] vestibular nuclear neurons, and primary vestibular neurons[13]. Previous large-scale studies have shown a clear deterioration of balance with increasing age.[14] The wobble board test we devised was sufficiently difficult in older subjects, but for younger subjects, it will need modifications so that all subjects score positively under normal conditions.

The design of the study did produce limitations in the eventual analysis of the results. The number of participants was limited by the size of this expedition party. The number of altitude elevations at which measurements could take place was small, and the frequency of testing was probably not high enough. This limited the statistical power in analyzing results and lessened the possibility of making more conclusive statements. In addition, the wide age range (21–61 years) exposed a difference in difficulty in performing the test across the ages. Whether this affected the results is difficult to ascertain, as all participants found that a high level of concentration was required to perform. In addition, for practical reasons, we designed the test procedure to have a time period of 60 seconds. We have not performed other studies to know whether this is the optimal length of time for the test. Last, as in the case of other studies at altitude, the difficulty in our ability to control environmental factors at altitude may have affected the test results.

Ataxia assessed by this wobble board is probably related to AMS. One study at altitude showed that oxygenation did not improve ataxia but did improve AMS symptoms and scores, indicating that ataxia may not correlate with AMS, using current scoring systems.[15] Larger numbers are required to overcome the limitations of self-assessment scores and the range of symptoms included in the Lake Louise questionnaire.

Conclusions

We conclude that the wobble board test was easy to use but was shown to have some limitations with a learning curve and a distinct effect of age on the results. A positive result may indicate the presence of AMS, but whether wobble board scores are truly predictive of AMS requires further studies with more regular measurements in a larger number of subjects.

References

1. Ward MP, Milledge JS, West JB, eds. High altitude medicine and physiology. In: *High Altitude Cerebral Edema*. 3rd ed. London: Arnold 2000:248.
2. Hultgren HN, ed. High altitude cerebral edema. In: *High Altitude Medicine*. Stanford, CA: HN Hultgren:326–327.
3. Beazley M, Hillenbrand P, Johnson B, Forster PJG, Wright AD, Imray CHE, and BMRES. Recommended changes in Lake Louise acute mountain sickness (AMS) scoring. *Adv Exp Med Biol*. 1999;474:364.
4. Sampson JR, Cymerman A, Burse RL, Maher JT, Rock PB. Procedures for the measurement of acute mountain sickness. *Aviat Space Environ Med*. 1983;54:1063–1073.
5. Roach C, Bartsch P, Hackett PH, Oelz O. The Lake Louise acute mountain sickness scoring system. In: Sutton JR, Houston CS, Coates G, eds. *Hypoxia and Molecular Medicine*. Burlington, VT: 1993:272–74.
6. Imray CHE, Barnett NJ, Walsh S, BMRES. Near infrared spectroscopy in the assessment of cerebral oxygenation at high altitude. *Wilderness Environ Med*. 1998;9:198–203.
7. Kent M. *The Oxford Dictionary of Sports Science and Medicine*. Queen City Printers. Oxford, England: Oxford University Press: 1994.
8. Nordahl SH, Aasen T, Owe JO, Molvaer J. Effects of hypobaric hypoxia on postural control. *Aviat Space Environ Med*. 1998;69:590–595.
9. Calandriello L, Veneziano L, Francia A, et al. Acetazolamide responsive episodic ataxia in an Italian family refines gene mapping on chromosome 19 p13. *Brain*. 1997; 120:805–812.
10. Denier C, Ducros A, Vahedi K, et al. High prevalence of CAC NAIA truncations and broader clinical spectrum in episodic ataxia type 2. *Neurology*. 1999;52:1816–1821.
11. Sappey-Marinier D, Vighetto A, Peyron R, Broussolle E, Borimartin A. Phosphorus and proton magnetic resonance spectroscopy in episodic ataxia type 2. *Ann Neurol*. 1999; 46:256–259.
12. Sjobeck M, Dahlen S, Englund E. Neuronal loss in the brainstem and cerebellum—part of the normal ageing process? A morphometric study of the vermis cerebelli and the inferior olivary nucleus. *J Geron Ser A Biol Sci Med Sci*. 1999;54B:363–368.
13. Lopez I, Honrubia V, Baloh R. Ageing and the human vestibular nucleus. *J Vest Res*. 1997;7:77–85.
14. Physical Fitness Laboratory. *Physical Fitness Standard of Japanese People*. 3rd ed. Tokyo: Tokyo Metropolitan University Fumaiac; 1982.

Wilderness and Environmental Medicine, 16, 62–66 (2005)

ORIGINAL RESEARCH

The Sharpened Romberg Test for Assessing Ataxia in Mild Acute Mountain Sickness

Brian G. Johnson MB; Alex D. Wright, MB; Margaret F. Beazley, MB; Timothy C. Harvey, MB; Peter Hillenbrand, MB; Christopher H. E. Imray, MB; and the Birmingham Medical Research Expeditionary Society

From Chirk Surgery, Chirk, Wrexham, UK (Dr Johnson); Walsall Manor Hospital, West Midlands, UK (Drs Wright and Harvey); Lauric Pike Health Centre, Birmingham, UK (Dr Beazley); Good Hope Hospital, Sutton Coldfield, West Midlands, UK (Dr Hillenbrand); Walsgrave Hospital, Coventry, West Midlands, UK (Dr Imray); and The Medical School, University of Birmingham, Edgbaston, Birmingham, UK (BMRE Society).

Objective.—To evaluate the Sharpened Romberg Test (SRT) as a measure of ataxia in subjects with mild acute mountain sickness in order to determine its sensitivity and specificity.

Methods.—The SRT was performed in 23 subjects during ascent to 5260 m.

Results.—The SRT was more often abnormal than the traditional heel-to-toe test, and at the highest altitude it was related to higher median Lake Louise symptom scores with predictive values of 60% sensitivity and 89% specificity. Our evaluation of the SRT appears to agree with similar studies on ataxia showing a lack of correlation between ataxia and symptoms of acute mountain sickness at altitudes below 5260 m.

Conclusion.—The SRT was easy to perform and provided a quantitative assessment of truncal ataxia in the field without the need for specialized equipment.

Key words: acute mountain sickness, altitude, ataxia, cerebral regional oxygenation, high-altitude cerebral edema, Sharpened Romberg Test

Introduction

Objective neurological signs are not usually associated with acute mountain sickness (AMS), but the development of truncal ataxia may be a useful indicator that the benign, self-limiting problem of AMS is developing into the potentially fatal syndrome of high-altitude cerebral edema (HACE).[1,2] Ataxia is presently assessed by the Lake Louise scoring system and heel-to-toe tandem walking test.[3] These have replaced the previously used Environmental Systems Questionnaire[4] and the classic Romberg test.[5] The current clinical tests for ataxia are at best only semiquantitative and, in our experience, rarely positive in subjects with moderate to severe AMS.

To study ataxia more accurately, other authors have used static platform posturography and have shown that stability of stance deteriorates significantly at high altitude.[6] but postural ataxia may not be related to other symptoms of AMS.[7] Static platform posturography requires expensive and sensitive equipment that is generally used in experiments in pressure chambers or mountain huts. It may be difficult to use in field experiments and is not practical for ordinary mountain expeditions; therefore, we have been seeking ways of measuring ataxia at altitude more easily. Our initial results with a wobble board[8] showed no relation between ataxia and Lake Louise AMS scores but a possible relation with cerebral oxygenation. However, age was an important determinant in ataxia scores by this method, and the test required several attempts before learning was achieved, thereby making it impractical in the field.[9]

Modified versions of the Romberg test have been used in a variety of areas in medicine.[10,11] The Sharpened Romberg Test (SRT)[12] is now widely used in the assessment of divers recovering from decompression sickness.[13,14] It has been accepted as a useful measure of ataxia because it can be easily quantified and is more sensitive than the standard test.[15] For these reasons, we

Presented at the 13th International Hypoxia Symposium, Banff, Canada, February 18–22 2003.

Corresponding author: Dr Brian Johnson, Chirk Surgery, 1–2 Castle Rd, Chirk, Wrexham, LL14 5BS, UK (e-mail: a.wright@bmres.org.uk).

hypothesized that the SRT might be extended to the assessment of ataxia at altitude. The aims of this study were to evaluate the SRT as a measure of ataxia in subjects with mild AMS and whether such measurements of ataxia related to other features of AMS or to cerebral regional oxygenation.

Methods

SUBJECTS AND STUDY DESIGN

Twenty-three healthy unacclimatized subjects (mean age 40.6 years, range 22–65) were assessed during ascent to 5260 m. Baseline readings were recorded at an altitude of 150 m (Birmingham, UK). The group then traveled by air to 3610 m for days 1 to 5, by bus to 4750 m for days 5 to 8, and by bus again to 5260 m for days 8 to 12 (Bolivia). One subject left the study for nonmedical reasons on day 6. One subject was withdrawn from the study because of HACE developing on day 6. One subject was taking acetazolamide for prophylaxis of AMS, and 3 subjects started acetazolamide on days 6, 8, and 9 because of increasing altitude sickness; otherwise, no other medications were being used for AMS or which would have interfered with balance or the central nervous system. Alcohol was not allowed in the 10 hours preceding testing.

CLINICAL ASSESSMENT OF AMS

Self-completed Lake Louise questionnaires[3] were completed each morning and evening. A score of 3 or higher from the questionnaire alone indicated AMS. An additional question on balance was asked with the following scores: 0 = no loss of balance, 1 = mild unsteadiness, 2 = moderate unsteadiness, and 3 = difficulty in standing. Two experienced physicians performed clinical assessment of a standard heel-to-toe test—walking along a straight line 3 m long—on the day after arrival at 3610 m (day 2), on arrival at 4750 m (day 5), on days 6 and 7 at 4750 m, on arrival at 5260 m (day 8), and on day 9 at 5260 m. The assessment of the heel-to-toe test was scored by the clinical assessment method suggested by the Lake Louise consensus,[3] with balancing maneuvers or worse being taken to indicate a positive test.

SHARPENED ROMBERG TEST

Each subject stood erect on a level surface wearing flat shoes with his or her feet aligned in a strict tandem heel-to-toe position, arms crossed over the chest, and the open palm of the hand falling on the opposite shoulder. Once stable, the subject closed his or her eyes and attempted to maintain that position for 60 seconds. If the subject failed to maintain the position by movement of either arms or feet or by opening his or her eyes, the time taken to failure was noted. If not achieved, the subject attempted up to 3 further trials of 60 seconds, and a sum of the times was recorded. If the first test was successful, no further testing was required and the subject assumed a score of 240 seconds (60 × 4). If a test of 60 seconds was completed on the second or third trial, all subsequent tests assumed a score of 60.

Tests were performed at 150 m (baseline), on the morning after arrival at 3610 m (day 2), on the next morning at 3610 m (day 3), on the evening of arrival at 4750 m (day 5), on the next morning at 4750 m (day 6), and on the morning after arrival at 5260 m (day 9). All subjects on the expedition volunteered to participate and actively collaborated with the recorder to achieve as good of a result as possible.

REGIONAL CEREBRAL OXYGENATION

Infrared spectroscopy[16] with a Critkon 2020 monitor (Johnson and Johnson Medica LTD, Newport, UK) was used to measure regional cerebral oxygenation (rSO_2) in 18 subjects at 5260 m.

STATISTICS

The presence or absence of AMS was analyzed by chi-square tests, differences in AMS scores were analyzed by Wilcoxon rank sum test, and rSO_2 was measured by Student's t test. Significance was determined at $P < .05$.

Results

Results for the SRT are summarized in Table 1. At baseline, the SRT results were normal (240 seconds) in 22 of the 23 subjects. One subject scored 171 seconds. At 3610 m, 10 of the 23 subjects (43%) had abnormal SRT results, but abnormal results did not relate to the presence or absence of AMS. Mean age was not significantly different in those with abnormal SRT results (48.8 years; SD 13.3) compared with those without ataxia (38.8 years; SD 12.4). On the next morning, 10 subjects had abnormal SRT results, but only 1 of the 23 subjects had AMS. At 4750 m, 5 of the 22 subjects (22.7%) had abnormal SRT results, but none had AMS. On the next morning, 3 of the 22 subjects had abnormal SRT results, but again no relation was with 8 subjects who had AMS.

Nine of the 21 subjects (43%) had abnormal SRT results after arrival at 5260 m, and 11 had an AMS score ≥3 (chi-square $P < .05$). Mean age was not significantly different in those with ataxia (46.4 years; SD 10.4) com-

Table 1. Number of subjects with abnormal and normal results for the Sharpened Romberg Test (SRT) and the heel-to-toe test (HTT) and with or without acute mountain sickness (AMS)†

Altitude (m)	SRT		Score(s)			HTT		AMS	
			Median	SD	Range	Abnormal	Normal	With	Without
150	Abnormal	1	171			...	...	...	...
	Normal	22				...	...	...	...
3610	Abnormal	10	147	38	88–197	2	8	5	5
	Normal	13				2	11	2	11
4750	Abnormal	5	170	43	108–205	1	4	0	5
	Normal	17				1	16	0	17
5260	Abnormal	9	182	36	107–216	1	8	7*	2
	Normal	12				0	12	4	8

†A normal SRT is 240 seconds. Acute mountain sickness was scored using the Lake Louise self-completed questionnaire on the same morning of the SRT. A score of 3 or higher indicated the presence of AMS.
*The relationship of SRT to AMS by chi-square testing, $P < .05$.

pared with those without ataxia (40.6 years; SD 14.3, $P < .3$). The sensitivity of the SRT in predicting AMS was 71% at 3610 m and 60% at 5260 m and specificity increased from 69% to 89% at 5260 m.

SELF-REPORTING ATAXIA

Five subjects on 7 occasions reported loss of balance in the questionnaire completed on the same morning but before the SRT results were measured. On 6 of the 7 occasions, the SRT results were abnormal at the same time. However, the SRT results were abnormal on 31 of the 106 occasions when no ataxia was reported.

HEEL-TO-TOE TEST

Four of the 23 (17%) tests were abnormal after arrival at 3610 m, 2 of the 22 (9%) were abnormal at 4750 m, and only 1 of 20 (5%) were abnormal at 5260 m (Table 2). Of the 7 occasions when an abnormal heel-to-toe test was recorded, an abnormal SRT result was noted in 4 tests and a normal SRT result was noted in 3 tests, whereas 19 of the 59 (32%) normal heel-to-toe tests were associated with abnormal SRT results. The sensitivity of the heel-to-toe test in predicting the result of the SRT varied between 11% and 20% and the specificity varied between 85% and 100% at the different altitudes. The small number of positive heel-to-toe abnormalities did not allow calculation of the sensitivity and specificity of this test in predicting AMS. However, AMS was present on only 2 of the 7 occasions when a positive heel-to-toe test was recorded.

Table 2. Number of subjects with abnormal and normal results for the Sharpened Romberg Test (SRT) and the heel-to-toe test (HTT)*

Altitude (m)	SRT		HTT		P
	Abnormal	Normal	Abnormal	Normal	
3610	10	13	4	19	ns
4750	5	17	2	20	ns
5260	9	12	1	20	ns

*No significant association was found between the tests.

REGIONAL CEREBRAL OXYGENATION

The mean (SD) rSO_2 at 5260 m was not significantly different in those with normal SRT results (range 62%–66%) compared with those with abnormal SRT results (range 58%–65%).

Discussion

The SRT was easy to perform in the field, requiring only a flat surface in a quiet environment and 1 observer with a watch. The test appeared to have no learning effect, which was confirmed by another study of fit individuals.[14] Our results showed that truncal ataxia was a clinical feature occurring in a significant number of subjects ascending to high altitude. Test scores improved during acclimatization at 3160 m and 4750 m but were not re-evaluated at 5260 m. Age did not appear to have a significant effect on the results, unlike our findings of ataxia

measured on a wobble board or the findings of other studies that used the SRT.[10,12,17]

An association with Lake Louise symptoms scores was demonstrated at 5260 m only, though the relatively small number of subjects may have precluded us from assessing this at lower altitudes where the AMS scores were lower. The SRT appeared to be more sensitive than the heel-to-toe test, with over 3 times the number of abnormal readings on days arriving at altitude. Although the self-reporting of ataxia appeared to be highly specific, the large number of positive SRT results in subjects not reporting ataxia would make the questionnaire a very insensitive method of assessment.

The SRT would also have some limitations as a field test in the mountains, with physical elements of the environment, variable mental application of the participant, drugs, alcohol, orthopedic conditions, and possible fatigue all able to influence the ability of the participant to give his or her best test effort. There is also discussion about how long the test should be conducted; therefore, it is not standardized.[13]

Analysis of the SRT scores for the 5 subjects who either started acetazolamide for increasing altitude sickness or were developing HACE would have been helpful in showing the SRT's usefulness. However, in 2 subjects, there was no measurement of the SRT in the preceding 12 hours. In 1 subject, the measurement was normal 12 hours before his AMS score changed from 1 to 3. In another subject, the SRT measurement was normal 10 hours before he deteriorated quickly, and he was thought to be developing significant HACE. In another subject, the SRT measurement was abnormal (192 seconds) 17 hours before he was thought to be developing HACE. In all 5 subjects, heel-to-toe testing was normal 12 hours before their illnesses.

Baumgartner et al[5] used a static posturography platform on ascent to 4559 m and reported similar findings to our own, with ataxia occurring at altitude in almost half the subjects, but their results were not associated with AMS assessed by the Environmental Symptoms Questionnaire. Cymerman et al[5] assessed postural instability and AMS during exposure to simulated altitude of 4300 m and failed to show correlation with either the prevalence or the severity of AMS.[6] This is in keeping with our results that showed no connection with AMS scores by the Lake Louise method at equivalent altitudes to the scores of these other studies. However, we did find an association at a higher altitude (5260 m). Baumgartner and Bartsch[18] recorded that, unlike symptoms of AMS, ataxia did not improve with short-term oxygenation. Our findings support their hypothesis that the postural ataxia induced by moderate to high altitude may result from hypoxia affecting specific parts of the brain that are not involved in the pathogenesis of AMS and that these hypoxia-related effects, unlike AMS, need more time for recovery. Our findings on rSo_2 also suggest that global cerebral hypoxia is not required for ataxia.

Recovery from ataxia as measured by the SRT was significantly slower than AMS at 3610-m altitude but not at 4650-m altitude with repeated assessment on subsequent days. Further studies on ataxia at altitudes above 5000 m are needed to ascertain whether a relationship exists with other features of AMS and to document the time course of ataxia during acclimatization. For the SRT to be useful for predicting AMS, regular measurements twice daily would appear to be necessary, and even then rapid deterioration may still occur after a normal result. Further studies are required to determine the usefulness of the SRT in the diagnosis of AMS and HACE.

Conclusion

The SRT provided a simple quantitative assessment of truncal ataxia, which could be performed in the field without the need for specialized equipment. An abnormal result was found more commonly in the SRT than in the standard heel-to-toe test and was associated with other symptoms of AMS at 5260 m. The relationship of the SRT to other clinical features of AMS at lower altitudes requires further study.

Acknowledgment

The Mount Everest Foundation supported this work.

References

1. Ward MP, Milledge JS, West JB. High altitude cerebral edema. In: *High Altitude Medicine and Physiology*. 3rd ed. London: Arnold; 2000:248.
2. Hackett PH, Rennie ID, Levine HD. The incidence, importance and prophylaxis of acute mountain sickness. *Lancet*. 1976;2:1149–1154.
3. Roach C, Bartsch P, Hackett PH, Oelz O. The Lake Louise acute mountain sickness scoring system. In: Sutton JR, Houston CS, Coates G, eds. *Hypoxia and Molecular Medicine: Proceedings of the 8th International Hypoxia Symposium*. Burlington, VT: Queen City Printers; 1993:272–274.
4. Sampson JB, Cymerman A, Burse RL, Maher JT, Rock PB. Procedures for the measurement of acute mountain sickness. *Aviat Space Environ Med*. 1983;54:1063–1072.
5. Ferrazzini G, Maggiorini M, Kriemler S, Bartsch P, Oelz O. Successful treatment of acute mountain sickness with dexamethasone. *Br Med J*. 1987;294:1380–1382.

6. Cymerman A, Muza SR, Beickeman BA, Ditzler DT, Fulco CS. Postural instability and acute mountain sickness during exposure to 24 hours of simulated altitude (4300 m). *High Alt Med Biol.* 2001;4:500–514.
7. Baumgartner RW, Eichenberger U, Bartsch P. Postural ataxia at altitude is not related to mild to moderate mountain sickness. *Eur J Appl Physiol.* 2002;86:322–326.
8. Wright A, Johnson B, Simmons J. A new method for measuring unsteadiness at altitude. *High Alt Med Biol.* 2001; 2:104.
9. Bradwell AR, Johnson B, Imray C, Simmons J, Wright AD. Wobble board, acute mountain sickness and cerebral regional oxygenation. *High Alt Med Biol.* 2002;3:454.
10. Iverson BD, Gassman MR, Shaddeau SA, Turner ME Jr. Balance performance, force production and activity levels in non-institutionalised men 60–90 years of age. *Phys Ther.* 1990;70:348–355.
11. Kilburn KH, Thornton JC. Formaldehyde impairs memory, equilibrium and dexterity in histology technicians: effects which persist for days after exposure. *Arch Environ Health.* 1987;42:117–120.
12. Fregly AR, Graybiel A. An ataxia test battery not requiring rails. *Aerosp Med.* 1968;39:277–282.
13. Fitzgerald B. A review of the Sharpened Romberg Test during medicine. *SPUMS.* 1996;26:142–146.
14. Lee CT. Sharpening the Sharpened Romberg. *SPUMS* 1996;28:125–132.
15. Notermass NC, Van Dijk GW, Van Der Graff Y, Van Gijn J, Worke JHJ. Measuring ataxia: quantification based on the standard neurological examination. *J Neurol Neurosurg Psychiatry.* 1994;57:2–26.
16. Imray CHE, Barnett NJ, Walsh S, the Birmingham Medical Research Expeditionary Society. Near infrared spectroscopy in the assessment of cerebral oxygenation at high altitude. *Wilderness Environ Med.* 1998;9:198–203.
17. Briggs RC, Gossman MR, Birch R, Drews JE, Shaddeau SA. Balance performance among non-institutionalised elderly women. *Phys Ther.* 1989;69:748–756.
18. Baumgartner RW, Bartsch P. Ataxia in mountain sickness does not improve with short-term oxygenation inhalation. *High Alt Med Biol.* 2002;3:283–292.

Effect of sildenafil and acclimatization on cerebral oxygenation at altitude

Colin W. M. CHAN*, Helen HOAR*, Kyle PATTINSON†, Arthur R. BRADWELL*, Alexander D. WRIGHT*, Christopher H. E. IMRAY‡ and the Birmingham Medical Research Expeditionary Society*

*Immunodiagnostics Research Laboratory, The Medical School, University of Birmingham, Vincent Drive, Edgbaston, Birmingham B15 2TT, U.K., †Nuffield Department of Anaesthetics, University of Oxford, The John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, U.K., and ‡County Vascular Unit, University Hospitals Coventry and Warwickshire NHS Trust, Clifford Bridge Road, Coventry CV2 2DX, U.K.

ABSTRACT

Phosphodiesterase-5 inhibitors decrease hypoxic pulmonary vasoconstriction under hypobaric hypoxia, but are not known to affect cerebral blood flow or oxygenation. The present study was designed to evaluate the effect of sildenafil on cerebral haemodynamics during acute exposure to altitude and after acclimatization. Ten subjects were studied 1 and 3 days after rapid ascent to 3480 m before and for two consecutive hours after taking sildenafil (50 mg). Before acclimatization, HR (heart rate) rose at 1 h (76.3 ± 1.0 beats/min compared with 72.5 ± 1.5 beats/min at baseline; $P < 0.05$) and had returned to baseline at 2 h (71.3 ± 1.1 beats/min; $P > 0.05$). Mean BP (blood pressure) fell from 96.0 ± 2.0 mmHg at baseline to 91.7 ± 2.5 ($P < 0.001$) at 1 h and 89.8 ± 1.8 mmHg ($P < 0.0001$) at 2 h, whereas SaO_2 (arterial oxygen saturation) increased from 83.9 ± 0.5% at baseline to 85.3 ± 0.4% ($P < 0.0001$) at 1 h and 85.0 ± 0.5% ($P < 0.01$) at 2 h. MCAV [MCA (middle cerebral artery) velocity] and P_{ETCO_2} (end-tidal partial pressure of CO_2) were unchanged, but rSO_2 (regional cerebral oxygen saturation) rose progressively at 1 h (62.7 ± 0.8%; $P < 0.05$) and 2 h (65.3 ± 0.9%; $P < 0.0001$) compared with baseline (59.3 ± 1.3%). After 3 days of acclimatization, resting rSO_2 and R_{MCA} (MCA resistance) increased and oxygen delivery fell. Changes in HR and mean BP after sildenafil were similar to day 1, but SaO_2 did not change. However, rSO_2 increased [61.7 ± 0.9% at baseline to 65.0 ± 1.0% ($P < 0.0001$) at 1 h and 64.0 ± 0.9% ($P < 0.001$) at 2h], despite a reduction in MCAV [65.3 ± 1.8 cm/s at baseline to 61.3 ± 1.5 cm/s ($P < 0.01$) at 1 h and 60.9 ± 1.7 cm/s ($P < 0.0001$) at 2 h] and P_{ETCO_2} [4.1 ± 0.05 kPa at baseline to 4.0 ± 0.04 kPa at 2 h ($P < 0.01$)]. These observations suggest that sildenafil improves cerebral oxygenation at altitude. Whereas the early changes before acclimatization may be largely pulmonary in origin, the later observations may be a direct cerebral effect which warrants further study.

INTRODUCTION

Increasing numbers of people travel to or work at altitude and risk development of AMS (acute mountain sickness) [1]. The brain is sensitive to relatively minor fluctuations in cerebral oxygenation and is normally protected by cerebral autoregulatory responses which provide stable D_{O_2} (oxygen delivery), particularly by increasing cerebral blood flow.

Acute hypobaric hypoxia also affects the pulmonary circulation resulting in pulmonary hypertension and this may be associated with high-altitude pulmonary oedema.

Key words: acclimatization, altitude, cerebral regional oxygen saturation, hypoxia, middle cerebral artery velocity, phosphodiesterase-5, sildenafil (Viagra®).

Abbreviations: AMS, acute mountain sickness; BP, blood pressure; D_{O_2}, oxygen delivery; HR, heart rate; MCA, middle cerebral artery; MCAV, MCA velocity; NIRS, near-IR spectroscopy; NO, nitric oxide; eNOS, endothelial NO synthase; PDE5, phosphodiesterase-5; P_{ETCO_2}, end-tidal partial pressure of CO_2; R_{MCA}, MCA resistance; rSO_2, regional cerebral oxygen saturation; SaO_2, arterial oxygen saturation.

Correspondence: Dr Colin W. M. Chan (email colin.chan@mac.com).

There has been recent interest in the use of sildenafil, a selective PDE5 (phosphodiesterase-5) inhibitor, which has been shown to be effective in reducing pulmonary hypertension. Sildenafil has variable vasodilating effects on different vascular beds attributable to the differential expression of PDE5 in the endothelium of blood vessels throughout the body. The presence of other synergistic factors is postulated to play a role as well, e.g. the presence of NO (nitric oxide) released from non-cholinergic non-adrenergic penile nerve endings, which has been utilized in the treatment of erectile dysfunction. The profound effect of sildenafil in abolishing the rise in pulmonary artery pressure during acute hypoxia-induced pulmonary hypertension in human and eNOS (endothelial NO synthase)-deficient mice experiments has raised the potential therapeutic value of sildenafil and its analogues [2]. Furthermore, it has been suggested that sildenafil might prove to be of therapeutic benefit to travellers and indigenous populations not well adapted to altitude in the prevention of pulmonary hypertension and oedema [3].

It has been assumed that PDE5 is distributed widely throughout the vasculature, including the cerebral vascular bed. Thus sildenafil induces headache and aggravates migraine at sea level, suggesting a vasodilatory effect despite no demonstrable change having been shown in MCA (middle cerebral artery) diameter [4,5]. Immunolocalization studies have demonstrated PDE5 within neuronal tissue in rat Purkinje fibres [6], but the enzyme has not been specifically identified within cerebral blood vessels. To date, sildenafil has not been shown to affect cerebral perfusion. Given its potential value in reducing altitude related pulmonary hypertension, we sought to evaluate the effect of sildenafil on cerebral blood flow and oxygenation on acute ascent to high altitude and after acclimatization.

MATERIALS AND METHODS

Two studies were performed. The first was a pilot experiment undertaken to assess the cerebrovascular changes at 150 m (Birmingham, United Kingdom) produced by sildenafil on six healthy male subjects (age 34–60 years). The aim of the main study was to evaluate the time dependency and acclimatization response to sildenafil and was carried out in ten healthy subjects (seven male and three female; age 30–65 years) at 1 and 3 days after acute ascent by cable car to 3480 m (Refugio Guide del Cervino, Aosta, Italy). Barometric pressures were 99.1 kPa in Birmingham, and 66.2 kPa and 66.4 kPa on days 1 and 3 respectively, at 3480 m. Five subjects were common to both studies.

Study protocol

Subjects were rested in the supine position for 5 min prior to any measurements. Sildenafil (50 mg; Viagra®, Pfizer) was administered orally following baseline measurements and repeat measurements made after 1 h at 150 m and at 1 and 2 h at 3480 m. HR (heart rate), BP (blood pressure), Sa_{O_2} (arterial oxygen saturation), P_{ETCO_2} (end-tidal partial pressure of CO_2), rS_{O_2} (regional cerebral oxygen saturation) and MCAV (MCA velocity) were recorded with five measurements made at each time point. Subjects were not taking nitrates or any other cardiovascular drugs. The side-effect profile was evaluated by direct questioning of subjects upon completion of the experiment at 3480 m. The presence of AMS was scored using the Lake Louise self-completed questionnaire [7].

The Research and Ethics Committee of the South Birmingham Health Authority granted approval for the studies, and subjects gave written informed consent.

Cerebral NIRS (near-IR spectroscopy)

In the pilot study, continuous non-invasive cerebral NIRS was performed at 150 m using a Critikon 2020 cerebral redox spectroscope (Johnson and Johnson Medical Ltd). The dual detector sensor position was standardized to a point over the right fronto-parietal region with sensor margins 3 cm from the midline and 3 cm above the supra-orbital crest taking care to avoid the sagittal sinus. A Blue-line Tubifast bandage (Seton Healthcare Group) was used to keep the sensor in place, and maintained a standard probe pressure. rS_{O_2} was derived from the equation:

$$rS_{O_2} = (\text{oxygenated haemoglobin}/\text{total haemoglobin}) \times 100$$

In the main study at 3480 m, an Invos Adult Cerebral Oximeter (Somanetics; Somanetic Corporation) was used to measure cerebral oxygenation. Bilateral frontal probes were positioned and kept in place using Blue-line Tubifast bandage as before.

Transcranial Doppler

Continuous transcranial Doppler assessment of MCAV was measured by one of two experienced operators using a 2 MHz pulsed-wave, range-gated Doppler ultrasound (MultiDop T1; DWL Elektronische Systeme). The right MCA was identified by recognition of the characteristic waveform and typical flow velocity profile, and was insonated at 45–60 mm through the temporal bone window. The MCA time-averaged mean velocity (MCAV; cm/s) was recorded.

Measurement of Sa_{O_2}, P_{ETCO_2}, HR and BP

Sa_{O_2} and HR were monitored using an Ohmeda Biox 3740 Pulse Oximeter. Mean BP and P_{ETCO_2} were measured using a Datex-Ohmeda S/5 portable critical care monitor. Data were logged either manually (BP, P_{ETCO_2}, HR and Sa_{O_2}) or input via a multichannel I/O port to the hard drive of the transcranial Doppler for subsequent offline analysis.

Table 1 Time course effect of sildenafil on systemic parameters and cerebral haemodynamics on days 1 and 3 after arrival at 3480 m

Results are means ± S.E.M., $n = 10$. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ and ****$P < 0.0001$ compared with the pre-sildenafil value, as determined by a paired Student t-test. ††$P < 0.01$ and ††††$P < 0.0001$ between the 1 and 2 h time points, as determined by a paired Student t-test. ‡‡‡‡$P < 0.0001$ compared with the pre-sildenafil values on day 1, as determined by an unpaired Student t-test.

	Day 1			Day 3		
	Pre-sildenafil	1 h	2 h	Pre-sildenafil	1 h	2 h
HR (beats/min)	72.5 ± 1.5	76.3 ± 1.0*	71.3 ± 1.1††††	61.6 ± 1.2‡‡‡‡	67.4 ± 1.2***	61.0 ± 0.9††††
Mean BP (mmHg)	96.0 ± 2.0	91.7 ± 2.5****	89.8 ± 1.8****††	102.0 ± 2.7	92.0 ± 2.6***	93.8 ± 2.7**
Sa_{O_2} (%)	83.9 ± 0.5	85.3 ± 0.4****	85.0 ± 0.5**	87.4 ± 0.6‡‡‡‡	86.7 ± 0.4	88.4 ± 0.5††††
P_{ETCO_2} (kPa)	4.2 ± 0.05	4.2 ± 0.05	4.1 ± 0.05	4.1 ± 0.05	4.0 ± 0.05	4.0 ± 0.04**
MCAV (cm/s)	67.5 ± 1.4	65.0 ± 1.7	66.2 ± 1.4	65.3 ± 1.8	61.3 ± 1.5**	60.9 ± 1.7****
rSo_2 (%)	59.3 ± 1.3	62.7 ± 0.8*	65.3 ± 0.9****††	61.7 ± 0.9	65.0 ± 1.0****	64.0 ± 0.9***

Estimated cerebral Do_2 and R_{MCA} (MCA resistance)

Do_2 to the brain is proportional to the product of arterial oxygen content and brain blood flow. Since the haemoglobin concentration is unlikely to have altered within 3 days and the barometric pressure remained virtually unchanged, an estimate of the cerebral Do_2 was made using the formula:

$$Do_2 = SaO_2 \times MCAV$$

R_{MCA} was calculated as follows:

R_{MCA} (resistance units) = mean arterial BP/MCAV.

The Do_2 and R_{MCA} were calculated for individual subjects at each time point.

Statistics

Statistical and graphical analyses were performed using StatView 5.01 (SAS Institute Inc.) and Deltagraph 5 (SPSS Inc. and Red Rock Software) by unpaired and paired Student's t tests based on the parametric distribution of data. Results are expressed as mean values with data spread represented by ± 1 S.D. P values < 0.05 were considered significant.

RESULTS

In the pilot study, there were no changes in HR (72 ± 9.6 and 69.2 ± 6.5 beats/min), BP (97.5 ± 11.8 and 95.5 ± 13.5 mmHg), Sa_{O_2} (96.5 ± 1.6 and 95.0 ± 1.5 %), MCAV (53.1 ± 13.2 and 49.5 ± 6.5 cm/s) or cerebral rSo_2 (69.4 ± 1.8 and 68.8 ± 1.4 %) before and 1 h after sildenafil administration respectively.

On the first day of the main study, there was one subject who had a Lake Louise symptom score of 3. There was no recorded AMS on day 3. The responses to sildenafil on days 1 and 3 are shown in Table 1. On day 1, there was a rise in the mean HR at 1 h, which then returned to the baseline level at 2 h. Mean BP was reduced at 1 h and continued to fall at 2 h. Sa_{O_2} increased at 1 h and remained so during the second hour. P_{ETCO_2} remained unchanged. MCAV did not change significantly after sildenafil on day 1 (Figure 1B), but cerebral oxygenation improved at 1 h and continued to rise at 2 h (Figure 1A). The calculated Do_2 (Figure 1C) and R_{MCA} (Figure 1D) did not change.

On day 3, HR rose at 1 h and then returned to the baseline level at 2 h. Mean BP fell at 1 h and remained so at 2 h. Although Sa_{O_2} did not alter at 1 or 2 h compared with pre-sildenafil values, there was a small fall in P_{ETCO_2} at 2 h. The mean MCAV fell and cerebral oxygenation increased. The calculated Do_2 at all time points on day 3 was reduced compared with day 1 ($P < 0.01$; Figure 1C). Following sildenafil, Do_2 fell at 2 h on day 3 (35.5 ± 1.5 to 33.1 ± 1.2 units; $P < 0.05$). The baseline R_{MCA} was higher on day 3 compared with day 1 (1.7 ± 0.1 compared with 1.4 ± 0.1 units respectively; $P < 0.05$), but this difference was abolished with sildenafil at 1 and 2 h (Figure 1D).

The main side-effect noted was facial flushing in seven subjects of whom five felt that this was mild and the remaining two considered this moderately severe. Headache was noted in three subjects (two subjects had mild symptoms and one moderately severe but not incapacitating). Three subjects experienced mild nasal congestion and two subjects noticed bloodshot eyes although none experienced photophobia. One subject had mild indigestion and one other had mild transient postural hypotension.

DISCUSSION

Sildenafil is a cGMP-specific phosphodiesterase inhibitor that causes selective vasodilatation through a reduction of intracellular calcium in vascular smooth muscle. This is effected by inhibiting PDE5, which prevents the breakdown of pre-existing cGMP, the second messenger in the NO pathway. The presence of raised levels of NO is a prerequisite for PDE5 inhibitors such as sildenafil to work, as demonstrated by the prolongation of erectile

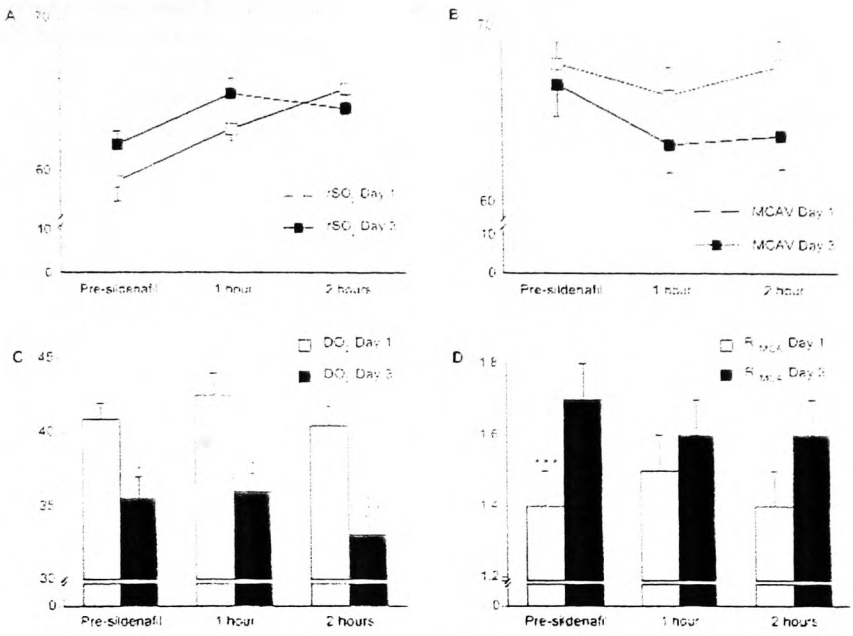


Figure 1 Effect of acclimatization and sildenafil on rSo_2 (A), MCAV (B), Do_2 (C) and R_{MCA} (D)

Results are means ± S.E.M. (single-ended error bars); $n = 10$. $^{*}P < 0.01$ comparing values at day 1 and day 3 at specified time points; $^{**}P < 0.05$ comparing pre-sildenafil with the 2 h time point on day 3; and $^{***}P < 0.05$ comparing the pre-sildenafil time point on day 1 with that at day 3. Statistical analyses on rSo_2 and MCAV are shown in Table 1.

function when non-cholinergic non-adrenergic (nitroxidergic) penile nerves are stimulated [8].

Although the reduction in systemic BP due to the vasodilatory effect of sildenafil is modest [9], there is a significant reduction in pulmonary arterial pressure in cases of pulmonary hypertension [10], presumably due to the background increase in NO in the pulmonary vasculature secondary to chronic hypoxia. Thus far, sildenafil has not been demonstrated to have an effect on cerebral blood flow by transcranial Doppler nor are there any data on the effect of sildenafil on cerebral oxygenation as measured by NIRS. The effect of sildenafil on the cerebral vasculature has been postulated but not demonstrated previously [11]. The present study describes the effect of sildenafil on cerebral blood flow and oxygenation at sea level and 3480 m. The absence of any change in cerebral oxygenation and blood flow at sea level is consistent with data reported previously [4].

Transcranial Doppler insonation of the MCA is accurate and reliable in the measurement of cerebral blood flow [12] and has been shown to be robust in assessing cerebral haemodynamics under high-altitude conditions [13]. MCAV as measured by transcranial Doppler has a linear relationship with cerebral blood flow within a wide range of flow values as measured by the ^{133}Xe clearance technique [12]. Furthermore, MCAV measurements under conditions of acute hypobaric hypoxia have been validated against sea-level measurements and are an accurate indicator of cerebral blood flow and Do_2 [14]. We have used previously cerebral NIRS under hypobaric conditions for cerebral hypoxia and have found this measure to be sensitive and reproducible as well as robust [15–17].

A comparison between the rSo_2 and MCAV curves in response to sildenafil for 1 day (unacclimatized) and 3 days (acclimatized) is shown in Figure 1. On day one, sildenafil caused a progressive improvement in cerebral oxygenation at 1 and 2 h. There is a similar rise at 1 h on day 3, but this effect appears to plateau at 2 h. This improvement, however, does not appear to be dependent on cerebral blood flow as there is no change in MCAV on day 1 and, paradoxically, a reduction in MCAV on day 3. The calculated Do_2 (Figure 1C) demonstrates the effect of acclimatization. Do_2 is proportionate to the MCAV and the Do_2 profile follows the changes in MCAV with sildenafil. The reduction in MCAV on day 3 is likely to be secondary to the overall improvement in SaO_2 and possibly a decrease in P_{ETCO_2} with acclimatization. At high altitude, the cerebral circulation is exposed to various competing influences: arterial hypoxaemia is a potent cerebral vasodilator, whereas arterial hypocapnia is a potent vasoconstrictor [18]. Both these effects are reflected in R_{MCA} (Figure 1D) and are modulated by acclimatization. In the present study there was an increase in R_{MCA} and a decrease in Do_2 with acclimatization that was overcome by sildenafil. On acute exposure to high altitude, hypoxia-induced cerebral vasodilatation appears to override the vasoconstrictor effects of hypocapnia but, by day 3, improved peripheral oxygenation with acclimatization increased R_{MCA}. In the present field study,

an indirect measure of Do_2 has been made by calculating the product of Sao_2 and MCAV which are both non-invasive measurements. Calculated Do_2 did not take into account any changes in plasma volume that may have occurred at altitude, thus changes in Do_2 after sildenafil largely reflected changes in MCAV.

The different profiles in the time-course experiment suggest that there may be multiple mechanisms at work and the observed effects of sildenafil when acclimatized may be intracranial rather than systemic. It may be postulated that the improvement in cerebral oxygenation with sildenafil on day 1 may be due, in part, to an increase in Sao_2. Despite the improvement in Sao_2 due to acclimatization, the response to sildenafil on day 3 is not correlated with any change in Sao_2. This suggests that the improvement in cerebral oxygenation is predominantly intracranial. NIRS provides a measure of the proportion of oxygenated blood in the cerebral capillaries. It does not distinguish how much is in the arterial or venous part of the capillary bed. The proportion of total blood in the cerebral capillaries has been estimated at 28% arterial and 72% venous [19,20]. It is possible that changes in these proportions could occur both at altitude with acclimatization and with sildenafil. The observed large changes in cerebral NIRS with more modest changes in MCAV would tend to support this model. A further possibility is differential vasodilatation with sildenafil (i.e. mid-sized arteries versus smaller downstream arterioles) which may potentiate the observed differences in cerebral oxygenation.

The presence of PDE5 in the cerebral arteries or microvasculature has thus far not been demonstrated, and our present findings of a change in MCAV with PDE5 inhibition suggest indirectly that this enzyme may in fact be present under hypobaric hypoxia. The absence of a discernible change in MCAV at sea level implies that a hypoxic drive is a precondition to cerebrovascular sensitivity to sildenafil. This is the first time that PDE5 inhibition has been demonstrated to affect cerebral oxygenation (both unacclimatized and acclimatized subjects) and cerebral blood flow (acclimatized subjects). Possible explanations for the unmasking of this cerebral response at altitude may be the priming effect of increased levels of local NO within the cerebral vascular bed consequent upon hypobaric hypoxia, or perhaps hypoxic up-regulation of hitherto indiscernible PDE5 at altitude. The role of NO priming has yet to be explored with respect to PDE5 inhibition, but experimental evidence showing loss of protection by ischaemic preconditioning when eNOS and nNOS (neuronal NOS) knockout mice are exposed to focal cerebral ischaemia suggests an important role for NO in the cerebrovascular response to sildenafil [21].

Although the potential role of PDE5 inhibition in the treatment of pulmonary hypertension has been highlighted previously, the present study demonstrates the wider influence of sildenafil on the cerebral vasculature. Under conditions of high-altitude hypoxia, sildenafil has a positive influence on cerebral oxygenation and an attenuation of cerebral blood flow. However, our present study was not designed to establish any therapeutic benefit from improved cerebral oxygenation. The mechanism by which these effects take place is not currently known and will need to be investigated further. These findings may influence our knowledge of PDE5 localization and direct further studies towards a potentially therapeutic role for PDE5 inhibitors in the management of cerebral hypoxia.

ACKNOWLEDGMENTS

We are grateful for the technical assistance of ScanMed Ltd, Datex-Ohmeda for the loan of the S/5 portable critical care monitor, and to Selly Oak Hospital, Birmingham, U.K. for the loan of a back-up Critikon 2020 cerebral redox spectroscope.

REFERENCES

1 Hackett, P. H. and Roach, R. C. (2001) High-altitude illness. N. Engl. J. Med. **345**, 107–114
2 Zhao, L., Mason, N. A., Morrell, N. W. et al. (2001) Sildenafil inhibits hypoxia-induced pulmonary hypertension. Circulation **104**, 424–428
3 Wilkins, M. R., Aldashev, A. and Morrell, N. W. (2002) Nitric oxide, phosphodiesterase inhibition, and adaptation to hypoxic conditions. Lancet **359**, 1539–1540
4 Kruuse, C., Thomsen, L. L., Jacobsen, T. B. and Olesen, J. (2002) The phosphodiesterase 5 inhibitor sildenafil has no effect on cerebral blood flow or blood velocity, but nevertheless induces headache in healthy subjects. J. Cereb. Blood Flow Metab. **22**, 1124–1131
5 Kruuse, C., Thomsen, L. L., Birk, S. and Olesen, J. (2003) Migraine can be induced by sildenafil without changes in middle cerebral artery diameter. Brain **126**, 241–247
6 Kotera, J., Fujishige, K. and Omori, K. (2000) Immunohistochemical localisation of cGMP-binding cGMP-specific phosphodiesterase (PDE5) in rat tissues. J. Histochem. Cytochem. **48**, 685–693
7 Roach, R. C., Bartsch, P., Hackett, P. H. and Oelz, O. (1993) The Lake Louise acute mountain sickness scoring system. In Hypoxia and Mountain Medicine (Sutton, J. R., Houston, C. S. and Coates, G., eds.), pp. 272–274, Queen City Printers, Burlington, VT
8 Cheitlin, M. D., Hutter, A. M., Brindis, R. G. et al. (1999) ACC/AHA Expert Consensus Document: Use of sildenafil (Viagra) in patients with cardiovascular disease. Circulation **99**, 168–177
9 Seftel, A. (2002) Effects of sildenafil citrate (Viagra) on blood pressure in normotensive and hypertensive men. J. Urol. **168**, 2318–2319
10 Peacock, A. J. (2003) Treatment of pulmonary hypertension. Br. Med J. **326**, 835–836.
11 Arnavaz, A., Aurich, A., Weissenborn, K., Hartmann, U., Emrich, H. M. and Schneider, U. (2003) Effect of sildenafil (Viagra®) on cerebral blood flow velocity: a pilot study. Psychiatry Res. **122**, 207–209
12 Clark, J., Skolnick, B., Gelfand, R. et al. (1996) Relationship of ^{133}Xe cerebral blood flow to middle cerebral arterial flow velocity in men at rest. J. Cereb. Blood Flow Metab. **16**, 1255–1262
13 Imray, C. H., Walsh, S., Clarke, T. et al. (2003) Effects of breathing air containing 3% carbon dioxide, 35% oxygen or a mixture of 3% carbon dioxide/35% oxygen on cerebral and peripheral oxygenation at 150 m and 3459 m. Clin. Sci. **104**, 203–210

14 Tauboll, E., Sorteberg, W., Owe, J. O. et al. (1999) Cerebral artery blood velocity in normal subjects during acute decreases in barometric pressure. Aviat. Space Environ. Med. 70, 692–697
15 Imray, C. H., 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 Imray, C. H., Brearey, S., Clarke, T. et al. (2000) Cerebral oxygenation at high altitude and the response to carbon dioxide, hyperventilation and oxygen. Clin. Sci. 98, 159–164
17 Imray, C. H., Clarke, T., Forster, P. J. et al. (2001) Carbon dioxide contributes to the beneficial effect of pressurization in a portable hyperbaric chamber at high altitude. Clin. Sci. 100, 151–157
18 Poulin, M. J., Fatemian, M., Tansley, J. G., O'Connor, D. F. and Robbins, P. A. (2002) Changes in cerebral blood flow during and after 48 h of both isocapnic and poikilocapnic hypoxia in humans. Exp. Physiol. 87, 633–642
19 McCormick, P. W., Stewart, M., Goetting, M. G. and Balakrishnan, G. (1991) Regional cerebrovascular oxygen saturation measured by optical spectroscopy in humans. Stroke 22, 596–602
20 Wolff, C. B. and Imray, C. H. (2003) Partitioning of arterial and venous volumes in the brain under hypoxic conditions. Adv. Exp. Med. Biol. 540, 19–23
21 Atochin, D. N., Clark, J., Demchenko, I. T., Moskowitz, M. A. and Huang, P. L. (2003) Rapid cerebral ischemic preconditioning in mice deficient in endothelial and neuronal nitric oxide synthases. Stroke 34, 1299–1303

Received 26 January 2005/5 April 2005; accepted 3 May 2005
Published as Immediate Publication 3 May 2005, doi:10.1042/CS20050036

Wilderness and Environmental Medicine, **15**, 000–000 (2004)

Self-Assessment of Acute Mountain Sickness in Adolescents: A Pilot Study

Christopher H. E. Imray, FRCS; Caroline H. Kennedy; Kyle Pattinson, FRCA; Stephen Brearey; Alex Wright, FRCP and the Birmingham Medical Research Expeditionary Society

From the Coventry and Warwickshire County Vascular Unit, Coventry and Warwickshire University Hospital, Walsgrave, Coventry, United Kingdom (Dr Imray); the King Henry VIII School, Coventry, United Kingdom (Ms Kennedy); the University Department of Anaesthesia, Queen Elizabeth Hospital, Birmingham, United Kingdom (Dr Pattinson); the Department of Paediatrics, Alder Hey Hospital, University of Liverpool, Liverpool, United Kingdom (Mr Brearey); and the Immunodiagnostic Research Laboratory, The Medical School, University of Birmingham, Edgbaston, Birmingham, United Kingdom (Dr Wright and BMRE Society).

Objective.—To perform a pilot study exploring the prevalence of acute mountain sickness (AMS) in adolescents on ascent to altitude and evaluating whether this age group is capable of self-assessment of AMS using the Lake Louise scoring system.

Methods.—Twelve teenagers aged 15 to 18 years old (5 girls) traveled for 21 days between 2400 and 5500 m. Each member of the expedition completed a Lake Louise self-assessment questionnaire on a daily basis. Group leaders (nonmedical) were informed about any subject with a score of 3 or more. Appropriate treatments were then initiated. Detailed analysis of data was undertaken on return to the UK.

Results.—There was 100% completion of 252 questionnaires. Eleven of the 12 subjects (91.7%) had symptom scores greater than or equal to 3, consistent with a diagnosis of AMS, on at least one day (range, 0–8). Symptoms of AMS were more common in the female group members ($P = .041$).

Conclusions.—AMS seems to be a common problem among adolescents. There are increasing numbers of adolescents traveling to high altitudes, and there seems to be a lack of information about the prevalence of AMS in this age group. Motivated adolescents seemed capable of self-monitoring for AMS using the Lake Louise questionnaire. Combined with an appropriate ascent profile and support, we feel this approach may contribute to safety in the mountains and merits further study.

Key words: adolescents, acute mountain sickness

Introduction

Increasing numbers of adolescents are traveling to high altitudes on school expeditions, school adventure holidays, and during gap years. There is little information about the prevalence, severity, and disease course of acute mountain sickness (AMS) in this age group.

A common clinical problem, AMS affects otherwise fit individuals of all ages who ascend to high altitudes. All travelers to altitudes over 2500 m (8000 feet) are potentially susceptible to AMS.[1,2] Symptoms include headache, lethargy, shortness of breath, sleep disturbance, loss of appetite, and nausea and vomiting, and they usually appear within the first 3 days of being in a high altitude [illegible] in the Himalayas, the prevalence of AMS has been reported to vary from 43% to 63%[3] and from 9% to 69% in the Alps.[5] The sickness severity depends upon a number of factors, including rate of ascent, the altitude achieved, recent previous acclimatization, and the susceptibility of the individual to the syndrome.

Severe symptoms from AMS in both children and adolescents have been reported.[6] Compared with the amount of literature concerning adults, the prevalence and disease process of AMS in children and adolescents has not been studied as well.[7] Wu[8] studied 464 children (0–15 years old) traveling across the Tibetan plateau and found that 34% had AMS and 1.5% had high altitude pulmonary edema. The prevalence was very similar to

Presented in part to the 13th International Hypoxia Symposium, Banff, Canada, February 2003.

Corresponding Author: Chris Imray, FRCS, Coventry and Warwickshire County Vascular Unit, Coventry and Warwickshire University Hospital, Clifford Bridge Rd, Walsgrave, Coventry, CV2 2DX, United Kingdom (e-mail: chrisimray@aol.com).

Table 1. Daily Lake Louise acute mountain sickness (AMS) scores for the group (n = 12)

Day	*Altitude*	*Altitude gain*	*Headache*	*Dizziness*	*GIT**	*Sleep*	*Activity*	*AMS score (total)*
1	3250 m	+3250 m	7	7	2	3	4	23
2	3250 m	0 m	8	6	2	3	2	21
3	3500 m	+250 m	4	6	4	3	2	19
4	3500 m	0 m	8	3	5	1	2	19
5	3000 m	−500 m	1	0	1	1	0	3
6	4200 m	+1200 m	5	5	3	6	5	24
7	3900 m	−300 m	5	1	2	6	3	17
8	2400 m	−1500 m	3	1	1	3	3	11
9	3250 m	+850 m	2	1	4	3	3	13
10	3700 m	+450 m	4	0	4	1	3	12
11	4600 m	+900 m	7	7	7	2	7	30
12	4800 m	+200 m	6	4	5	7	9	31
13	5200 m	+400 m	7	8	6	5	6	32
14	4500 m	−700 m	2	3	6	2	2	15
15	5100 m	−600 m	4	3	6	2	7	22
16	4800 m	−300 m	4	2	1	2	6	15
17	5500 m	+700 m	6	3	3	1	5	16
18	4600 m	−900 m	0	0	0	1	0	1
19	3700 m	−900 m	0	0	0	1	0	1
20	3250 m	−450 m	0	1	0	0	0	1
21	3250 m	0 m	0	0	0	0	0	0

*GIT, gastrointestinal trace symptoms.

the 5355 adults he also studied.[8] However, children may be more susceptible to the syndrome because its prevalence seems to decrease with increasing age.[3,9] There is also evidence that although AMS among adolescents is less common than in children, it may be more common than in adults.[10] Pulmonary edema also seems to be more common among children ascending to high altitudes with a recent or active viral respiratory illness.[11] A death from high altitude pulmonary edema in a 15-year-old was reported,[12] but we suspect there may be other deaths or serious events that are currently not formally reported.

It was the purpose of this pilot study to explore the prevalence of AMS in adolescents at altitude and to assess the practicality of using the self-assessment Lake Louise questionnaire in this age group.

Methods

Twelve teenagers aged 15 to 18 years old (5 girls) traveled for 21 days between 2400 and 5500 m. The mean age of the subjects was 16.1 years. All members of the group were fit and healthy with no underlying medical conditions and normally resided at 100 to 200 m. None of the group had previous exposure to high altitude.

The group traveled by air from the UK, arriving in Cusco (3250 m) on day 1 and spent 4 days at 3000 to 3500 m acclimatizing. The group then trekked the Inca Trail to Machu Picchu (4 days) climbing to 4200 m. After a rest day in Cusco, the group trekked for 10 days around the peak of Ausengate. The group then ascended to a maximum height of 5500 m before returning to Cusco (Table 1).

SYMPTOMS AND SIGNS OF AMS

Every evening, each member of the expedition completed a Lake Louise self-assessment questionnaire.[3] This was collected and scored by a single investigator (C.H.K.). Group leaders (nonmedical) were informed about any person with a score of 3 or more. Treatment, descent, or both were then initiated. No prophylactic or therapeutic drug treatment for AMS was used during the expedition. Detailed analysis of data was undertaken on return to the UK.

STATISTICS

Statistical significance was assessed by unpaired t-tests, regression analysis, and Wilcoxon signed rank tests (StatView for Windows, Abacus Concepts Inc, Berkley, CA). P values $<.05$ were considered significant.

Table 2. Lake Louise active mountain sickness (AMS) scores by sex (n = 12)

	Headache	*Dizziness*	*GIT**	*Sleep*	*Activity*	*AMS score*
Male 1	10	4	3	0	2	19
Male 2	2	4	7	6	9	28
Male 3	3	5	0	0	0	8
Male 4	3	3	1	3	4	14
Male 5	0	0	0	0	0	0
Male 6	2	5	5	0	8	20
Male 7	11	8	6	4	3	32
Male total	31	29	22	13	26	121
Female 1	5	1	6	7	5	24
Female 2	9	3	6	5	11	34
Female 3	16	8	9	12	8	53
Female 4	8	9	14	8	6	45
Female 5	13	11	4	9	14	51
Female total	51	32	39	41	44	207

*GIT, gastrointestinal tract symptoms.

Results

All 12 subjects completed the daily questionnaires, as requested, over the 21-day expedition (252 questionnaires; 100% completion).

In this study, 11 of the 12 subjects had symptom scores greater than or equal to 3 on at least one day (after a recent increase in altitude and with an associated headache) consistent with a diagnosis of AMS (91.7%). The subjects had a score of 3 or more on 43 days of a possible 252 days (17.1%). However, onset, duration, and severity were variable (Table 1). During the trip, 3 of the subjects (all female) had to be carried by horse because of fatigue, and 1 of the subjects had to be taken down the mountain to a lower altitude because of AMS (Lake Louise symptom score of 7). The time course of AMS symptoms in this age group lasted 24 to 48 hours. The range of days when a subject had a score of 3 or more was 0 to 8. The AMS scores correlated with a recent gain in altitude (Table 1).

Table 3. Days with AMS score greater than or equal to 3 by sex (n = 12)

Male 1	2	Female 1	4
Male 2	3	Female 2	5
Male 3	1	Female 3	8
Male 4	2	Female 4	6
Male 5	0	Female 5	7
Male 6	2		
Male 7	3		
Male total	13	Female total	30

*AMS, acute mountian sickness.

AMS was more frequently reported in the female members of the group. Over the 21-day expedition, the 7 male subjects had scores of 3 or more on 13 days, whereas the 5 female subjects had a score of 3 or more on 43 days (P = .041). There was no difference in the incidence of headache (P = .15), dizziness (P = .28), or gastrointestinal symptoms (P = .08). The female subjects suffered more from poor sleep (P = .043) and a reduction in overall activities (P = .043) (Tables 2 and 3).

Discussion

With increasing numbers of adolescents traveling to high altitudes, more information about AMS in this age group is required. The largest published series to date that looks at morbidity in youth expeditions to developing countries has noted a huge increase in the numbers of adolescents undertaking adventurous travel.[14] In 1994, 945 young people traveled abroad with a major UK company; 4 years later, the number had increased to 2460.[14] The study was a retrospective review of the medical records of those that traveled in 1996. There was no specific assessment of AMS, but some information relating to the condition was available. Eighty-six percent of the individuals who traveled above 2500 m suffered from headaches, and this appeared more often in younger travelers.

Although resident populations at high altitudes include adolescents, travel to high altitudes by lowland adolescent sojourners is often for the first time. They usually have little or no previous experience with such travel, so susceptibility to AMS is unknown. Supervision is usually by nonmedical group leaders. Objectives,

which may be entirely appropriate for most of the group, may not be suitable for those individuals more susceptible to AMS. There are also potential risks associated with group travel. Because the youth travelers are often below the age of consent, and their parents or guardians are usually not present at high altitudes with them (unlike with children), difficult decisions about drug prophylaxis or treatment must be made by the expedition organizers. Perhaps by increasing the awareness of AMS, both among the adolescents and the tour organizers, it may be possible to reduce such potential risks.[15]

In 2001, a Consensus Statement on behalf of the International Society of Mountain Medicine suggested that the prevalence of AMS in children was similar to that in adults.[6] Yaron et al[16] found no difference in the prevalence of AMS at a moderate altitude (3109 m) in preverbal children and adults. However, a recent publication looked at AMS in a small number of children, teenagers, and adults after an acute ascent by road to 3500 m, where one night was spent, and then a day trip to 4400 m.[10] The prevalence of AMS was 100% in the children (n = 6), 50% in the teenagers (n = 10), and 27% in the adults (n = 15). There is evidence that the prevalence of AMS seems to decrease with age. In a study of 615 subjects aged 8 to 51 years old ascending to the prospective shelters on Cotapaxi (4800 m) and Chimborazo (5000 m), the prevalence of AMS was more frequent in the 8- to 22-year-old group ($P < .01$).[17] In a large study of 558 children (aged 9–14 years old), the authors found AMS in 28% of them after ascent to 2835 m. However, it should be noted that 21% of the same group of children had symptoms traveling to a camp at sea level, suggesting the nonspecific nature of the symptoms. Girls tended to have more headaches, dizziness, shortness of breath, and insomnia.[18]

The Lake Louise acute mountain sickness scoring system was a consensus agreement that was introduced as a research tool in 1991 in an attempt to standardize assessment of AMS.[12] Given the nonspecific nature of the symptoms, signs, and laboratory findings, there is no gold standard for the diagnosis of AMS. In particular, whereas the questionnaire is a relatively sensitive tool, specificity can be variable, and false positives can be problematic.

This is the first report of self-assessment of AMS in adolescents. Despite no previous experience of either travel to altitude or the scoring system, the subjects found the scoring system to be quick and easy to learn, use, and interpret. They were able to determine from their assessment what members in their group had AMS, and they were then able to alert their group leaders so appropriate action could be taken. The AMS prevalence of 91.7% is higher than previously described in adults.[3,5] This may be caused by the small sample size or the particular ascent profile used in this study, or this percentage may represent a true higher prevalence of AMS in this age group.

Lake Louise AMS scores increased with recent significant ascent in altitude (Table 1). There is also evidence that after a period at altitude, subjects did acclimatize satisfactorily. From day 13 to day 18, there was a decrease in the Lake Louise scores, although the subjects continued to ascend, reaching the summit at 5500 m. As the group became more acclimatized, symptom scores reduced. This confirms observations published elsewhere.[19] Although none of the subjects was very ill with AMS, this condition remains a potentially serious condition.[20]

In this study, AMS was found to be more common in the female group members (Table 2). This observation could have several explanations. First, this could be true to form, and female adolescents may have a higher susceptibility to AMS. Girls in this age group may be more truthful in the reporting of mild or minor symptoms than boys. Alternatively, girls in this age group may have a higher background incidence of many of the symptoms, such as headaches. Fitness might affect the perception of the reduction in normal activities. No attempt to correlate AMS scores with menstrual cycle was made. There is evidence of a difference between sexes in the reporting of musculoskeletal injuries. Female marine corps recruits were 1.72 times more likely to report them than male recruits (95% CI, 1.29–2.30).[21]

Further information comparing the prevalence and severity of AMS in both adults and adolescents on similar ascent profiles is currently being sought. If the prevalence between the two age groups is similar, then we can be reassured that adequate attention is paid to graduated ascent in adolescents and that there is awareness of the disease so travel at high altitudes remains reasonably safe. However, if the adolescents have an increased prevalence or severity of AMS compared with the adults then the safety of using adult ascent profiles in adolescents needs to be seriously questioned.

Adult studies demonstrate a variable susceptibility to AMS, and it seems likely that this is the case among adolescents. A blanket approach to the prevention of AMS in adults is not widely accepted, so understandably there are concerns about a similar approach among teenagers and those organizing their expeditions.

Conclusion

This study demonstrates that a motivated group of adolescents is capable of self-monitoring for AMS using the adult Lake Louise questionnaire. The Lake Louise

scoring system should be used to complement rather than replace standard techniques (such as alert leaders enquiring after students who appear unwell, who fail to come to meals, or who are late into camp). The scoring system is no substitute for common sense and experience; however, its simplicity, the involvement of the adolescent in self-assessment, and the increased level of awareness of the condition in both the individual and the group are likely to improve safety. Combined with an appropriate ascent profile and experienced support, we feel this approach may contribute to safer travel in the mountains and merits further study.

References

1. Milledge JS. High altitude. In: Harries M, Williams C, Stanish WD, Micheli LJ, eds. *Oxford Textbook of Sports Medicine*. Oxford, England: Oxford University Press; 1994:255–270.
2. Ward MP, Milledge JS. *High Altitude Medicine and Physiology*. London, England: Chapman and Hall Medical; 1995.
3. Hackett PM, Rennie D, Levine HF. The incidence, importance, and the prophylaxis of acute mountain sickness. *Lancet*. 1976;:1149–1154.
4. Dumont L, Mardirosoff C, Tramer MR. Efficacy and harm of pharmacological prevention of acute mountain sickness: quantitative systematic review. *BMJ*. 2000;321:267–272.
5. Maggiorini K, Buhler B, Walter K, Oelz O. Prevalence of acute mountain sickness in the Swiss Alps. *BMJ*. 1990; 301:853–855.
6. Pollard AJ, Niermeyer S, Baryy P, et al. Children at high altitude: an international consensus statement by an ad hoc committee of the International Society of Mountain Medicine, March 12, 2001. *High Alt Med Biol*. 2001;2:389–403.
7. Pollard AJ, Murdoch DR, Bartsch P. Children in the mountains. *BMJ*. 1998;316:874–875.
8. Wu T. Children on the Tibetan plateau. *Newsl Int Soc Mt Med*. 1994;4:5–7.
9. Honigman B, Theis MK, Koziol-McLain J, et al. Acute mountain sickness in a general tourist population at moderate altitudes. *Ann Intern Med*. 1993;118:587–592.
10. Moraga FA, Osorio JD, Vargas ME. Acute mountain sickness in tourists with children at Lake Chungara (4400 m) in Northern Chile. *Wilderness Environ Med*. 2002;13: 31–35.
11. Durmowicz AG, Noordeweir E, Nicholas R, Reeves JT. Inflammatory processes may predispose children to high altitude pulmonary edema. *J Pediatr*. 1997;130:838–840.
12. Schoene RB. Fatal high altitude pulmonary edema associated with absence of left pulmonary artery. *High Alt Med Biol*. 2001;2:405–406.
13. Roach RC, Bartsch P, Hackett PH, Oelz O. Lake Louise acute mountain sickness scoring system. In: Sutton JR, Houston CS, Coates G, eds. *Hypoxia and Mountain Medicine*. Burlington, VT: Queen City Printers; 1992:272–274.
14. Dallimore J, Cooke FJ, Forbes K. Morbidity on youth expeditions to developing countries. *Wilderness Environ Med*. 2002;13:1–4.
15. Pattinson K. Altitude sickness in youth groups. *Wilderness Environ Med*. 2003;14:153.
16. Yaron M, Niermeyer S, Lindgren KN, Honigman B. Evaluation of diagnostic criteria and incidence of acute mountain sickness in preverbal children. *Wilderness Environ Med*. 2002;13:21–26.
17. Serranos-Duenas M. Acute mountain sickness: the clinical characteristics of a cohort of 615 patients. *Med Clin (Barc)*. 2000;115:441–445.
18. Theis MK, Honigman B, Yip R, McBride D, Houston CS, Moore LG. Acute mountain sickness in children at 2835 m. *Am J Dis Child*. 1992;147:143–145.
19. Purkayastha SS, Ray US, Arora BS, et al. Acclimatization at high altitude in gradual and acute induction. *J Appl Physiol*. 1995;79:487–492.
20. Porcelli MJ, Gugelchuk GM. A trek to the top: a review of acute mountain sickness. *J Am Osteopath Assoc*. 1995; 95:718–720.
21. Almeida SA, Trone DW, Leone DW, Shaffer RA, Patheal SL, Long K. Gender differences in musculo-skeletal injury rates: a function of symptom reporting. *Med Sci Sports Exerc*. 1999;31:1807–1812.

NEAR INFRA-RED SPECTROSCOPY AND ARTERIAL OXYGEN EXTRACTION AT ALTITUDE

Christopher B Wolff*, Neil Richardson, Oliver Kemp and Christopher Imray.

1. ABSTRACT

The ratio of oxygenated to total haemoglobin (Hb), rSO_2, obtained by near infra-red spectroscopy (NIRS), includes both arterial and venous blood of the region explored. The relationship of arterial oxygen extraction, E, and saturation, SaO_2, to rSO_2 can be expressed, for normally functioning tissue, as $E = 1.39(1-rSO_2/SaO_2)$. Cerebral E is constant below 5000 m at which the calculated value is reduced. The decline in E corresponds to SaO_2 values below 90% (approximately). The oxygen extraction of brain, liver, muscle and kidney have been examined with NIRS and found to be reduced at 5000 m. E is constant for all altitudes below 5000 m for brain, liver and muscle but is elevated at intermediate altitude (2400 m) for the kidney. Cerebral oxygen extraction is constant for the lower levels of exercise and, if the calculated extraction value assumptions still hold at lower SaO_2 values, reduced at intermediate altitudes for the higher work rates. The present study confirms constancy of oxygen extraction and hence the ratio of oxygen delivery to oxygen consumption (1/E), when working within physiological limits, and appears to show where those limits lay and, to some extent, show how matters change beyond ordinary physiological limits.

2. INTRODUCTION

Cerebral oxygen delivery is sustained at the same value as at sea level at moderate altitude (Wolff, 2000; Wolff, Barry and Collier, 2002). The product of middle cerebral artery velocity (MCAV) and arterial oxygen saturation (SaO_2) is also constant at the same value as at sea level for moderate altitudes but is reduced at 5000 m after relatively rapid ascent (Wolff and Imray, 2004). Since both oxygen delivery (cerebral blood flow, CBF, times arterial oxygen content, CaO_2) and MCAV times SaO_2 agree on

* Applied Physiology, Block 9, St Thomas's Hospital, Lambeth Palace Rd., London, SE1 7EH, UK.

constancy at moderate altitudes it is assumed that MCAV times SaO_2 is proportional to, and a surrogate for, oxygen delivery. The constancy of MCAV times SaO_2 is illustrated in figure 1A, from Wolff and Imray (2004). The reduced value at 5050 m and also, a value taken at sea level in subjects breathing 12.5% oxygen, are also illustrated in figure 1A. On the right, figure 1B, the 'DO_2' values at SaO_2 below around 90% are the same reduced values (5050 m and 12.5% at sea level).

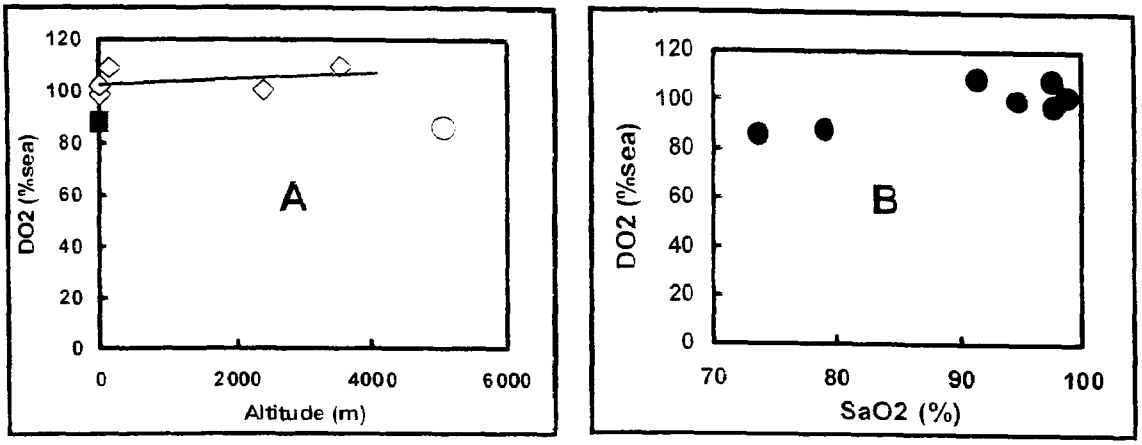


Figure 1. Cerebral oxygen delivery as a percentage of the sea level value (mean of two values). A regression line has been fitted to values at all altitudes other than 5050 m in A (◇) and its slope is not significant (equation: DO_2%sea = 102 - 0.01 x altitude). The 5050m point (○) and the one recorded at sea level on 12.5% O_2 (■) show reduced oxygen delivery. In B DO_2 values are plotted against SaO_2. *Reproduced from Wolff and Imray (2004) – with permission.*

Wolff and Imray (2004) showed that there was a relationship between SaO_2, the ratio (p) of arterial to venous volume in the area sampled by near infra-red spectroscopy (NIRS), oxygen extraction (E) and the NIRS derived ratio of oxygenated to total blood (rSO_2) in the region of interest:

$$rSO_2 = (SaO_2.p + SaO_2 (1 - E)) / (p + 1)) \qquad \text{Equation 1}$$

3. ANALYTICAL METHODS

It was shown in Wolff and Imray (2004) that p and E were unaltered at recorded altitudes below 5050m, corresponding with the constancy of oxygen delivery illustrated in figure 1A. The equation relating rSO_2, SaO_2, p and E derived in Wolff and Imray (2004) has been re-arranged here to give an equation for E:

$$E = (p + 1)(1 - rSO_2 / SaO_2). \qquad \text{Equation 2}$$

In the range where E and p are unchanging (lower altitudes) substitution for p can be made from the independent estimate made by McCormick, et al. (1991). They found that the arterial volume, Va, was 28% of the total blood volume, Va + Vv, where Vv is the venous volume. This gives Va/Vv = 0.39 = p. The present paper illustrates how this estimate of E changes with hypoxia.

4. RESULTS

4.1 Cerebral oxygen extraction – comparison with oxygen delivery

The values for rSO_2 and SaO_2 from Wolff and Imray (2004) and from an slow ascent to high altitude in Nepal (Chamlang base-camp; 5000 m, Medex 2003) have been entered into equation 2 to obtain values of

E (assuming a value for p of 0.39). E has then been plotted against altitude (figure 2, left panel) and, also, against arterial oxygen saturation (figure 2, right hand panel).

The constancy of the values for cerebral oxygen extraction for all recorded points breathing air below 5030 m (and with SaO_2 above 90%) correspond with the findings for of oxygen delivery shown in figure 1. There is constancy of E, just as for DO_2, for the lower altitudes and higher SaO_2 values, and reduced values for E for the highest altitudes (5050 and 5030 m) and lower SaO_2 values (below 90%).

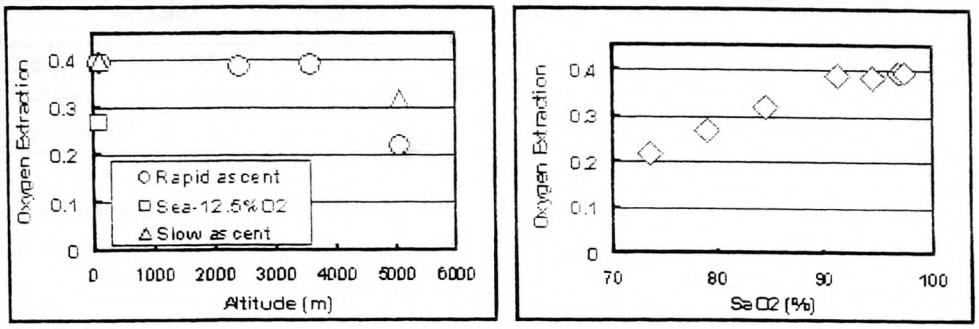


Figure 2. Cerebral oxygen extraction, calculated from $E = 1.39 (1 - rSO_2/SaO_2)$ is shown here versus altitude on the left and against SaO_2 on the right. The points are for the same altitudes as are shown in figure 1 (from Wolff and Imray, 2004; sea level, 2400, 3549 and 5050 m and at sea level breathing 12.5% O_2) with the addition of the mean value from a slower ascent to 5030m in 2003 (Medex, 2003 Chamlang base camp).

The extra value obtained from the slow ascent to Chamlang base camp at 5030 m (Nepal, 2003) shows a reduction in oxygen extraction, less severe than that seen for the very similar altitude (5050 m), but the latter was for a rapid ascent. Where oxygen extraction values are plotted against SaO_2 they are constant above SaO_2 90% but fall linearly below that, the highest of the reduced points being from the slow ascent to 5030 m.

4.2 Oxygen extraction of brain, liver, muscle and kidney

Values of rSO_2 and SaO_2 have been obtained (source?) from the brain, liver, resting thigh muscle and kidney at sea level, 2400 m and 5050 m (table 1). Oxygen extractions have, again, been calculated from $E = 1.39 (1 - rSO_2/SaO_2)$ and appear in the lower section of table 1. E has been expressed as a percentage of the sea level value, E%, and values are illustrated in figure 3, plotted against altitude on the left and SaO_2 on the right.

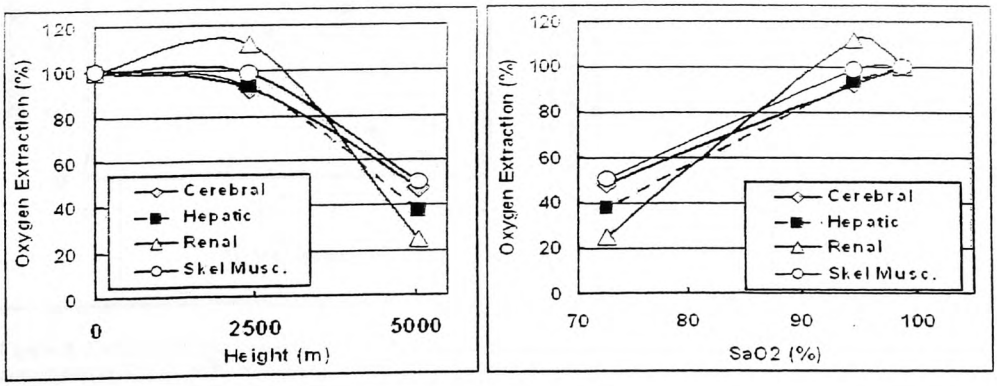


Figure 3. Oxygen extraction, expressed as a percentage of the sea level value, for brain, liver, resting skeletal muscle and kidney, obtained at sea level, 2400 m and 5050 m. For brain, liver and muscle oxygen extraction was much the same at 2400 m as at sea level; but for the kidney oxygen extraction was higher. Oxygen extraction, according to the equation $E = 1.39 (1 - rSO_2/SaO_2)$, is expressed as a percentage of the sea level value. It is reduced at 5050 m for all four organs.

Since, either E or p may have changed at the higher altitude (5000 m) and lower SaO_2 (~73%) the values calculated for E may be incorrect. However, they are unlikely to be normal. End tidal PCO_2 is also given in the table ($EtCO_2$) for comparison with other altitude studies. The end-tidal PCO_2 in the table for 5050 m, 29.4 mm Hg (acute ascent) is higher than in the study of Wolff et al (2002, Everest base-camp) where mean PCO_2 was 26.2 mm Hg (± 0.57; SEM), arterial PO_2 43.6 mm Hg. The subjects were longer acclimatized probably accounting for the lower PCO_2.

	SaO_2	$EtCO_2$	Cer rSO_2	Hep rSO_2	Ren rSO_2	Sk. M rSO_2
Sea	98.8	37.4	69	74.3	75.6	73.1
2400m	94.6	36.4	68.2	72.7	69.7	70.3
5050m	72.6	29.4	62.1	65.8	68.4	63.1
			Cerebral	Hepatic	Renal	Muscular
Fractional $E = 1.39\ (1-rSO_2/SaO_2)$		Sea Level	0.42	0.34	0.33	0.36
		2400m	0.39	0.32	0.37	0.36
		5050m	0.2	0.13	0.08	0.18

Table 1. Measured values of SaO_2. End tidal PCO_2 ($EtCO_2$, mm Hg), Cerebral rSO_2 (Cer. rSO_2), Renal rSO_2 (Ren. rSO_2) and resting skeletal muscle rSO_2 (Sk. M rSO_2). Measurements were made at sea level 2400m and 5050 m. The lower section shows the values obtained for oxygen extraction, expressed in fractional form again for each organ, calculated from the equation given on the left.

4.3 Cerebral oxygen extraction – effects of exercise and individual variation at rest

Cerebral oxygen extraction has been calculated (using equation 2) for rest and the full range of exercise at 150 m 'sea level', 3610 m, 4750 m and 5260 m. The results are illustrated in figure 4, left panel against percentage of VO_{2Max} (maximum exercise), right panel against oxygen consumption (VO_2) and, in figure 5A against SaO_2 (%). For 150 m E% fell progressively with increasing exercise intensity (figure 4); for higher altitudes all showed a fall up to 50% VO_{2Max} then a rise towards the resting E value for the higher levels of exercise.

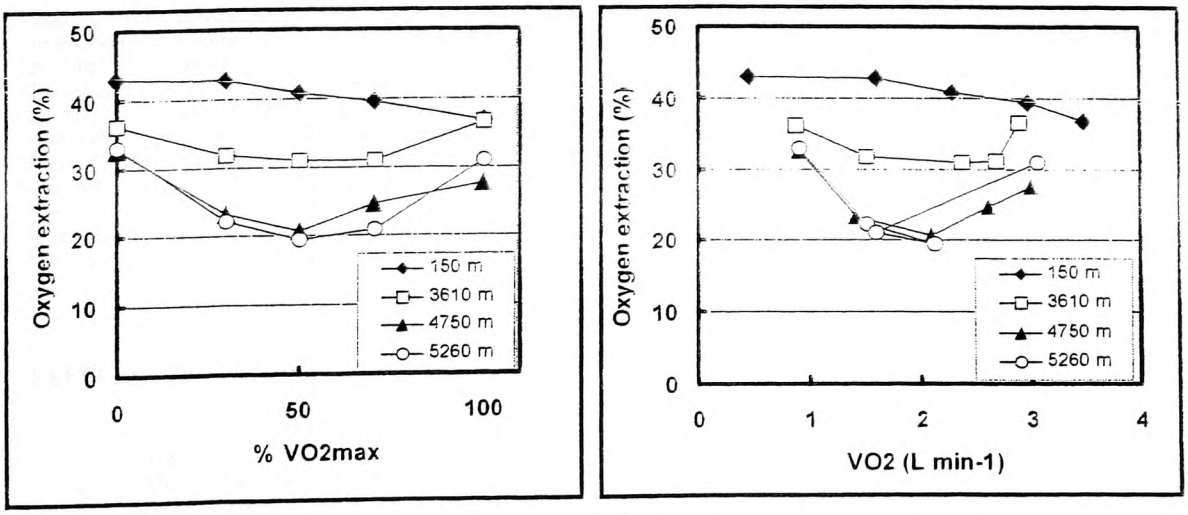


Figure 4. Cerebral oxygen extraction expressed as a percentage, for exercise between rest and VO_{2max}. The exercise studies have been undertaken at 150 m, 3610 m, 4750 m and 5260 m. Each point represents the average of [redacted] subjects. Values are plotted against percent of VO_{2max} on the left, SaO_2 on the right.

The values of E in exercise are also plotted against SaO_2 in figure 5A. The lower SaO_2 values (mid range of exercise for all attitudes above sea level – lowest at VO_2 max for sea level) correspond with the lowest values for E (figure 5A) but E values are a little higher than the trend shown in figure 2 (right hand panel),

which are reproduced in figure 5A (open squares).

Variations due to individual differences for resting subjects at sea level and 5030 m (slow ascent to Chamlang base-camp) are shown in figure 5B.

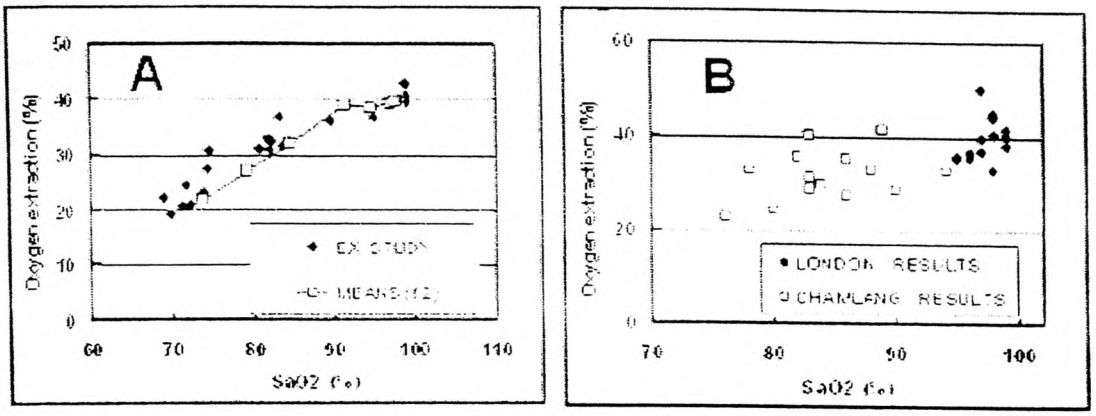


Figure 5. A. Values of cerebral E (%) from the exercise study, for all altitudes and levels of exercise intensity, plotted against SaO_2 (♦) with, for comparison, mean resting values (□) from section 4.1 above (figure 2, right). B. Resting values of cerebral E (%) measured at sea level (London) and after slow ascent to 5030 m (Chamlang base-camp) showing variability between subjects.

5. DISCUSSION

Reductions in oxygen extraction for brain and also for liver kidney and muscle at the highest altitudes – around 5000 m, according to the equation, could be in error if large changes occurred in either oxygen consumption or the ratio of the NIRS sampled volume of arterial blood to venous blood occurred. The consistency and parallel nature of cerebral oxygen extraction and oxygen delivery with arterial oxygen saturations below 90% suggest a progressive pattern of deterioration of function once outside the physiological range (SaO_2 90%: figures 1 and 2).

The increased renal extraction for the modest altitude shown in figure 3 is compatible with sustained glomerular filtration and hence renal VO_2 with a reduced renal arterial oxygen content. The ratio of oxygen delivery to metabolic rate is therefore reduced and this means there is greater oxygen extraction. The lowered tissue oxygen tension is the cause of erythropoietin secretion and hence the erythropoietic response

The reduced cerebral oxygen extraction extraction in the middle range of exercise (figure 4) appears largely compatible with the tendency, once outside the physiological range of SaO_2 to fall as saturation falls. However, the values at each arterial saturation appear to be a little higher (figure 5) than those at rest (figure 2, and 5A).

Figure 5B shows the range of variation of resting individuals both at sea level and altitude

The present study suggests consistent constancy of oxygen extraction when SaO_2 is in the normal 'physiological' range (above around 90% - except for the kidney) and progressive reduction in oxygen extraction for lower SaO_2 values. It is possible the real limits depend rather on oxygen content since all subjects of the present studies were normal subjects, hence presumably having normal haemoglobin values.

REFERENCES

1. WOLFF, C.B. (2000) Cerebral blood flow and oxygen delivery at high altitude. High Altitude Medicine and Biology, 1 (1), 33-38.
2. WOLFF, C.B., BARRY P AND COLLIER, D.J. (2002) Cardiovascular and respiratory adjustments at altitude sustain cerebral oxygen delivery – Severinghaus revisited. Comp. Bioch. and Physiol. Part A. 132, 221-229.
3. WOLFF, C.B. and IMRAY, C.H.E. (2004) partitioning of arterial and venous volumes in the brain under hypoxic conditions. Adv. Exp. Med. Biol., 540, 19-23.
4. WOLFF, C.B. (2003) Cardiac output, oxygen consumption and muscle oxygen delivery in submaximal exercise: normal and low O_2 states. Adv. Exp. Med. Biol. 510, 279-284.
5. McCORMICK, P.W. STEWART, M. GOETTING M.G. and BALAKRISHNAN, G. (1991) Regional cerebrovascular oxygen saturation measured by optical spectroscopy in humans. Stroke 22, 596-602

advanced training taking place following acquisition of a CCT [6]. Does this not imply that the CCT will lead to a permanent post that is closer to the European 'specialist' model than the more autonomous UK consultant post of today? I believe it does, and if this is the case, the concerns about the lack of experience at the end of training are less important as a 'specialist' model becomes a reality.

Whatever the nature of the future specialist grade, it is essential that the speciality does not allow training time to be eroded further. The great challenge is to ensure that good models of training are developed around EWTD-compliant rotas. I do not think this is the case at present as the implementation of the EWTD has been precipitate in many instances and its effect on training has yet to be fully determined.

A. Tomlinson
University Hospital of
North Staffordshire,
Stoke-on-Trent ST4 6QG, UK
E-mail: andy.tomlinson@
doctors.org.uk

References

1 Chikwe J, de Souza AC, Pepper JR. No time to train the surgeons. *British Medical Journal* 2004; 328: 418–9.
2 Buck N, Devlin HB, Lunn JN. *The Report of a Confidential Enquiry into Perioperative Deaths*. London: Nuffield Provincial Hospitals Trust/Kings Fund, 1987.
3 Goodman N. Only repeal of the European Working Time Directive will help. *British Medical Journal* 2004; 328: 1133.
4 Department of Health. Working group on specialist medical training. *Hospital Doctors: Training for the Future*. London: Department of Health, 1993.
5 Department of Health. Modernising medical careers. *The Response of the Four UK Health Ministers to the Consultation on 'Unfinished Business – Proposals for Reform of the Senior House Officer Grade'*. London: Department of Health, 2003.
6 Department of Health. Modernising medical careers: the next steps. *The Future Shape of Foundation, Specialist and General Practice Training Programmes*. London: Department of Health, 2004.

Airway alert information following difficult intubations

We read with interest the 'Difficult Airway Society guidelines for the management of the unanticipated difficult intubation' (Henderson *et al. Anaesthesia* 2004; 59: 675–694). We wish to draw attention to the importance of follow-up after difficult intubation. This process ought to involve counselling the patient and taking measures to prevent similar incidents in the future. We believe the airway alert form, introduced by Barron *et al.* [1], is an important tool that can be used to provide the necessary information to clinical staff in relation to future anaesthesia for the patient. Furthermore, the need for such information is doubly important in a case of unanticipated difficult intubation, in order to aim to optimise future airway management. However, previous studies have shown that follow-up of difficult intubation is not widely practised [1,2]. We provide all our patients who are Cormack & Lehane Grade 3 or 4 on direct laryngoscopy with an airway alert form and include the following information: pre-operative airway assessment; ease of face mask ventilation; description of findings and grade of the direct laryngoscopic view; equipment/manoeuvre that failed to achieve intubation; equipment/manoeuvre that successfully achieved intubation; ease of extubation; special postoperative airway care requirements; and future plans.

An abundance of useful information is available on the Difficult Airway Society website (http://www.das.uk.com).

K. Chandradeva
S. M. Ghosh
Queen Mary's Sidcup NHS Trust
Kent DA14 6LT, UK
E-mail: chandra.chandradeva@
qmms.nhs.uk

References

1 Barron FA, Ball DR, Jefferson P, Norte J. 'Airway Alerts'. How UK anaesthetists organise, document and communicate difficult airway management. *Anaesthesia* 2003; 58: 73–7.
2 Pigott A, Brandon E. Difficult intubations – how good are we at alerting others? *Anaesthesia* 2004; 59: 1044–5.

Another double 'tails-up' capnograph

We were interested to read the recent correspondence about a double 'tails-up' capnograph trace caused by a leak in the sampling line during positive pressure ventilation (Rassam *et al.*, *Anaesthesia* 2004; 59: 1034–5). We noticed a similar trace during spontaneous respiration. As part of a research project investigating respiratory control, healthy volunteers received varying concentrations of carbon dioxide through a standard '40%' Venturi mask (Intersurgical, Wokingham, UK). The gas mixtures were delivered to the Venturi device at 10 l.min^{-1}, which is the same flow rate when used in a clinical situation for oxygen therapy. A Datex-Ohmeda Capnomac Ultima (Datex-Ohmeda, Helsinki, Finland) measured inspired and expired carbon dioxide and was connected to a personal computer for data logging. Carbon dioxide was sampled from within the subjects' nostrils.

The double 'tails-up' capnograph was noticeable in all volunteers when we were delivering 8% carbon dioxide (see Fig. 1). During this part of the experiment the volunteers were hyperventilating significantly and had raised their minute volume by approximately four times normal. The double 'tails-up' trace was less evident when 4% carbon dioxide was delivered, and not noticed at lower inspired levels, when the inspired carbon dioxide concentration was lower than the subjects' end-tidal carbon dioxide.

Our explanation for this trace is as follows: at the start of inspiration (Fig. 1, point a) the inspired carbon dioxide trace rapidly rises to match the carbon dioxide delivered by the Venturi device. As the inspiratory flow rate then increases above the flow rate delivered by the Venturi device (point b) air is entrained around the mask, and the inspired carbon dioxide concentration falls. Towards the end of inspiration the

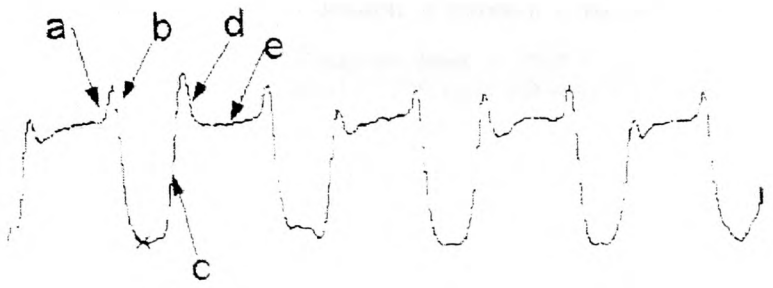


Figure 1 The double 'tails-up' capnography trace, seen with 8% inspired CO_2. For an explanation of points a–e, see text.

inspiratory flow rate falls and the proportion of entrained air decreases, resulting in the inhaled concentration returning towards that delivered by the Venturi (point c). The down stroke (point d) represents exhalation from the anatomical dead space, which contains some of the carbon dioxide containing mixture that is inhaled. The end-tidal carbon dioxide level (point e) remains significantly lower than that delivered by the Venturi device because the total carbon dioxide delivered is insufficient to raise alveolar carbon dioxide further (due to dilution with entrained ambient air). We believe the variability in the height of the peaks of each tail may be explained by the capnograph response time being insufficient, in these conditions of marked hyperventilation.

How is this relevant to clinical practice? Outside a carefully controlled research environment there are few reasons to deliver extra carbon dioxide. However this trace does illustrate the limitations of the 'fixed performance' Venturi mask during hyperventilation. A similar trace for supplemental oxygen could easily be imagined in a critically ill, acidotic patient who is hyperventilating. In this scenario, the patient would receive considerably less oxygen than expected, which may have important clinical implications.

K. Pattinson
University of Oxford
Oxford OX3 9DU, UK
E-mail: kyletsp@postmaster.co.uk

C. Imray
University Hospitals Coventry and Warwickshire NHS Trust
Coventry CV2 2DX, UK

Effect of injected epinephrine on the end-tidal carbon dioxide concentration

Increased end-tidal carbon dioxide concentration ($EtCO_2$) has been reported in patients with phaeochromocytoma undergoing adrenalectomy (Asai & Shingu, *Anaesthesia* 2004; 59: 830–1) and was attributed to increased catecholamine release during manipulation of the tumour, resulting in a hypermetabolic state and increased carbon dioxide production. An identical increase in $EtCO_2$ can also occur if epinephrine at a concentration of 1 in 200 000 is injected into the nasal mucosa of patients undergoing general anaesthesia for nasal surgery. The $EtCO_2$ increases transiently, in most of cases by about 1 kPa, accompanied by an increase in heart rate and blood pressure. The increase in $EtCO_2$ can be attributed, as in cases of phaeochromocytoma, to the resulting hypermetabolic state and increased carbon dioxide production.

Z. Tabboush
M. Diab
Kingdom Hospital
Riyadh 11671, Saudi Arabia
E-mail: Zafer@cyberia.net.lb

'Low' femoral vein puncture

Dr Wilson and colleagues have described their experience in ultrasound guided 'low approach' femoral vein cannulation (*Anaesthesia* 2004; 59: 725). While I agree with the possible benefits suggested by the authors, I have reservations about marking the course of femoral vein and then attempting a 'blind puncture'. A far safer technique is to puncture the vein under direct sonographic guidance. Beginners can use the biopsy guide attachment device supplied by the manufacturers while more experienced operators can perform the punctures without needing this. The technique is simple and can be easily mastered. While Dr Wilson and colleagues have never hit the artery, there is no guarantee that such an event would not occur in future as the technique they are using is 'blind'. Inadvertent arterial puncture in mid-thigh region can cause profuse bleeding as there is no bony point against which the artery can be compressed to achieve haemostasis.

A. K. Saxena
Post Graduate Institute of Medical Education & Research
Chandigarh, India-160012
E-mail: fatakshay@yahoo.com

Continuous paravertebral block for thoraco-abdominal oesophageal surgery

The role of paravertebral blockade for postoperative analgesia for patients undergoing unilateral surgical procedures of either the thorax or abdomen, including thoracotomy, cholecystectomy and nephrectomy is well established [1]. In thoracic surgery a paravertebral catheter can be placed under direct vision at the time of thoracotomy and local anaesthetic can then be infused postoperatively. We reviewed 20 patients who had undergone such a procedure where postoperative analgesia was provided by a continuous paravertebral infusion and patient controlled analgesia with intravenous morphine. Intraoperatively, the patients had received fentanyl (1–2 $\mu g.kg^{-1}$), a

A novel treatment for symptomatic carotid dissection

T Joseph, N Kandiyil, D Beale, C Tiivas and C H E Imray

Postgrad. Med. J. 2005;81;6-
doi:10.1136/pgmj.2004.029421

CASE REPORT

A novel treatment for symptomatic carotid dissection

T Joseph, N Kandiyil, D Beale, C Tiivas, C H E Imray

Postgrad Med J 2005;81:e6 (http://www.postgradmedj.com/cgi/content/full/81/958/e6). doi: 10.1136/pgmj.2004.029421

Carotid dissection is a rare but significant cause of stroke. The neurological damage in such cases is mainly attributable to thromboembolism.[1] Current treatment includes supportive therapy and antiplatelet agent either alone or with anticoagulation. This is not supported by randomised trials[2] but it is logical. Presence of microemboli in cerebral circulation is a risk factor for ischaemic stroke after transient ischaemic attack (TIA)[3] and transcranial Doppler examination (TCD) can detect them in middle cerebral artery circulation.[4] Controlling microemboli improves the outcome in recurrent TIA and after carotid endarterectomy.[5 6] We found this strategy effective in the treatment of a symptomatic carotid dissection unresponsive to anticoagulation.

We report a case of carotid artery dissection treated successfully by controlling microemboli from the dissected artery and discuss its validity.

CASE REPORT

A 45 year old, right handed man presented with a severe left sided headache, fluctuating weakness, and numbness in his right arm. He also had temporary loss of vision in his left eye and dysphasia. He reported a twisting movement of his neck eight days before this. In the past he had migraine and he was hypertensive.

Physical examination confirmed expressive dysphasia, mild weakness of his right arm muscles, and impaired sensation. His pulse was regular and his blood pressure was normal.

He had normal blood parameters including lipids. Aspirin and clopidogrel were started after confirming multiple low attenuation areas in the left frontoparietal cortex on a computed tomogram. A duplex scan of carotid arteries showed normal extracranial arteries but there was high resistance waveform, consistent with distal obstruction suggesting subintimal dissection (fig1). This was confirmed by magnetic resonance angiogram (figs 2 and 3). Therefore heparin infusion was started.

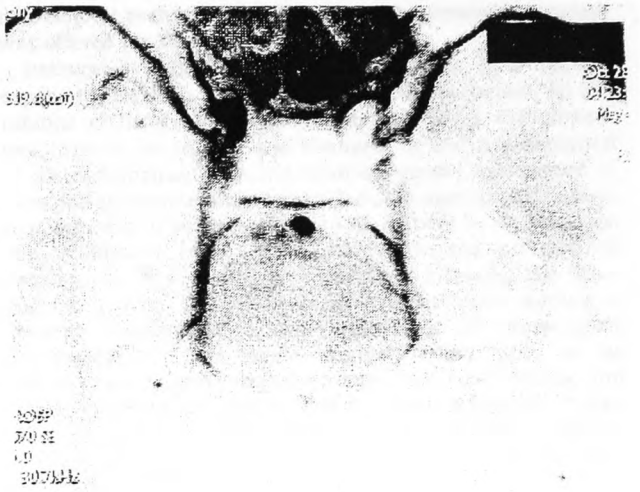


Figure 2 MRI of left internal carotid artery with the site of dissection at the base of skull.

He continued to have fluctuating neurological symptoms despite adequate anticoagulation. This prompted a TCD that showed microemboli in his left middle cerebral artery (MCA) circulation at a rate of 48 per hour. Thus a thromboembolic stroke secondary to carotid dissection was diagnosed.

Further treatment was discussed between radiologists, neurologists, and vascular surgeons. We decided to control microemboli with Dextran therapy based on local experience.

Abbreviations: TIA, transient ischaemic attack; TCD, transcranical Doppler examination; MCA, middle cerebral artery

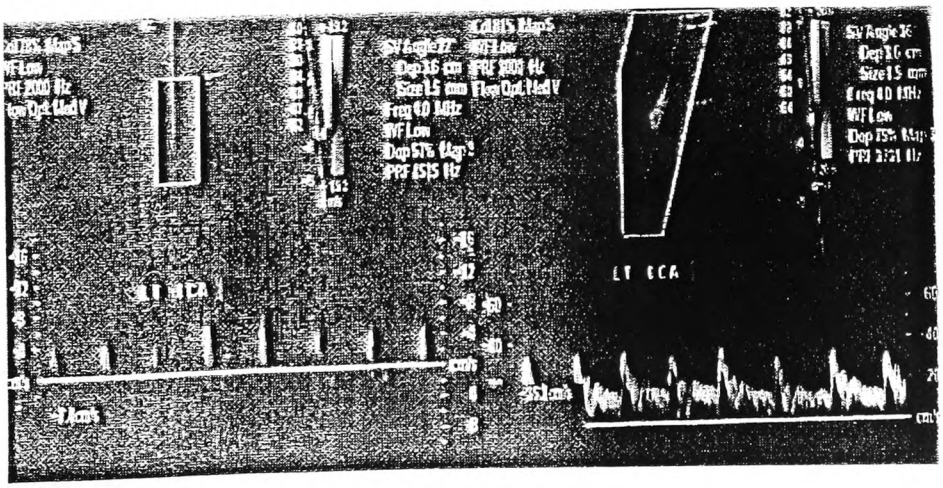


Figure 1 Wave forms from duplex scan of left carotid system. The left half shows the waveform on presentation, suggestive of distal obstruction. On the right half normal waveform from a repeat scan is shown and this suggests re-canalisation of the dissected segment.

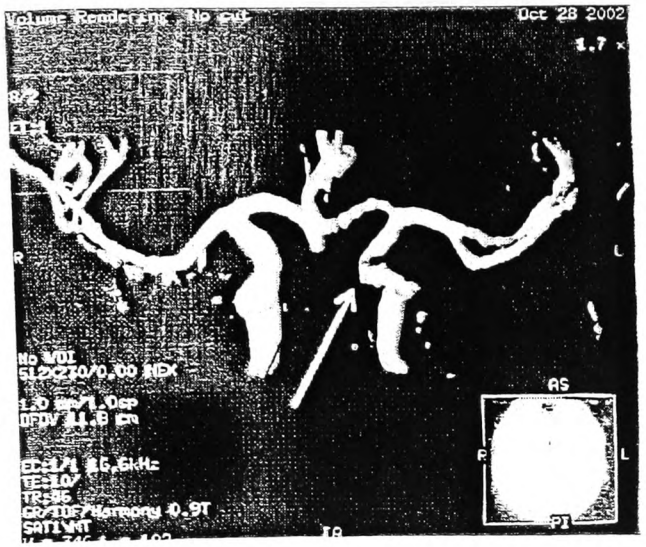


Figure 3 Reconstruction of the carotid system and the focal reduction in diameter of left internal carotid artery, suggestive of dissection.

He was given Dextran 40 as per the local protocol*. The fluctuating neurological symptoms settled and a repeat TCD showed no microemboli. Heparin infusion was stopped immediately. Dextran infusion was stopped after eight days. The patient recovered fully and was discharged receiving treatment with aspirin 150 mg and clopidogrel 75 mg. Coumarin was not given for fear of bleeding.

He was readmitted two weeks later with recurrent symptoms. Computed tomography showed no intracranial bleed and TCD scan detected microemboli in left the MCA. Dextran infusion improved his symptoms once again and stopped the microembolisation. He was given warfarin (target INR 2–3) on discharge. Repeat Duplex showed resolution of the high resistance waveform, indicating re-canalisation (fig 1).

DISCUSSION

The incidence of spontaneous carotid artery dissection is 2.5–3/100 000 per year.[1] This accounts for 2% of ischaemic strokes[2] but in young people carotid artery dissection causes up to 20% of strokes. The incidence is equal in both sexes and peaks in the fifth decade.

Factors such as severity of stenosis caused, site of the dissection and extent of collaterals influence the clinical picture and prognosis. Within a month after the dissection up to 80% patients develop focal neurological deficit. The long term prognosis is good, with re-canalisation of the artery. Early pathogenesis of neurological deficit in carotid dissections is unclear but 90% of infarcts are attributable to thromboembolic events rather than reduced flow. Medical treatment includes anticoagulation with heparin followed by coumarin or solely antiplatelet agents.[1 2] Surgery or endovascular approach is considered in unresponsive patients.

TCD assesses velocity of flow in MCA and detects transient microembolic signals in it. Mollina *et al* found microemboli in 13 of 28 acute dissections. Six of 13 with emboli showed neurological deterioration, whereas only 1 of 15 without emboli deteriorated.[4] Microemboli are a frequent phenomenon after acute stroke, and continue for some days. These microemboli are a significant independent predictor of early ischaemic recurrence in patients with stroke or TIA.[3] A similar association between stroke and microemboli is established from studies on patients with significant carotid stenosis and after carotid endarterectomy. Postoperative microemboli are usually platelet aggregates generated by the exposed thrombogenic vessel wall. These aggregates may develop into occlusive thromboemboli causing infarcts. A similar mechanism may explain symptoms after carotid dissection. TCD directed Dextran treatment to control microemboli after carotid endarterectomy and in patients with recurrent TIA is shown to be effective in preventing neurological events.[4 5] Therefore the same treatment strategy was offered for this patient.

Dextran is a polysaccharide used mainly as a volume expander. Dextran with molecular weight below 60 000 inhibits erythrocyte aggregation by increasing the electronegetivity of the cells. It also changes the electrical potential of the endothelium. Dextran inhibits platelet aggregation in vitro and adenosine diphosphate induced aggregation in vivo. It is believed to suppress factor VIII activity by an effect on von Willibrand factor. Clots formed in the presence of dextran are lysed easily and Dextran increases the antiplasmin activity. Dextran induced haemodilution leading to reduced viscosity and passive dilatation of microvessels attributable to the colloid osmotic effect adds to its effectiveness in thromboprophylaxis. The exact dosing and timing of administration are still not clear. A dose of 1.5 g/kg body weight is considered safe. Side effects include cardiac overload, haemorrhagic complications, anaphylactoid reactions, and renal dysfunction.[1]

The treatment of this patient was an act of desperation helped with background knowledge of TCD directed Dextran therapy to control microemboli. While we agree that the combination of antiplatelet agents together with the effect of already infused heparin before the introduction of intravenous Dextran does compound the temporal relation noted with the clinical improvement and disappearance of microemboli on the first occasion, it is worth noting that the improvement was maintained despite stopping the heparin and this temporal correlation was reproduced on re-admission. Because most infarcts in carotid dissections are attributable to thromboemboli it may well be reasonable to recommend TCD examination in symptomatic cases of internal carotid artery dissection to identify those patients who are at risk from microemboli Controlling the microemboli with Dextran 40 infusion seems to give immediate protection, particularly when adequate heparinisation fails to control symptoms, as happened in this case.

* 20 ml bolus followed by a continuous infusion at a rate of 20 ml/h and increments of 20 ml/h until microemboli are controlled or to a maximum of 100 ml/h.

Authors' affiliations
T Joseph, N Kandiyil, D Beale, C Tiivas, C H E Imray, University Hospitals of Coventry and Warwickshire, Walsgrave Hospital, Coventry UK

Funding: none.

Competing interests: none.

Correspondence to: Mr T Joseph, 46 Unitt Drive, Liberty Walk, B64 6DB; TJo5366012@aol.com

Submitted 5 October 2004
Accepted 19 November 2004

REFERENCES

1 **Schievink WI.** Spontaneous dissection of the carotid and vertebral arteries. *N Engl J Med* 2001;344:898–906.
2 **Lyrer P, Engelter S.** Antithrombotic drugs for carotid artery dissection. *Cochrane Library*. Issue 4. Oxford: Update Software, 2000.

3 **Valton L**, Larrue V, Faw-le Traon A, *et al*. Microembolic signals and risk of early recurrence inpatients with stroke or transient ischemic attack. *Stroke* 1998;**29**:2125–8.
4 **Lennard NS**, Vijayasekar C, Tiivas, *et al*. Control of emboli in patients with recurrent or crescendo transient ischaemic attacks using preoperative transcranial Doppler-directed Dextran therapy. *Br J Surg* 2003;**90**:166–70.
5 **Naylor AR**, Hayes PD, Allroggen H, *et al*. Reducing the risk of carotid surgery: a 7-year audit of the role of monitoring and quality control assessment. *J Vasc Surg* 2000;**32**:750–9.
6 **Schievink WI**, Mokri B, Whisnant JP. Internal carotid artery dissection in a community: Rochester, Minnesota, 1987–1992. *Stroke* 1993;**24**:1678–80.
7 **Schievink WI**, Mokri B, O'Fallon WM. Recurrent spontaneous cervical artery dissection. *N Engl J Med* 1994;**330**:393–7.
8 **Molina CA**, Alvarez-Sabin J, Schonewille W, *et al*. Cerebral microembolism in acute spontaneous internal carotid dissection. *Neuroimaging* 2001;**11**:63–6.
9 **bergqvist D**. Dextran. In: Verstraete M, Fuster V, Topol EJ, eds. *Cardiovascular thrombosis: thrombocardiology and thromboneurology*. 2nd ed. Philadelphia: Lippincott-Raven, 1998:235–50.
10 **Consensus committee of the ninth international cerebral hemodynamic symposium**. Basic identification criteria of Doppler microembolic signals. *Stroke* 1995;**26**:1123.

Monitoring intracranial pressure, perfusion and metabolism

Kyle Pattinson BM FRCA
Guy Wynne-Jones MBBS FRCS PhD
Christopher HE Imray MBBS FRCS

Key points

The intraventricular drain is considered to be the most accurate way of measuring intracranial pressure.

Intracranial pressure monitoring is not without risks.

Jugular bulb oximetry is a useful second-line monitor for refractory intracranial hypertension.

Transcranial Doppler can provide much useful information about cerebral perfusion.

Understanding the limitations of any monitoring device is crucial to its effective use.

Kyle Pattinson BM FRCA
Clinical Lecturer in Anaesthesia
Nuffield Department of Anaesthetics
University of Oxford
The John Radcliffe Hospital
Headley Way
Oxford
OX3 9DU
Tel: 01865 851138
Fax: 01865 220027
E-mail: kyletsp@postmaster.co.uk
(for correspondence)

Guy Wynne-Jones MBBS FRCS PhD
Specialist Registrar in Neurosurgery
Queen Elizabeth Hospital
Birmingham
B15 2TH

Christopher HE Imray MBBS FRCS
Consultant Vascular Surgeon
Coventry and Warwickshire County Vascular Unit
Coventry and Warwickshire University Hospital
Clifford Bridge Road
Coventry
CV2 2DX

Cerebral monitoring is important for management of severe head injury. It is also used in subarachnoid haemorrhage, stroke, intracerebral haematoma, meningitis, encephalopathies, hepatic failure, after neurosurgery and in patients undergoing carotid artery surgery. This article provides an overview of cerebral monitoring techniques available in clinical practice.

Intracranial pressure measurement

The normal level of mean intracranial pressure (ICP) in a resting healthy adult in the horizontal position is 7–10 mm Hg. The normal ICP is pulsatile and reflects the cardiac and respiratory cycles. Fourier analyses give three different 'slow' waveforms (Table 1). An ICP >15 mm Hg is considered pathological, although this varies with the condition. Treatment would be instituted at a lower ICP in a patient with benign intracranial hypertension than one with an acute severe head injury. A number of studies have shown that prolonged elevation of ICP carries a poor prognosis[1] and treatment of elevated ICP decreases mortality. In head injured patients, levels >20 mm Hg are usually treated. An ICP monitoring device is often the earliest method to detect a surgically treatable cause of raised ICP, such as an expanding haematoma. The Brain Trauma Foundation publishes clinical guidelines regarding ICP monitoring.[2]

Derived values from ICP and its waveform give useful information:[3]

(i) estimation of the *pressure–volume compensatory reserve* of the brain can be calculated by correlating the amplitude of the ICP pulse waveform with the mean ICP; and

(ii) the *cerebrovascular pressure-reactivity index* is calculated by correlation of the ICP response to slow spontaneous changes in arterial blood pressure. This can be used to assess disturbances of cerebral autoregulation.

ICP is usually measured with devices placed in a ventricle, subdural space, subarachnoid space or directly into the brain parenchyma.[4] The risks associated with these methods of ICP measurement include infection, haemorrhage, incorrect position, malfunction and obstruction. Clinically significant infection and haemorrhage is rare.

Intraventricular catheter

The gold standard for ICP measurement is the intraventricular catheter, which is traditionally inserted through a right frontal burr hole into the lateral ventricle. Placement can be difficult if the ventricle is either displaced or compressed. The intraventricular catheter can be used to remove cerebrospinal fluid (CSF) and administer drugs (e.g. antibiotics). It may be connected to either a saline manometer or a transducer. The reference point for the transducer is the foramen of Munro as this is close to the centre of the head. For ease the external auditory meatus is often used. If the head position is changed the transducer must be repositioned. Use of the intraventricular catheter is complicated by infection with quoted rates of 1–5%. Blockage may be overcome by flushing the system; repeated flushing should be avoided, as this will significantly increase the risk of infection. The use of antibiotic impregnated catheters may lower the infection rate.

Intraparenchymal monitors

The Camino transducer uses a fibreoptic cable to direct light to a miniature displaceable mirror at the catheter tip that is placed in brain tissue. ICP distorts the mirror and the reflected light intensity is transduced into pressure. This system is not dependent upon a saline-filled catheter. Codman have produced a microchip sensor placed at the end of a flexible nylon tube. ICP changes the resistance within the sensor and this is reflected as a voltage change. These sensors are inserted into the brain

doi: 10.1093/bjaceaccp/mki035

Table 1 The waveforms seen on the ICP trace

	Associated with	Amplitude	Duration
A (plateau) waves	Cerebral vasodilatation Reduced cerebral compliance	50–200 mm Hg	5–20 min
B waves	Changes in respiratory pattern	<50 mm Hg	1 minute
C waves	Blood pressure and systemic vasomotor tone	<20 mm Hg	7–15 s

Table 2 Effects of altered Sjv_{O_2}

Low Sjv_{O_2}	1. Increased cerebral oxygen extraction Systemic hypoxia Reduced cerebral blood flow Increased ICP 2. Increased cerebral oxygen demand Seizures Pyrexia
High Sjv_{O_2}	1. Abnormally high cerebral blood flow (loss of autoregulation) 2. High ICP causing shunting of blood past capillary bed

through a small burr hole via a 4 mm screw. They are considered to be almost as accurate as the ventricular drain, and have relatively low rates of infection and haemorrhage. They are particularly useful when the ventricles are inaccessible because of compression from raised ICP. The main disadvantages of this type of system are: (i) they cannot be recalibrated *in vivo*; (ii) they measure localized pressure, which may not be reflective of global ICP; (iii) therapeutic CSF drainage is not possible; and (iv) they may be subject to drift when used for long periods.

Subdural pressure transducers

Subdural pressure transducers are the least invasive and most easily placed of the ICP monitors described in this review. The dura is pierced and as the hollow device fills with CSF, the pressures equalize, and this closed fluid filled tubing transmits the pressure to a transducer. The rates of infection and haemorrhage are low, but the device is considered less accurate and there may be problems caused by occlusion with debris and misplacement. It is not possible to remove CSF with this device.

Jugular bulb oximetry

The jugular bulb is a dilatation of the internal jugular vein just below the base of the skull. It receives blood directly from the brain; measurement of oxygenation of this blood gives an estimation of cerebral oxygen consumption. The internal jugular vein is cannulated in a retrograde direction with a catheter containing a spectrophotometric fibreoptic probe and a lumen for aspiration of blood. Infrared light at three wavelengths measures haemoglobin concentration and oxygen saturations.[5] The position of the catheter tip should be confirmed by a lateral x-ray, the ideal position is above the disc between the first and second cervical vertebrae and close to skull base. This approximates with the level of the mastoid air cells.

In the uninjured brain, reduced cerebral oxygen delivery (e.g. arterial desaturation) causes an increase in cerebral blood flow resulting in improved oxygen delivery (autoregulation). In patients with brain injury, autoregulation may be deranged and the cerebral vasculature may be unable to compensate for changing oxygen requirements. The normal jugular saturation (Sjv_{O_2}) ranges from 55 to 71%, a figure that is lower than mixed venous saturations, reflecting the greater cerebral oxygen extraction compared with the rest of the body.

Sjv_{O_2} is dependant upon arterial oxygen saturation, cerebral blood flow and cerebral metabolic rate. As long as the first two factors remain constant, the Sjv_{O_2} varies with cerebral oxygen uptake. Significant increases and decreases of Sjv_{O_2} are associated with poorer outcome (Table 2).

Sjv_{O_2} monitoring is mainly used in the management of severe head injury. It confirms the deleterious effects a low cerebral perfusion pressure, and reflects the effects of interventional therapies. For example, hyperventilation is used to acutely reduce ICP, but can lead to critical cerebral vasoconstriction and ischaemia. Sjv_{O_2} monitoring can be used to define how much hyperventilation can be safely used. Sjv_{O_2} monitoring can also be used to optimize cerebral perfusion pressure; 70 mm Hg is considered optimal but it may be possible to lower this aim, minimizing the administration of vasopressors, if adequate cerebral oxygenation is confirmed.

Unfortunately the merits of Sjv_{O_2} monitoring are limited by difficulties in obtaining accurate readings and in their interpretation. Frequent recalibration is required and protein build-up at catheter tip causes further error. If the catheter tip is not correctly positioned, accuracy will be affected by significant contamination with scalp and facial blood. Too rapid aspiration of a blood sample may also lead to inaccuracy as this may lead to contamination with extracerebral blood. The Sjv_{O_2} reflects global rather than regional oxygenation, and may be affected by a number of variables other than cerebral oxygen uptake. Its relevance to focal injury should be questioned. As the monitor is invasive its insertion may lead to local complications. Because of these limitations the Brain Trauma Foundation only recommends Sjv_{O_2} monitoring as a second-line device to help guide the treatment of raised ICP refractory to standard treatment.

Transcranial Doppler ultrasonography

Transcranial Doppler (TCD) is a non-invasive ultrasound-based technique used to measure blood velocity in the cerebral arterial system.[6] Measurements are usually taken from the middle cerebral artery, although any major branch of the Circle of Willis or the basilar artery can be assessed if an appropriate 'window' can be found. A pulsed 2 MHz signal is transmitted through the temporal bone to a depth of 5–6.5 cm. Initially the beam is focused at a depth of 5 cm; the depth of focus is then varied to optimize the signal.

The signal is reflected by the solid components of blood (mostly red blood cells) and is distorted according to the Doppler shift principle; the change in wavelength is recorded in the same probe that delivers the signal. A waveform is displayed, which gives information on systolic, diastolic and the mean blood flow velocity (FV_{mean}).

The FV_{mean} is a weighted mean that takes into account the different velocities of formed elements in the blood vessel and has a normal value of ~55 cm s^{-1} in the middle cerebral artery. The shape of envelope from peak systolic flow to the end diastolic flow with each cardiac cycle is known as the waveform pulsatility. This pulsatility reflects the distal cerebral vascular resistance, providing there is not any stenosis or vasospasm and that blood rheology and pressure remain constant.

The main uses of TCD in anaesthesia and critical care are:

1. *To differentiate between vasospasm and hyperaemia in patients with subarachnoid haemorrhage and brain injury.* TCD is used for diagnosis of and differentiation between high velocity states such as cerebral vasospasm or hyperaemia (hyperperfusion syndrome). The Lindegaard ratio is the flow velocity of the middle cerebral artery divided by the velocity measured in the extracranial internal carotid artery. A high flow velocity (>120 cm s^{-1}) in association with a Lindegaard ratio of <3 implies hyperaemia. A Lindegaard ratio >3 is likely to imply vasospasm.

2. *Determination of adequacy of collateral circulation during carotid surgery.* In order to perform a carotid endarterectomy, it is necessary to clamp the common, internal and external carotid arteries. At this point the adequacy of cerebral perfusion to the ipsilateral middle cerebral territory needs to be assessed. If there is an adequate collateral circulation through the Circle of Willis then no further action needs to be taken. However, if there is an inadequate collateral supply then a shunt needs to be inserted before a hypoperfusion stroke occurs. TCD is one of a number of modalities that can be used to assess the adequacy of the cerebral collateral circulation. A fall to one-third to half of baseline is generally felt to require shunt insertion. Having inserted the shunt it is possible to use TCD to confirm the restoration of flow, and that the shunt is serving its intended purpose.

3. *TCD can be also be used to monitor patients who have suffered strokes or transient ischaemic attacks arising from the carotid artery.*[7] Immediately after such an event, microemboli can be detected in the middle cerebral artery, and the number of microemboli (the embolic load) is related to the risk of further embolic events. Microemboli are also seen after carotid endarterectomy, and again a high microembolic load is associated with an increased incidence of stroke. TCD can be used to detect these emboli, and can monitor the efficacy of antiplatelet agents which have been shown to both reduce the embolic load and reduce the incidence of stroke following carotid surgery.

4. *Estimation of perfusion pressure*: the pulsatility index (PI) gives an estimation of cerebral vascular resistance. $PI = (FV_{systolic} - FV_{diastolic}) / FV_{mean}$. The normal value for the PI ranges from 0.6 to 1.1 and has been shown to correlate with cerebral perfusion pressure.

Near-infrared cerebral spectroscopy

Near-infrared cerebral spectroscopy (NIRS) is used as a non-invasive monitor of brain oxygenation.[8] A forehead sensor shines infrared light through the surface layers of the brain and the light that re-emerges is sensed by a dual detector system. One detector is placed approximately 3 cm from the light source, and the other ~4 cm from the light source. The detector closer to the light source is assumed to detect reflected light that has passed through more scalp and subcutaneous tissues whereas the light detected by the distal detector would have a greater component of scalp, subcutaneous tissues and brain. The difference of the signals is assumed to represent a reading from the brain tissue ~2.5 cm below the surface. A computer algorithm based upon the Beer–Lambert law is used to display concentrations of oxygenated and deoxygenated haemoglobin. The monitor aims to give a real-time, non-invasive display of cerebral oxygen levels, and has been shown to correlate well with jugular bulb saturations in healthy volunteers under conditions of isocapnic hypoxia. Unfortunately the monitor is subject to significant error.[9] Currently, cerebral NIRS remains an interesting research tool, with its place in clinical practice still being evaluated.

Invasive brain tissue oximetry

Two commercially available sensors are available which measure brain oxygen levels directly. One device (Licox) is a polarographic Clark electrode, the other (Neurotrend) is a multi-parameter sensor that measures temperature, Po_2, Pco_2 and pH using a fibreoptic probe; tissue oxygen levels are measured by a phenomenon known as 'fluorescent quenching'. These devices can measure local changes in regional oxygenation that would not be noticed using jugular oximetry, and some centres are now using these devices as part of a multimodal monitoring technique described below.

Microdialysis

Microdialysis is achieved via a fine coaxial catheter that is inserted into the brain. The catheter has a dialysis membrane on its outer surface and low flow rates of dialysis fluid are passed through the catheter using a pump mechanism. Vials of fluid are removed every 10–60 min allowing the measurement of concentrations of substances in the cerebral extracellular fluid. Fluid is taken to a remote machine for analysis although continuous on-line analysis is now possible. Although the concentration of any substance that will pass across the dialysis membrane can be measured, the following substances are currently of interest in the injured brain:

(i) energy related metabolites (glucose, lactate, pyruvate, adenosine, xanthine);
(ii) neurotransmitters (glutamate, aspartate, GABA);

(iii) markers of tissue damage (glycerol, potassium, cytokines); and
(iv) exogenous substances (drugs).

Elevation of the lactate/pyruvate ratio is associated with derangements in metabolism after severe head injury, and is considered to be a useful marker of tissue ischaemia. Currently, microdialysis is used as a research tool.

Multimodality monitoring

Continuous monitoring of more than one parameter can help overcome some of the limitations of each method described. An example would be using Sjv_{O_2} monitoring to help tailor therapy based upon ICP, another example would be using Sjv_{O_2} with TCD monitoring to help differentiate between the ischaemic and hyperaemic phases of head injury. The assumption is that the measurement errors from different monitors will occur at different times with the different monitors. Unfortunately multimodality monitoring incurs greater costs in equipment, manpower and time, and further increases the complexity of treatment.

References

1. Saul TG, Ducker TB. Effect of intracranial pressure monitoring and aggressive treatment on mortality in severe head injury. *J Neurosurg* 1982 Apr; **56**(4): 498–503
2. Management of and prognosis of severe traumatic brain injury. Brain Trauma Foundation 2000: 47–69. http://www2.braintrauma.org/guidelines/
3. Czosnyka M, Pickard JD. Monitoring and interpretation of intracranial pressure. *J Neurol Neurosurg Psychiatry* 2004; **75**: 813–821
4. Zhong J, Dujovny M, Park H, Perez E, Perlin A, Diaz F. Advances in ICP monitoring techniques. *Neurol Res* 2003; **25**: 339–350
5. White H, Baker A. Continuous jugular venous oximetry in the neurointensive care unit—a brief review. *Can J Anaesth* 2002, **49**:6 623–629
6. Gupta AK. Monitoring the injured brain in the intensive care unit. *J. Postgraduate Medicine* 2002; **48**: 218–25
7. Imray C, Higman D, Tiivas C. Timing of surgery for symptomatic carotid stenosis. *Lancet* 2004 May 8; **363**(9420): 1553–4
8. Owen-Reece H, Smith M, Elwell C, Goldstone JC. Near infrared spectroscopy. *Br J Anaesth* 1999, **82**(3): 418–426
9. Fattinson K, Clutton-Brock T, Imray C. Validity of near-infrared cerebral spectroscopy. *Anaesthesia* 2004: **59**(1): 69–72

See multiple choice questions 99–101.

BJA

Correspondence

What does cerebral oximetry measure?

Editor—We feel that the recent paper by Yoshitani and colleagues[1] raises important issues. They demonstrated that, in patients undergoing elective hip arthroplasty, normovolaemic haemodilution caused no change in jugular bulb saturations (Sj_{O_2}) but decreased cerebral saturations (Sc_{O_2}) when measured with a cerebral oximeter (INVOS 4100S). Two explanations were offered for the unexpected disparity in readings. First, they postulated that subtle changes in regional Sc_{O_2} might not be revealed with the global measure provided by Sj_{O_2}. Second, they proposed that changes in near infrared path length induced by haemodilution could affect the Sc_{O_2} readings.

We feel the interpretation of the results deserves a more detailed appraisal. The INVOS 4100S gives a single readout for regional cerebral oxygen saturations using an algorithm based upon the Beer–Lambert law. In this study, both subject groups showed no change in Sj_{O_2} but a decrease in Sc_{O_2}. The disparity in readings could be consistent with a systematic error. We suspect the algorithm incorporated within the INVOS 4100S may not take into account the fall in haemoglobin concentration. The fall in oxygenation index has actually been found to correlate with blood loss in healthy volunteers.[2]

Cerebral oximetry does not take into account changes in the relative proportions of blood in the arterial or venous part of a capillary bed. The proportion of arterial blood in the cerebral capillaries had been estimated at 28%.[3] Hypoxia can induce changes in the cerebral arterial to venous volume ratio[4] and it would not be unreasonable to assume that other factors may also affect the cerebral arterial to venous volume ratio. A change in the relative proportions of arterial and venous blood in the cerebral capillaries may alter cerebral oximetry readings without a 'real' effect on cerebral tissue oxygenation.

We have previously expressed concerns[5] about the interpretation of cerebral oximetry in a clinical setting, and Yoshitani's paper has raised a most important issue concerning the effect of haemodilution upon the readings. A change in Sc_{O_2} could be attributable to many factors. In the clinical setting, changes in Sc_{O_2} should be interpreted with caution, particularly when there is significant blood loss.

K. T. S. Pattinson[1,*]
C. H. E. Imray[2]
A. D. Wright[3]
[1]*Oxford, UK*
[2]*Coventry, UK*
[3]*Birmingham, UK*
**E-mail: kyle.pattison@nda.ox.ac.uk*

Editor—We wish to thank Pattinson and colleagues for their comments in our recent article and are pleased to take this opportunity to reply. We demonstrated that there was a discrepancy between Sj_{O_2} and Sc_{O_2} values during normovolaemic haemodilution[1] and two possible explanations were offered (as above). Pattinson and colleagues[5] have suggested that our results deserve a more detailed appraisal and that various factors may have an effect on Sc_{O_2} values. Validation of near infrared spectroscopy measurements has not been established.

In our study, we demonstrated that there was a significant correlation between haemoglobin concentrations and Sc_{O_2} values. The results indicated haemoglobin concentration had a significant effect on Sc_{O_2} values. Kurth and colleagues[6] suggested that there was a significant negative correlation between haemoglobin concentrations and optical path length in an experimental model. We believe that optical path length had a strong effect on Sc_{O_2} values. As suggested above, the algorithm incorporated in the INVOS 4100S might not take into account the fall in haemoglobin concentration. The algorithm is not open for scrutiny (Somanetics, Troy, MI, USA). If a modified Beer–Lambert law, in which optical path length should be constant, was incorporated in INVOS 4100S, prolongation of optical path length would cause enhancement of changes in Sc_{O_2}. Therefore, if optical path length became longer with haemodilution, there would be an overestimation of changes in Sc_{O_2}.

Previous studies have demonstrated that various factors, such as haemoglobin concentrations, extracranial blood flow and changes in cerebral arterial to venous blood volume ratio had an effect on near infrared spectroscopy measurements.[7–9] However, it was difficult to evaluate the degree of effects of such factors on Sc_{O_2} values. We have only investigated the effect of haemoglobin concentration on Sc_{O_2} values. However, we need to evaluate the degree of effects of other factors on Sc_{O_2} in the near future.

K. Yoshitani*
M. Kawaguchi
Osaka, Japan
**E-mail: nkneji@mva.biglobe.ne.jp*

1 Yoshitani K, Kawaguchi M, Iwata M, *et al*. Comparison of changes in jugular venous bulb oxygen saturation and cerebral oxygen saturation during various of haemoglobin concentration under propofol and sevoflurane anaesthesia. *Br J Anaesth* 2005; **94**: 341–6
2 Torella F, Cowley R, Thornilley MS, McCollum CN. Monitoring blood loss with near infrared spectroscopy. *Comp Biochem Physiol A Mol Integr Physiol* 2002; **132**: 199–203
3 McCormick PW, Stewart MG, Goetting MG, Balakrishnan G. Regional cerebrovascular oxygen saturation measured by optical spectroscopy in humans. *Stroke* 1991; **22**: 596–602
4 Wolff CB, Imray CHE. Partitioning of arterial and venous volumes in the brain under hypoxic conditions. *Adv Exp Med Biol* 2003; **540**: 19–23
5 Pattinson K, Clutton-Brock T, Imray C. Validity of near-infrared cerebral spectroscopy. *Anaesthesia* 2004; **59**: 507–8
6 Kurth CD, Uher B. Cerebral hemoglobin and optical pathlength influence near-infrared spectroscopy measurement of cerebral oxygen saturation. *Anesth Analg* 1997; **84**: 1297–305
7 Kishi K, Kawaguchi M, Yoshitani K, *et al*. Influence of patient variables and sensor location on regional cerebral oxygen saturation measured by INVOS 4100 near-infrared spectrophotometers. *J Neurosurg Anesthesiol* 2003; **15**: 302–6
8 Germon TJ, Young AE, Manara AR, Nelson RJ. Extracerebral absorption of near infrared light influences the detection of increased cerebral oxygenation monitored by near infrared spectroscopy. *J Neurol Neurosurg Psychiatry* 1995; **58**: 477–9
9 Watzman HM, Kurth CD, Montenegro LM, Rome J, Steven JM, Nicolson SC. Arterial and venous contributions to near-infrared cerebral oximetry. *Anesthesiology* 2000; **93**: 947–53

doi:10.1093/bja/aei558

British Journal of Anaesthesia 95 (2): 274–8 (2005)

BJA

Correspondence

Oxygen administration can reverse neurological deficit following carotid cross-clamping

Editor—We read with interest Stoneham and Martin's recent case report[1] describing two patients who became neurologically obtunded during awake carotid surgery. They found that administration of oxygen 100% through a tight-fitting anaesthetic face mask and circle-breathing system reversed the neurological deficits, so that surgery could be completed without the need for shunting.

Two common mechanisms cause neurological deficits during carotid surgery: cerebral hypoperfusion, which is usually reversible; and macro-embolization, which is often irreversible. Most patients, undergoing loco-regional carotid surgery, will tolerate the cross-clamp phase without difficulty, however, in those patients who do become obtunded, a clear strategy needs to be agreed in advance by both anaesthetist and surgeon. We handle deficits that occur within the first 90 s by declamping the artery and allowing the deficit to recover. The operation is then continued under general anaesthesia and the carotid shunt can be inserted in a controlled fashion. A deficit that occurs more than 90 s after cross-clamp, but before the carotid arteriotomy (trial clamp for 5 min), is relatively straightforward to manage. Clamps are temporarily released, normal neurology restored, clamps are then reapplied allowing a shunt to be inserted before the patient becomes obtunded a second time. The most difficult situation, and that described in Stoneham and Martin's report[1] is when the patient deteriorates after the arteriotomy has been made, as clamp release is no longer an option. In this situation, the patient often begins to deteriorate in a fairly subtle fashion, then develops mild focal neurological deficits before finally becoming profoundly obtunded. These subtle neurological changes should be picked up at an early stage and the options of pharmacologically augmenting the blood pressure or increasing the $F_{I_{O_2}}$ are likely to be beneficial. If the deterioration in cerebral function is slow, this implies only a modest imbalance between the regional cerebral oxygen delivery (rCOD) and regional cerebral oxygen consumption (rCOC). Any strategy that improves rCOD or decreases rCOC may reverse the deficit. Pa_{CO_2}[2] and blood pressure[3] are important determinants of rCOD. Cerebral function is altered by hypoxia. When $F_{I_{O_2}}$ is decreased to 75% of normal, complex task performance is altered; at 65% short term memory is impaired; at 50% judgement is altered; unconsciousness occurs with $F_{I_{O_2}}$ between 30–40% of normal.[3]

Stoneham and Martin[1] did not measure Pa_{CO_2} at the time the patient was obtunded, but they speculate that that there might be 10% decrease in ventilation leading to an increase in Pa_{CO_2} of up to 0.5 kPa, causing a right shift in the oxygen dissociation curve, improving rCOD. The effect of Pa_{CO_2} on rCOD to the hypoxic 'normal' brain at altitude has been studied and suggests other mechanisms also come into play.[4 5] A rise in Pa_{CO_2} causes an increased rate and depth of respiration, increased cerebral blood flow, and right shift of the oxygen dissociation curve. These mechanisms improved rCOD, and this was confirmed with near infrared cerebral spectroscopy. Interestingly there appears to be a synergistic effect with a combination of supplemental oxygen and carbon dioxide giving the largest improvement in both Pa_{O_2} and cerebral oxygenation. There are animal data suggesting the hypoxic hypercarbic brain is less susceptible to hypoxic neuronal damage than the hypoxic hypocarbic brain.[6]

These case reports give important insights into the options as to how to manage patients with hypoperfusion deficits during loco-regional carotid surgery. Further studies into the manipulation of cerebral oxygen delivery during carotid endarterectomy are indicated. Clinical measurement of the balance between rCOD and rCOC is difficult, as patients undergoing awake carotid surgery rarely have jugular venous lines inserted. Cerebral near infrared spectroscopy, whilst having limitations in terms of absolute measurements,[7] may give continuous non-invasive assessments of the rCOD–rCOC balance.

C. H. E. Imray*
A. J. Thacker
M. K. Mead
Coventry, UK
**E-mail: chrisimray@aol.com*

Editor—As the increase in oxygen carrying capacity achieved by the administration of oxygen 100% with a close-fitting anaesthetic face mask in a patient with a normal haemoglobin and who is not desaturated ($\Delta Pa_{O_2} \times 0.00310$) is miniscule, how might these neurological deficits have been reversed?[1] By inducing an acute lipid shift? If so, what was the trigger? Free radicals? If so, might adverse effects have been detected had a prospective study been performed in which the neurocognitive tests used in an earlier study in your institution[8] were conducted preoperatively and 3 months later?

'Detailed cognitive assessment, using a battery of tests, shows some impairment in as many as 80% of patients [having open heart surgery] at the time they are discharged from hospital, which persists in around a quarter of them at six months'.[8] As neurocognitive impairment in patients undergoing conventional and off-pump coronary artery bypass grafting in your institution were similar it was 'speculated that the effects of surgical injury and anaesthesia might be as important as the use of cardiopulmonary bypass in causing impairment'. Hyperoxia might be a cause despite these two case reports.[6]

In a patient who develops an extradural haematoma after a head injury, mild concussion may be followed by a lucid interval after which neurological symptoms and even death from coma may develop; many injury clinics would be very wary of accepting these two case reports as evidence in support of the view that increasing $F_{I_{O_2}}$ to 1.0 during carotid artery surgery is universally beneficial. There are many possible causes of secondary brain injury in these circumstances.

'The introduction of routine intraoperative shunting and patch closure [in your institution], as well as allowing surgical trainees to perform supervised CEAs, has not affected perioperative morbidity and mortality rates or long-term outcome'.[9] Your results[10] appear, however, to fall far short of those routinely achieved in the US.[11] This difference, if real, could be technical. If so, using awake carotid surgery to reduce the need for shunts is unlikely to be a satisfactory solution. The difference might alternatively or additionally be a reflection of differences in the standards of anaesthetic practices in the UK and US.

Is mental functioning during awake neurosurgery, including intracranial revascularization, a reliable proxy for metabolic monitoring?[12] I suspect not because it has required detailed cognitive assessment to reveal the extent of the impairment after cardiac surgery and many neurocognitive disturbances appearing

after head injuries and brain surgery might have been avoidable events.[15]

R. G. Fiddian-Green
E-mail: richardfg@hotmail.com

Editor—Thank you for the opportunity to reply to correspondence about our recent case report concerning cerebral oxygenation during awake carotid surgery.[1] I am not aware of specific evidence supporting Imray and colleagues' differential approach to the management of cerebral hypoxia after cross-clamping depending on the speed of onset of the symptoms. For patients developing neurological deficits within 90 s of cross-clamping, other vascular teams would choose to keep the patient awake and to insert a shunt electively, keeping general anaesthesia as a 'last option'. We use a trial cross-clamp period of just 2 min, as most neurological deficits present within that time.[1–3] Others do not use a trial cross-clamp period at all, proceeding directly to arteriotomy after cross-clamping (Dr R. Telford, personal communication).

The $P_{a_{CO_2}}$ data that Imray and colleagues refer to are very interesting. One can only speculate about how important this was as a contribution to the improvement in cerebral oxygenation in our case report. Whatever the cause, I agree that non-invasive cerebral oximetry may provide the easiest technique of further investigation. Our pilot studies using cerebral oximetry so far do suggest that cerebral oxygenation is improved by supplemental oxygenation.

The thread of Dr Fiddian-Green's letter is more difficult to follow. He believes that standards in anaesthesia and surgery in the UK fall below those of the USA. He reaches this conclusion by comparing surgical data from Oxford going back to the mid-1970s with current data from the USA. In fact, over 75% of carotid surgery in Oxford is now performed awake. Routine shunting has been abandoned, using the awake patient's neurological state as the prime indicator of the need for shunting. Eversion endarterectomy, without patch closure is now performed by the majority of our surgeons.

Dr Fiddian-Green considers the increase in oxygen-carrying capacity of the blood when changing the $F_{I_{O_2}}$ from 0.3 to 1.0 to be 'miniscule'. Simple calculations (as detailed in the discussion section of our report) show that the increase was in fact an unexpected 8% of the total oxygen content—which could well have made a significant impact in a group of neurons close to their ischaemic threshold.

One must be cautious comparing cerebral hypoxia after carotid cross-clamping with the cognitive impairment that occurs after cardiac surgery or the neurological effects of raised intracranial pressure after an extradural haematoma. The pathophysiology and timescale in each case is different. The cerebral symptoms during awake carotid endarterectomy develop very acutely—a cerebrovascular accident is evolving before one's very eyes. We are not advocating the administration of oxygen 100% to all patients—rather, this becomes an addition to the anaesthetist's armamentarium in the management of this fascinating but challenging group of patients.

M. D. Stoneham
Oxford
E-mail: mark.stoneham@nda.ox.ac.uk

1 Stoneham MD, Martin T. Increased oxygen administration during awake carotid surgery can reverse neurological deficit following carotid cross-clamping. *Br J Anaesth* 2005; **94**: 582–5
2 Stoneham MD, Warner O. Blood pressure manipulation during awake carotid surgery to reverse neurological deficit after carotid cross-clamping. *Br J Anaesth* 2001; **87**: 641–4
3 Blass JP, Gibson GE. Consequences of mild grade hypoxia. *Adv Neurol* 1979; **2**: 229
4 Imray CH, Walsh S, Clarke T, *et al*. Birmingham Medical Research Expeditionary Society. Effects of breathing air containing 3% carbon dioxide, 35% oxygen or a mixture of 3% carbon dioxide/35% oxygen on cerebral and peripheral oxygenation at 150 m and 3459 m. *Clin Sci (Lond)* 2003; **104**: 203–10
5 Imray CH, Brearley S, Clarke T, *et al*. Cerebral oxygenation at high altitude and the response to carbon dioxide, hyperventilation and oxygen. The Birmingham Medical Research Expeditionary Society. *Clin Sci (Lond)* 2000; **98**: 159–64
6 Simon RP, Niiro M, Gwinn R. Brain acidosis induced by hypercarbic ventilation attenuating focal ischaemic injury. *J Pharm Exp Ther* 1993; **267**: 1428–31
7 Pattinson K, Clutton-Brock T, Imray C. Validity of near-infrared cerebral spectroscopy. *Anaesthesia* 2004; **59**: 507–8
8 Fiddian-Green RG. eLetter re: Taggart D. About impaired minds and closed hearts. *Br Med J* 2002; **325**: 1255–6
9 Fiddian-Green RG. eLetter re: Khaw KS, Wang CC, Ngan Kee WD, Pang CP, and Rogers MS. Effects of high inspired oxygen fraction during elective Caesarean section under spinal anaesthesia on maternal and fetal oxygenation and lipid peroxidation. *Br J Anaesth* 2002; **88**: 18–23
10 Hussain T, Senaratne JW, Green FR, Collin J, Hands L, Morris PJ. Vascular surgical society of great britain and ireland: twenty-three years of experience of carotid endarterectomy. *Br J Surg* 1999; **86**: 690
11 Cowan JA Jr, Dimick JB, Thompson BG, Stanley JC, Upchurch GR Jr. Surgeon volume as an indicator of outcomes after carotid endarterectomy: an effect independent of specialty practice and hospital volume. *J Am Coll Surg* 2002; **195**: 814–21
12 Fiddian-Green RG. eLetter re: Czosnyka M, Pickard JD. Monitoring and interpretation of intracranial pressure. *J Neurol Neurosurg Psychiatry* 2004; **75**: 813–21
13 Fiddian-Green RG. eLetter re: Smith M. Editorial I: Neurocritical care: has it come of age? *Br J Anaesth* 2004; **93**: 753–5
14 Lawrence PF, Alves JC, Jicha D, Bhirangi K, Dobrin PB. Incidence, timing, and causes of cerebral ischemia during carotid endarterectomy with regional anesthesia. *J Vasc Surg* 1998; **27**: 329–34; discussion 335–7

doi:10.1093/bja/aei570

Spinal endoscopy for chronic sciatica

Editor—We congratulate Dr Dashfield and colleagues on a well conducted, clinically relevant study. Caudal epidural placement of steroid and spinal endoscopic placement of steroid were found to be effective in patients with sciatica of 6–18 months. Superior, but not significantly superior results were found in the caudal epidural group. The conclusion must be that putting a patient through the longer, more uncomfortable, more costly and potentially more hazardous procedure of spinal endoscopy is difficult to justify on symptomatic grounds. We would tentatively accept this conclusion, but wish to emphasize some important caveats.

We refer particularly to a prospective observational study,[2] two prospective case series,[3 4] two retrospective evaluations[5 6] and a randomized double-blind controlled trial,[7] which have shown positive results with spinal endoscopy in patients with chronic low-back pain with radiculopathic leg pain who had previously obtained inadequate pain relief with traditionally placed caudal or lumbar epidural steroids. The reasons for this discrepancy are relevant to those who manage these patients on a day-to-day basis.

Firstly, all of these studies[2–7] involved different populations from those of the Dashfield and colleagues' study where no patients had undergone back surgery and mean symptom duration was

The CARESS Trial

To the Editor:

We read with interest the report by Markus et al of the CARESS trial,[1] in which dual antiplatelet therapy resulted in more effective control of microembolic signals (MESs) than single antiplatelet therapy. There was an associated reduction in the prevalence of transient ischemic attacks (TIAs) and strokes.

Immediately after a TIA or stroke, there is a rise in transcranial Doppler (TCD)-detected MESs. Those patients who continue to experience embolization are at greater risk of another neurological event.[2] Markus et al "emphasize the importance of operating urgently in patients wherever possible." However, a recent systematic review of the risks of carotid endarterectomy in relation to both the clinical indication for and timing of surgery has shown that urgent carotid surgery carries a much higher risk (19.2%, 95% CI 10.7% to 27.8%) than elective surgery (OR 3.9, 95% CI 2.7% to 5.7%; $P<0.001$; 13 studies).[3]

Recurrent or crescendo TIA patients represent a particularly high-risk group. It is possible to stop both emboli and further symptoms in these patients with TCD-directed intravenous antiplatelet agents, the dose being increased incrementally until the MESs cease. Consequently, it is possible to influence the timing of surgical intervention, allowing patients to undergo carotid endarterectomy safely on the next elective list,[4] avoiding the risks associated with urgent or emergency surgery[3] or the risks associated with delay in patients whose MESs persist despite oral antiplatelet therapy.[1,2]

MESs are surrogate markers for the risk of future embolic events. The pharmacological efficacy of therapeutic interventions can now be assessed rapidly, noninvasively, and inexpensively. TCD emboli detection appears to offer an important advance that enables optimal integration of medical therapy and timing of surgery.

Christopher H.E. Imray, MB,BS, FRCS, DiMM
Daniel J. Higman, MB,BS, FRCS, MS
Colette Marshall, MB,BS, FRCS
Consultant Vascular Surgeons
Coventry and Warwickshire County Vascular Unit
University Hospitals Coventry and Warwickshire NHS Trust
Coventry, United Kingdom

1. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, Ringelstein EB. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic signal detection. *Circulation*. 2005;111:2233–2240.
2. Sliwka U, Lingnau L, Stohlmann WD, Schmidt P, Mull P, Diehl RR, Noth J. Prevalence and time course of microembolic signals in patients with acute stroke. *Stroke*. 1997;28:358–363.
3. Bond R, Rerkasem K, Rothwell PM. Systematic review of the risks of carotid endarterectomy in relation to the clinical indication for and timing of surgery. *Stroke*. 2003;34:2290–301.
4. Lennard NS, Vijayasekar C, Tiivas, Chan CWM, Higman DJ, Imray CHE. Control of emboli in patients with recurrent or crescendo transient ischaemic attacks using preoperative transcranial Doppler-directed Dextran therapy. *Br J Surg*. 2003;90:166–170.

<LETTERS DOCTOPIC='Correspondence' DOCSUBJ='&NA;' DATE="November 15, 2005' VID='112' ISS='20' PPF='&NA;' PPL='
DOI='10.1161/CIRCULATION.AHA.105.560755'>

Letters to the Editor

Stroke welcomes Letters to the Editor and will publish them, if suitable, as space permits. They should not exceed 750 words (including references) and may be subject to editing or abridgment. Please submit letters in duplicate, typed double-spaced. Include a fax number for the corresponding author and a completed copyright transfer agreement form (published in every issue).

A Systemic Review of the Risk Factors for Cervical Artery Dissection

To the Editor:

We read with interest the review by Rubinstein et al[1] on risk factors for cervical artery dissection. In a case-control study, we had analyzed the role of recent infection on cervical artery dissection.[2] This study was referenced by the authors; however, our main findings were not correctly cited by the authors. In univariate analyses, recent infection and high-social status were significantly more common, and smoking was significantly less common in patients with cervical artery dissection (CAD) than in patients with cerebral ischemia of other origin. In conditional logistic regression analysis, infection within 1 week (odds ratio, 2.87; 95% CI, 1.18 to 7.00) and high-social status (odds ratio, 6.54; 95% CI, 1.88 to 22.7) remained significantly associated with CAD. Because coughing, sneezing, and vomiting that often occur during infection could explain the association between CAD and acute infectious disease, we systematically assessed the frequency of these mechanical factors. Recent cough, sneezing, and vomiting tended to be reported more often by CAD patients (60.5%) than by control patients (41.4%; $P=0.06$). In multivariate analysis, infection within 1 week, (odds ratio, 2.42; 95% CI, 1.01 to 5.8; $P=0.046$) but not cough, sneezing, or vomiting (odds ratio, 1.60; 95% CI, 0.67 to 3.8; $P=0.29$), was associated with CAD. This indicates that mechanical factors during infection do not explain the association between CAD and infections.

Therefore, the data given by Rubinstein et al[1] in the abstract and the text regarding infection are not correct and require revision together with conclusions in their review. From our study and the results by Guillon et al,[3] so far recent infection has to be regarded as a risk factor for cervical artery dissection. Furthermore, high-socioeconomic status may be another factor that is associated with the risk of CAD, although this certainly requires additional investigations.

Rubinstein et al[1] mentioned the possibility of a selection bias in our study. Our case-control study[2] was not part of a population-based register; however, it was based on consecutive patients in both groups. Given the fact that almost all of the younger patients with cerebral ischemia in the catchment area are treated in the University Center, the risk of selection bias can be rated as very low. In summary, 2 well-performed case-control studies found an independent association between recent infection and CAD that was not explained by factors such as mechanical stress to cervical arteries.[2,3]

Armin J. Grau, MD, PhD
Florian Buggle, MD
Department of Neurology
Klinikum der Stadt Ludwigshafen a.Rh. Bremserstr
Ludwigshafen, Germany

1. Rubinstein SM, Peerdeman SM, van Tulder MW, Riphagen I, Haldeman S. A systemic review of the risk factors for cervical artery dissection. *Stroke.* 2005;36:1575–1580.
2. Grau A, Brand T, Buggle F, Orberk E, Mytilineos J, Werle E, Conradt C, Krause M, Winter R, Hacke W. Association of cervical artery dissection with recent infection. *Arch Neurol.* 1999;56:851–856.
3. Guillon B, Berthet K, Benslamia L, Bertrand M, Bousser MG, Tzourio C. Infection and the risk of spontaneous cervical artery dissection: a case-control study. *Stroke.* 2003;34:e79–e81.

Response:

We would like to thank Drs Grau and Buggle for their interest in our article. They raise 2 important issues.

Their first objection may have to do with clarity of the text. We are not suggesting that the weak association refers to the relationship between dissection and the mechanical factors associated with infection, such as coughing, sneezing, or vomiting, but rather, the association between infection and dissection, even when these mechanical stressors are controlled for. Therefore, our article also agrees with the authors that recent infection may be an important risk factor, which is an association noted by others. However, this association may not be very strong. High socioeconomic status may also be an important risk factor and perhaps a subject for additional study; however, we did not identify any case-control studies that have confirmed this relationship.

Regarding the second point, case-control studies are notoriously sensitive to selection bias. Our objection was not whether patients were selectively identified (ie, consecutive), but rather that the control group chosen (ie, cerebral ischemia) may be inappropriate. Quite simply, controls must be a representative sample of the study base and must have an equal chance to develop the target disease as the cases. If not, it is a case of comparing apples with oranges. The mechanism of cerebral ischemia is quite clearly different from dissection, and we suggest that the risk factors may also differ (eg, "vascular risk factors"), which is why we proposed that healthy subjects might be a more suitable control. Otherwise, this may result in a potential overestimation of risk.

Note: This article was originally published online as a "systemic review." However, this was a typographic error and should have read, "a systematic review."

Sidney M. Rubinstein
Saskia Peerdeman
Maurits van Tulder
Scott Haldeman
Institute for Research in Extramural Medicine
(EMGO Institute)
VU University Medical Centre
Amsterdam, The Netherlands

Transcranial Doppler and Carotid Artery Disease Strokes: More Than Just Risk Stratification

To the Editor:

Two important studies addressing the role of transcranial Doppler ultrasound (TCD) microemboli detection and stroke prevention have been published recently.[1,2] Markus and MacKinnon[1] studied 200 patients within 3 months of a focal neurological event. Their study demonstrated that the presence of microembolic signals detected during 1 hour of TCD monitoring was an independent predictor of future stroke and transient ischemic attack (TIA). Two major implications were proposed, first that TCD emboli detection could be useful for risk stratification in patients with carotid stenosis and, second, that the technique could be used to assess the efficacy of antithrombotic therapy. In the recently published Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial,[2] dual antiplatelet therapy (aspirin plus clopidogrel) resulted in more effective control of microembolic signals than single antiplatelet therapy (aspirin alone). There was an associated reduction in the subsequent prevalence of TIAs and strokes.

Similar conclusions were drawn by the authors of both studies, in particular those patients with recent symptoms and emboli should be operated on urgently "wherever possible." However, a recent systematic review of the risks of carotid endarterectomy in relation to both the clinical indication for and timing of surgery has shown that urgent carotid surgery carries a much higher risk (19.2%; 95% CI, 10.7 to 27.8) than elective surgery (odds ratio, 3.9; 95% CI, 2.7 to 5.7; $P<0.001$; 13 studies).[3]

Immediately after a TIA or stroke, there is a rise in TCD-detected micoembolic signals. Those patients who continue to embolize are at greater risk of an additional neurological event.[4] Recurrent or crescendo TIA patients represent a particularly high-risk group. It is possible to stop both emboli and additional symptoms in these patients with TCD-directed IV antiplatelet agents, with the dose being incrementally increased until the micoemboli cease. Consequently, it is possible to influence the timing of surgical intervention, allowing patients to undergo carotid endarterectomy safely on the next elective list,[5] avoiding the risks associated with urgent or emergency surgery[3] or the risks associated with delay[6] in patients whose microemboli persist despite oral antiplatelet therapy.[1,2,4]

In the study by Markus and MacKinnon,[1] the time between index event and assessment was considerably >72 hours in most of the subjects examined. This leads to the conclusion that some reported strokes could have been prevented. We believe that earlier assessment would show a stronger beneficial influence of TCD-directed antithrombotic therapy followed by surgery when necessary. Microemboli are surrogate markers for the risk of future embolic events. The pharmacological efficacy of therapeutic interventions can now be assessed rapidly, noninvasively, and inexpensively. TCD emboli detection appears to offer an important advance enabling the optimal integration of both medical therapy and the timing of surgery, and the technique should be more widely available.

Kyle T.S. Pattinson, BM, FRCA
Nuffield Department of Anaesthetics
University of Oxford, John Radcliffe Hospital
Oxford, United Kingdom

Christopher H.E. Imray, MB, BS, FRCS
Coventry and Warwickshire County Vascular Unit
University Hospitals Coventry and Warwickshire NHS Trust
Coventry, United Kingdom

1. Markus HS, MacKinnon AM. Asymptomatic embolization detected by Doppler ultrasound predicts stroke risk in symptomatic carotid artery stenosis. *Stroke*. 2005;36:971–975.
2. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, Ringelstein EB. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic signal detection. *Circulation*. 2005;111:2233–2240.
3. Bond R, Rerkasem K, Rothwell PM. Systematic review of the risks of carotid endarterectomy in relation to the clinical indication for and timing of surgery. *Stroke*. 2003;34:2290–2301.
4. Slikwa U, Lingau L, Stohlmann WD, Schmidt P, Mull P, Diel RR, Noth J. Prevalence and time course of microembolic signals in patients with acute stroke. *Stroke*. 1997;28:358–363.
5. Lennard NS, Vijayasekar C, Tiivas C, Chan CWM, Higman DJ, Imray CHE. Control of emboli in patients with recurrent or crescendo transient ischaemic attacks using preoperative transcranial Doppler-directed Dextran therapy. *Br J Surg*. 2003;90:166–170.
6. Coull A, Lovett J, Rothwell P, on behalf of the Oxford Vascular Study. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public organization of services. *BMJ*. 2004;328:326–328.

Response:

Like Pattinson and Imray, we agree that Doppler embolic signal detection shows great promise in identifying patients with symptomatic carotid stenosis at high risk of early recurrent stroke. This group of patients may well benefit from more aggressive antiplatelet therapy. It is also possible that the use of the technique, combined with more aggressive antiplatelet therapy to reduce embolization in active embolizers, could allow carotid endarterectomy to be delayed in some patients.

However, based on considerable current evidence, patients with stable symptomatic carotid stenosis should be operated on as soon as possible. It has been clearly shown from analysis from the ECST and NASCET trials that the stroke risk in the first 2 weeks is very high.[1] The metaanalysis that the authors quote showed no difference in the odds of stroke and death after early carotid endarterectomy for established stroke compared with late surgery.[2] The excess risk was only seen in the smaller group of patients with unstable symptoms, ie, progressing stroke or crescendo transient ischemic attacks (TIAs). Therefore, in the majority of patients with a single ischemic TIA, or stroke with small infarct, current evidence suggests that carotid endarterectomy should be performed as soon as possible. In the more unstable patient with progressing symptoms, crescendo TIAs, or a large infarct, transcranial Doppler may well be useful in guiding treatment to allow stabilization before elective surgery. It may also be useful in guiding treatment in patients with stable symptoms and TIA or minor stroke in the many units worldwide where endarterectomy cannot be performed immediately as a result of logistic and resource issues.

In addition, before recommending its widespread implementation, some caution is required. Ideally, it should be shown in a large clinical study that this approach, when implemented on a widespread clinical scale, does allow stroke to be prevented. This will depend not only on the ability of embolic signals to predict stroke, as we have recently demonstrated, but also on the ability of clinical units to reliably implement the technique, including evaluation for embolic signals in real time. Current research studies, such as the 2 cited by Pattinson and Imray,[3,4] have used assessment of the presence of embolic signals at a later date by a single experienced observer on data stored on digital audiotapes.

Hugh S. Markus, FRCP
St. George's Hospital Medical School
London, UK

Andrew MacKinnon, MRCP
St. George's University of London
London, UK

1. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ; Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet*. 2004;363:915–924.
2. Bond R, Rerkasem K, Rothwell PM. Systematic review of the risks of carotid endarterectomy in relation to the clinical indication for and timing of surgery. *Stroke*. 2003;34:2290–2301.
3. Markus HS, MacKinnon AM. Asymptomatic embolization detected by Doppler ultrasound predicts stroke risk in symptomatic carotid artery stenosis. *Stroke*. 2005;36:971–975.
4. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, Ringelstein EB. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic signal detection. *Circulation*. 2005;111:2233–2240.

Use of Quantitative Magnetic Resonance Angiography to Stratify Stroke Risk in Symptomatic Vertebrobasilar Disease

To the Editor:

The recent article by Amin-Hanjani and coworkers[1] was interesting, but we believe that there are several flaws in their algorithmic approach. The authors erroneously conclude that distal blood flow reduction, especially in the basilar artery as demonstrated by phase contrast-quantified MRA (QMRA) and

A

Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION

Control of cerebral microemboli and symptoms with a TCD directed intravenous antiplatelet agent prior to elective retrograde stenting of a symptomatic critical innominate artery stenosis

Rajashekhar Rao, Colin Oliver, Carl A S Tiivas, Daniel J Higman, and Christopher H E Imray

STROKE/2005/447177 VERSION 1

Control of cerebral microemboli and symptoms with a TCD directed intravenous antiplatelet agent prior to elective retrograde stenting of a symptomatic critical innominate artery stenosis.

Raj Rao, Colin Oliver, Carl AS Tiivas, Daniel J Higman,
Christopher HE Imray

Coventry and Warwickshire University Hospitals,

Coventry CV2 2DX,

UK

Correspondence:

CHE Imray, Coventry and Warwickshire University Hospitals, Coventry, CV2 2DX

Email: chrisimray@aol.com

Telephone: 02476 602020 Ext 8944

Fax: 02476 538 621

Category: original article (case report)

Key words:

Innominate artery, carotid artery, stroke, transcranial Doppler, cerebral microemboli, stents.

Abstract

Background-

Innominate artery stenoses are often asymptomatic, but when symptomatic may cause major stroke. Optimal treatment of a patient with multiple recurrent TIAs arising from an innominate artery stenosis is uncertain.

Methods-

We report the case of a 58-year-old patient with multiple focal neurological events in the right anterior circulation associated with TCD detected microemboli and an innominate artery stenosis. A staged approach was used. TCD directed intravenous antiplatelet infusion controlled the microemboli and symptoms, and this was followed by elective retrograde endoluminal stenting of the innominate artery stenosis.

Results-

Postprocedure angiography demonstrated satisfactory positioning of the innominate stent and there was abolition of the microemboli. The patient had no further TIAs over a 4-month period. At 3-months, the CT angiogram and Duplex imaging showed a patent innominate artery. Neurological examination was normal.

Conclusion-

The successful angiographic and clinical results observed in this case of a symptomatic embolising innominate artery stenosis treated with TCD directed antiplatelet therapy followed by retrograde stenting contributes to the limited

literature of management of this difficult clinical scenario. To our knowledge this is the first case of a neurological unstable patient with an embolising innominate artery stenosis treated in this fashion.

Introduction

The high prevalence of stroke following an index transient ischaemic attack (TIA) arising from an internal carotid artery stenosis (ICAS) ranges between 20% in the first month[1] and 10.5% within ninety days[2]. The risk of a TIA and/or stroke due to embolism in innominate artery stenosis is less well documented but the majority are asymptomatic and diagnosed coincidentally during routine Duplex, angiographic or magnetic resonance angiography (MRA) investigation of the major neck arteries. When symptomatic, symptoms are either related to posterior cerebral circulation hypo-perfusion ischemia due to a subclavian steal syndrome, or embolic right anterior circulation symptoms. Occasionally both sets of symptoms will occur in the same patient.

We present a case report of a patient with a symptomatic innominate artery stenosis with multiple cerebral microemboli detected in the right middle cerebral artery (MCA). Both the emboli and symptoms were controlled with by a pre-operative transcranial Doppler directed antiplatelet infusion prior to retrograde endoluminal stenting.

Case report

A 58-year-old right-handed male patient presented with right-sided visual disturbance, pins and needles in his left arm and with an associated headache and dizzy spells. He had had these episodes up to 7 times per week within the previous 3 weeks and each episode lasted for about 3 minutes. On clinical examination there was a loud right carotid bruit and reduced right brachial arterial pressure. Clinical examination was otherwise unremarkable. He was an ex-smoker, not diabetic and had lipids within the normal range. His medication included aspirin 75mg od and simvastatin 40 mg od.

Three years previously, he was admitted to hospital after a short-lived 'fainting attack' from which he had fully recovered. At the time, he was investigated with CT brain and a cardiac exercise stress test both of which were normal. A Duplex scan of his neck and a CT angiogram performed showed a 70% stenosis of the innominate artery. With no focal symptoms, he was started antiplatelet therapy and was followed up routinely by the

stroke physicians.

On this occasion, following the development of focal symptoms, a carotid duplex using an Acuson 128XP/10 (Mountain View, CA, USA) was performed. It confirmed the tight innominate artery stenosis, and in addition there was a 50% stenosis of the right internal carotid artery (PSV 140cm sec^{-1}) and a mild stenosis of his left internal carotid artery. Transcranial Doppler monitoring of the right middle cerebral artery (MCA) was performed using a SciMed PC Dop 842 (Bristol, UK) with a 2MHz probe focused on the MCA at 5.0-5.5cms. Embolic signals were assessed by listening for the characteristic sound and appearance of their spectra, using previously published identification criteria[3]. There were 4 micro embolic signals in 1 hour of monitoring. The patient was admitted and administered a 20mls bolus of Dextran 40 intravenously followed by a continuous infusion at 20mls an hour. He had no further symptoms and repeated TCD monitoring confirmed no further cerebral microemboli whilst on the Dextran 40 infusion. He subsequently had a CT angiogram of his aortic arch, which demonstrated a tight stenosis of the innominate artery (Figure 1), but that his internal carotid artery was only 30-50% stenosed.

He underwent retrograde stenting of his innominate artery via his right common carotid artery 10 days after admission on an elective list. The intravenous anti-platelet agent infusion was continued until the morning of surgery. A loco-regional anaesthetic block was instilled and the right common carotid artery was exposed in a standard fashion. 3,500 units of intravenous heparin were administered, and there was no evidence of neurological obtundation on trial clamping the distal common carotid artery. The common carotid artery was punctured in a retrograde fashion and a hydrophilic guide wire used to traverse the innominate artery stenosis. The lesion was predilated and a balloon expandable Cordis Genesis stent (Johnson & Johnson) was inserted, and a completion angiogram performed. The right common carotid artery was vented via the puncture site, flushing out the potential embolic debris following stent insertion. The common carotid endoluminal access site was closed surgically, and flow was restored to the external carotid and the internal carotid artery sequentially. Post operatively TCD

monitoring of the MCA artery revealed no microembolic signals. The patient was discharged home after 48 hours on clopidogrel 75 mg od and aspirin 75 mg od. The clopidogrel was discontinued after one month. On follow up 4 months later he remains asymptomatic. A follow up CT angiogram has been performed (Figure 2,3).

Discussion

Cerebral microemboli are a frequent phenomenon following acute stroke, and continue for some days, and are a significant independent predictor of early ischaemic recurrence in patients with stroke or TIA[4]. A similar association between stroke and microemboli is established from studies on patients with significant carotid stenosis[5] and following carotid endarterectomy[6]. Postoperative microemboli are usually platelet-aggregates generated by the exposed thrombogenic vessel wall. These aggregates may develop into occlusive thromboemboli causing infarcts. TCD directed Dextran treatment has also been shown been used to control emboli and reducing the risk of postoperative carotid thrombosis following carotid endarterectomy[6,7].

Pre-operative TCD directed Dextran 40 therapy has been shown to be effective in controlling emboli in symptomatic carotid artery stenoses, allowing patients to undergo surgery on the next elective list[8,9] and avoiding the higher risks associated with emergency carotid surgery[10]. A patient with recurrent focal deficits associated with an embolising sub-intimal carotid artery dissection has been successfully treated with TCD directed antiplatelet agents[11].

Cerebral microemboli appear to be surrogate markers for future ischaemic events and if cerebral microemboli persist despite medical therapy, there appears to be an approximately forty-fold increase risk of further neurological events[12]. The CARESS Trial[13] recently demonstrated that dual therapy controls both microemboli and symptoms more effectively than mono therapy. However even in the dual therapy group, some patients continued to embolize and remained at significant risk of further events.

A number of interventions to treat a symptomatic innominate artery stenosis could be considered. Open surgery, involving a thoracotomy and bypass of the stenosis is possible but is maximally invasive. Various surgical and minimally invasive therapeutic options are possible, and when an innominate artery stenosis has caused flow related (rather than embolic) symptoms, antegrade stenting via the groin is an accepted approach. Even using cerebral protection device, we were concerned about iatrogenic distal embolisation using a conventional antegrade approach, particularly whilst the symptomatic lesion was being initially traversed with a guide wire. Pre-procedural pharmacological stabilisation of the plaque using TCD directed Dextran followed by retrograde endoluminal stenting appeared to offer the safest approach to this high risk lesion. It was then possible to temporarily achieve distal control of the internal carotid artery with carotid clamps, whilst the innominate lesion was traversed and stented, so preventing any embolic debris reaching the brain.

Using TCD directed intravenous antiplatelet agents (Dextran 40 or tirofiban), we have treated symptomatic embolisation from a sub-intimal dissection of the internal carotid artery[11], internal carotid artery stenoses[8,9] and an embolising innominate artery Converging lines of evidence suggest embolisation from large arteries which cause focal cerebral symptoms can be treated in the short term with TCD directed antiplatelet agents. TCD can assist in identifying the patients at higher risk of a subsequent neurological event, and the pharmacological efficacy of therapeutic interventions can now be assessed rapidly and non-invasively. TCD emboli detection appears to offer an important advance enabling the optimal integration of both medical therapy and the timing of any surgical intervention in patients with symptomatic large vessel disease.

We believe this is the first report of an embolising innominate artery stenosis treated in a two phases using a TCD-directed intravenous antiplatelet agent infusion to control symptoms prior to elective retrograde endoluminal stenting of the stenosis.

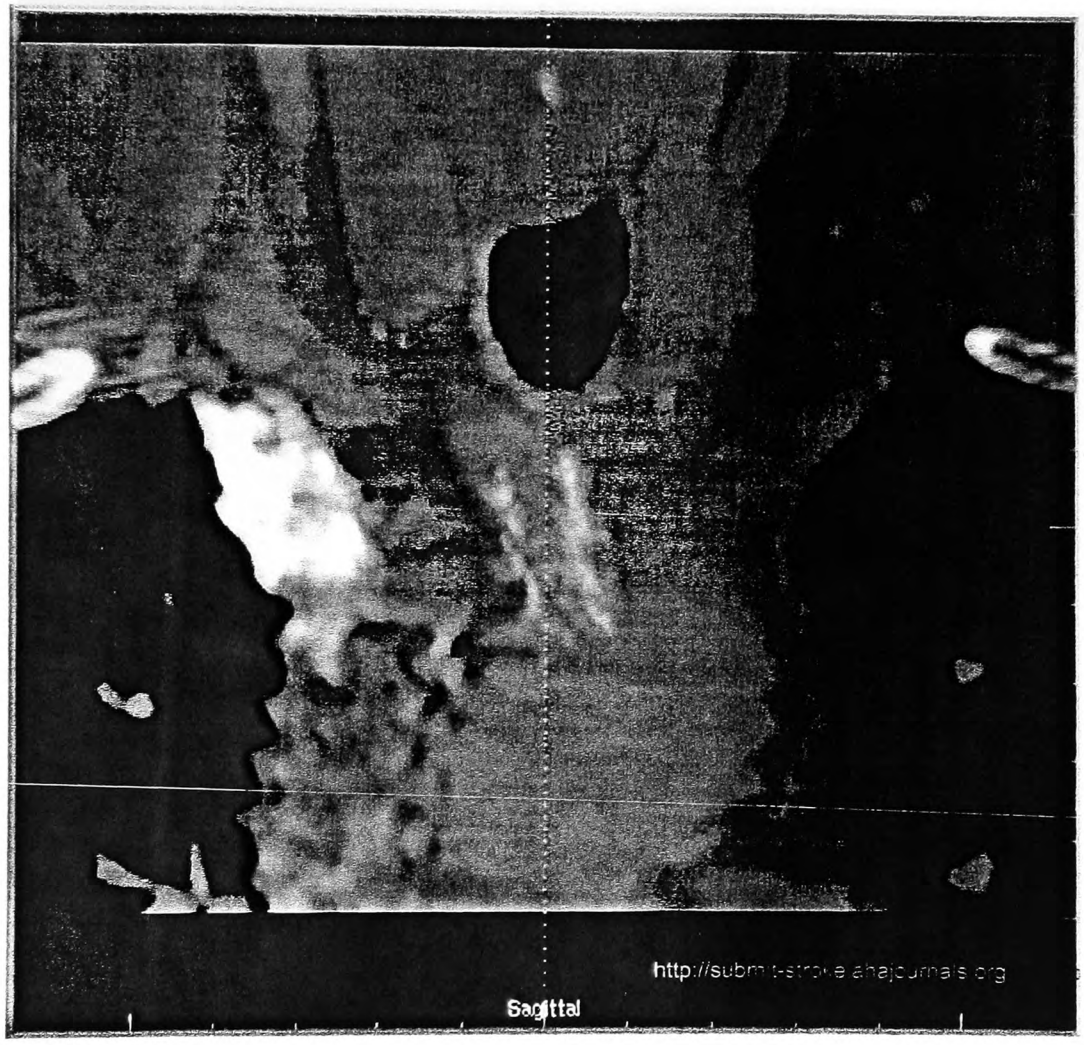
References

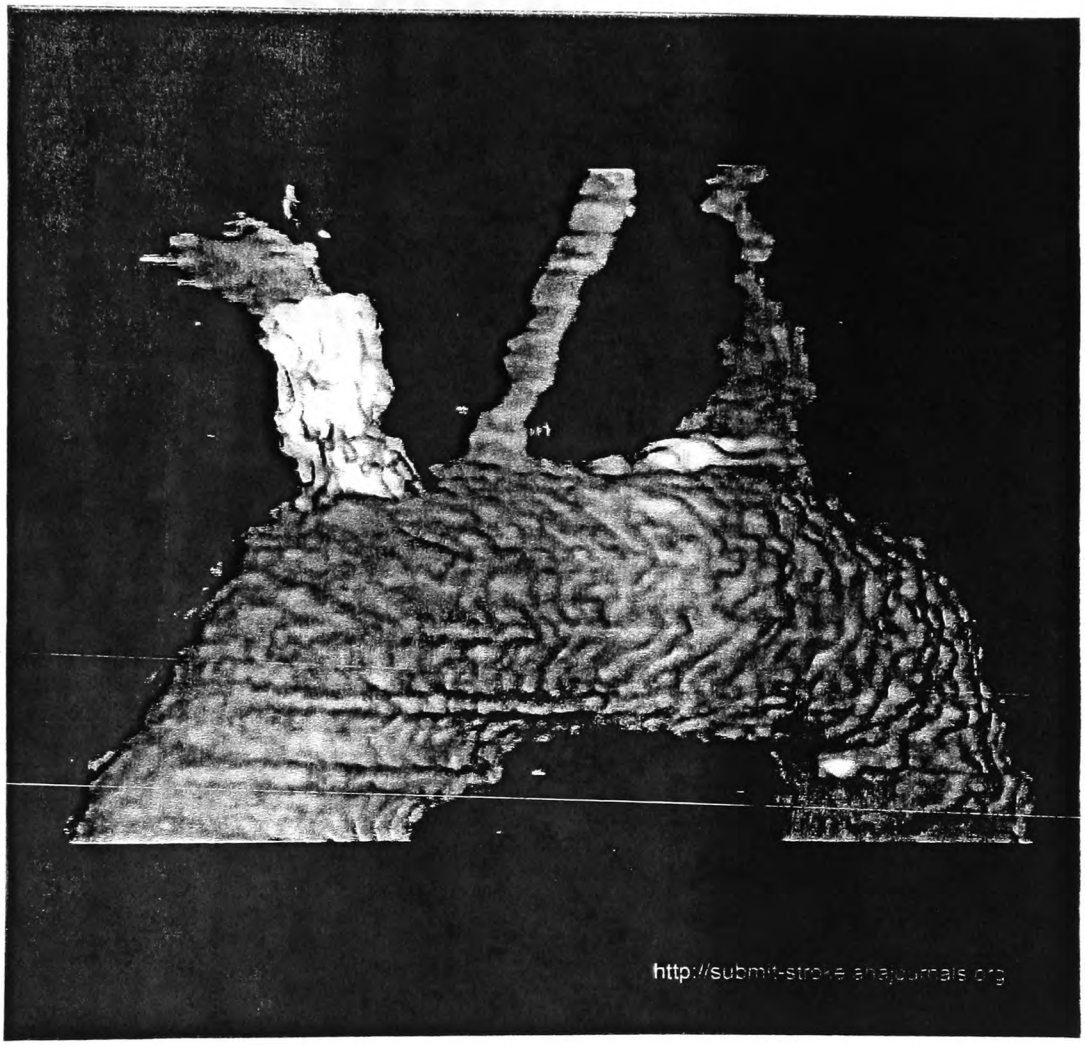
1. Coull A, Lovett J, Rothwell P on behalf of the Oxford Vascular Study. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public organization of services. BMJ 2004; **328**: 326-8
2. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. JAMA. 2000; **284**:2901-6
3. Basic identification criteria of Doppler microembolic signals, Consensus Committee of the Ninth International Cerebral Hemodynamic Symposium. Stroke. 1995; 26: p1123
4. Valton L, Larrue V, Pavy le Traon A, Massabuau P, Geraud G. Microembolic signals and risk of early recurrence inpatients with stroke or transient ischemic attack. Stroke 1998; **29**: 2125-2128
5. Markus HS, MacKinnon A. Asymptomatic embolization detected by Doppler ultrasound predicts stroke risk in symptomatic carotid artery stenosis. Stroke. 2005; **36**: 971-975
6. Naylor AR, Hayes PD, Allroggen H, Lennard N, Gaunt ME, Thompson MM, London NJ, Bell PR. Reducing the risk of carotid surgery: a 7-year audit of the role of monitoring and quality control assessment. J Vasc Surg. 2000 Oct; **32**(4): 750-9
7. Hayes PD, Lloyd AJ, Lennard N, Wolstenholme JL, London NJ, Bell PR, Naylor AR. Transcranial Doppler-directed Dextran-40 therapy is a cost-effective method of preventing carotid thrombosis after carotid endarterectomy. Eur J Vasc

Endovasc Surg 2000 Jan; **19(1)**: 56-61

8. Lennard NS, Vijayasekar C, Tiivas C, Chan CWM, Higman DJ, Imray CHE. Control of emboli in patients with recurrent or crescendo transient ischaemic attacks using preoperative transcranial Doppler-directed Dextran therapy. Br J Surg 2003; **90** : 166-170
9. Imray CHE, Tiivas CAS. Are some strokes preventable? The potential role of transcranial Doppler in transient ischaemic attacks of carotid origin. Lancet Neurology. 2005; Lancet Neurology 2005; **4(9)**: 580-6
10. Bond R, Rerkasem K, Rothwell PM. Systematic review of the risks of carotid endarterectomy in relation to the clinical indication for and timing of surgery. Stroke 2003 ; **34**: 2302-3
11. Joseph T, Kandiyil N, Beale D, Tiivas C, Imray CHE. A novel treatment for symptomatic carotid dissection. Postgraduate Medical Journal. 2005; **81(958)** : e6.
12. Goertler M, Blaser T, Krueger S, Hofmann K, Baeumer M, C-W Wallesch. Cessation of embolic signals after antithrombotic prevention is related to reduced risk of recurrent arterioembolic transient ischaemic attack and stroke. J Neurol Neurosurg Psychiatry 2002; **72**: 338-342
13. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, Ringelstein EB. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic signal detection. Circulation.2005; **111**: 2233-2240

K


http://submit-stroke.ahajournals.org
Sagittal


http://submit-stroke.ahajournals.org

N

Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION

A potential role for TCD directed antiplatelet agents in symptomatic carotid artery dissection

Christopher H. E Imray and Kyle T S Pattinson

STROKE/2005/447250 VERSION 1

This information is current as of November 1, 2005

A potential role for TCD directed antiplatelet agents in symptomatic carotid artery dissection.

Christopher HE Imray[1] and Kyle TS Pattinson[2]

[1]Coventry and Warwickshire County Vascular Unit,

Coventry and Warwickshire University Hospitals,

Clifford Bridge Road,

Walsgrave,

Coventry CV2 2DX, UK

[2]Nuffield Department of Anaesthetics,

University of Oxford,

The John Radcliffe Hospital,

Headley Way,

Oxford OX3 9DU, UK

Correspondence:

CHE Imray, Walsgrave Hospital, Clifford Bridge Road, Walsgrave, Coventry, CV2 2DX

Email: chrisimray@aol.com

Telephone: 02476 602020 Ext 8944

Fax: 02476 538 621

Category: Letter

P

Dear Sir,

We read with interest the debate regarding the role of anticoagulation in extracranial arterial dissection [1-3]. We agree with Norris[1] that artery to artery embolism is the most likely cause of stroke, and also agree with Lyrer[2] that there is no evidence supporting anticoagulation for extracranial internal carotid artery dissection (CAD). Donnan and Davis[3] make a most important contribution when they differentiate between the use of antithrombotic agents and antiplatelet agents in CAD.

The commonest mechanism of stroke in carotid artery dissection is hypothesised to be artery to artery embolism[1]. If this hypothesis is correct, then the situation would appear to be analogous to transient ischaemic attacks (TIAs) arising from a critical internal carotid artery stenosis. Transcranial Doppler (TCD) directed intravenous antiplatelet agents have been successful in treating these patients[4,5,6], both prior to- and following- elective surgery. In further support of this hypothesis, we have recently reported a 45 year old patient who was successfully treated with TCD directed antiplatelet agents[7] for recurrent focal deficits associated with an embolising sub-intimal carotid artery dissection.

Converging lines of evidence suggest that embolisation from large arteries can cause focal cerebral symptoms and can be treated in the short term with TCD directed antiplatelet agents[6]. TCD can rapidly and non-invasively assist both in identifying those patients at higher risk of a subsequent neurological event[8], and in assessing the efficacy of interventions[5]. TCD emboli detection appears to offer an important advance, enabling the optimal integration of both medical therapy and the timing of any surgical intervention, in patients with symptomatic large vessel disease. We advocate TCD interrogation of the middle cerebral artery (MCA) for microemboli in symptomatic CAD, particularly where there are fluctuating neurological signs. TCD directed antiplatelet agents could then be used to control cerebral microemboli and symptoms[7]. Elective surgical or endovascular intervention can then be considered where appropriate.

References

1. Extracranial Arterial Dissection: Anticoagulation Is the Treatment of Choice: For Norris JW. *Stroke,* 2005; **36**: 2041-2042
2. Extracranial Arterial Dissection: Anticoagulation Is the Treatment of Choice: Against. Lyrer PA. *Stroke,* 2005; **36**: 2042-2043
3. Extracranial Arterial Dissection: Anticoagulation Is the Treatment of Choice Donnan GA and Davis SM. *Stroke,* 2005; **36**: 2043-2044
4. Lennard NS, Vijayasekar C, Tiivas C, Chan CWM, Higman DJ, Imray CHE. Control of emboli in patients with recurrent or crescendo transient ischaemic attacks using preoperative transcranial Doppler-directed Dextran therapy. *Br J Surg,* 2003; **90**: 166-170
5. Imray CHE, Tiivas CAS. Are some strokes preventable? The potential role of transcranial Doppler in transient ischaemic attacks of carotid origin. *Lancet Neurol.*, 2005; **4**: 580-6
6. Naylor AR, Hayes PD, Allroggen H, Lennard N, Gaunt ME, Thompson MM, London NJ, Bell PR. Reducing the risk of carotid surgery: a 7-year audit of the role of monitoring and quality control assessment. *J Vasc Surg*, 2000; **32**: 750-9
7. Joseph T, Kandiyil N, Beale D, Tiivas C, Imray CHE. A novel treatment for symptomatic carotid dissection. *Postgraduate Med J.* 2005; **81**: e6
8. Markus HS, MacKinnon A. Asymptomatic embolization detected by Doppler ultrasound predicts stroke risk in symptomatic carotid artery stenosis. *Stroke.* 2005; **36**: 971-975