# 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

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## A B S T R A C T

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 ($P\text{a}CO_2$) and, to a lesser extent, to changes in the arterial partial pressure of oxygen

($P$aO$_2$). As the atmospheric pressure drops, the fall in $P$aO$_2$ 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 $P$aO$_2$, but the increased ventilatory rate lowers $P$aCO$_2$, resulting in subsequent inhibition of the respiratory centre. $P$aCO$_2$ 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 $P$aCO$_2$, 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$_2$ ($P$iCO$_2$) 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

$Pi_{CO_2}$, the end-tidal partial pressure of $CO_2$ ($PET_{CO_2}$), 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 ($rS_{O_2}$) is derived from the equation:

$$rS_{O_2} = \left( \frac{\text{oxygenated haemoglobin}}{\text{total haemoglobin}} \right) \times 100.$$

## 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, $PET_{CO_2}$, $Pi_{CO_2}$ 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 $PET_{CO_2}$

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 $CO_2$/$O_2$. $PET_{CO_2}$ 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 ($P < 0.005$), $Pa_{O_2}$ ($P < 0.0001$) and $Pa_{CO_2}$ ($P < 0.001$) were reduced. $Pa_{O_2}$ 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; $^†P < 0.001$ 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; $^†P < 0.01$, $^{††}P < 0.0005$ 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 $rS_{O_2}$

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 $rS_{O_2}$ fell on ascent to 3459 m (Table 3). Breathing either 3% $CO_2$ or 35% $O_2$ increased cerebral $rS_{O_2}$ 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 $rS_{O_2}$

Baseline muscle $rS_{O_2}$ 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 $rS_{O_2}$ at 150 m [73.3% (2.2%)] or at 3459 m [68.9% (3.6%)] on breathing 3% $CO_2$. At 3459 m, muscle $rS_{O_2}$ rose to 70.3% (3.6%) ($P < 0.001$) on breathing 35% $O_2$. Muscle $rS_{O_2}$ 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
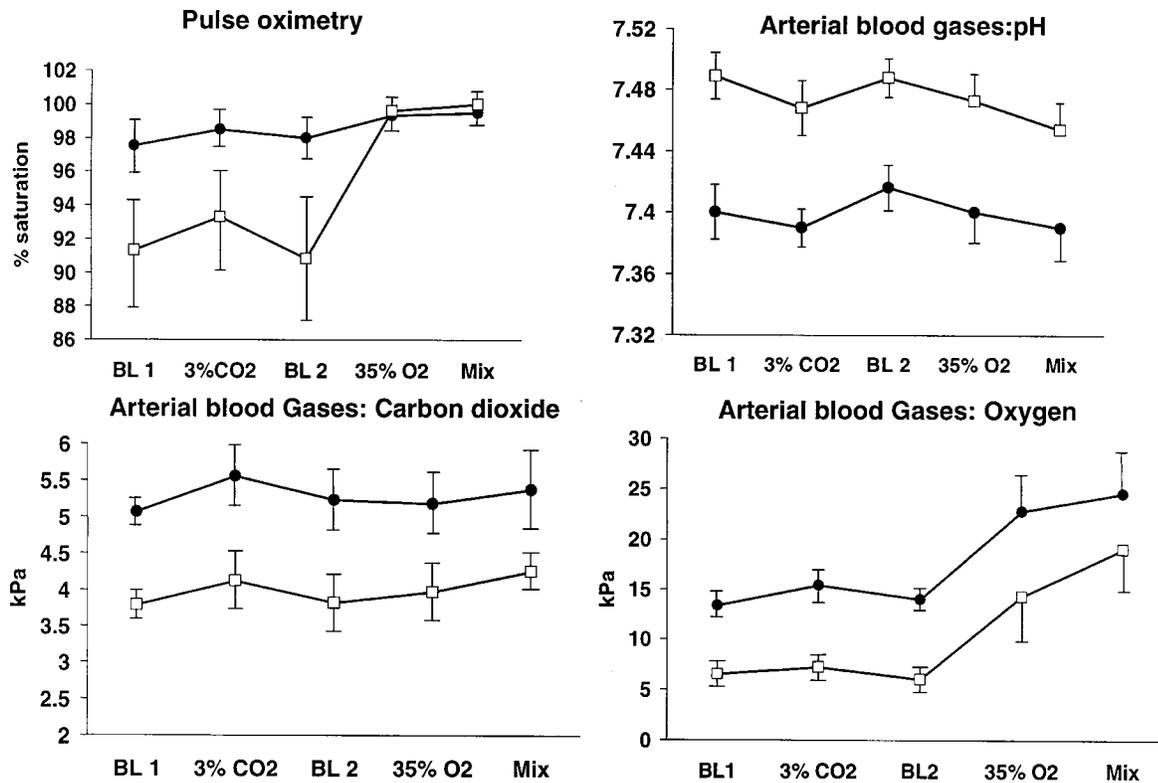
## Pulse oximetry



## Arterial blood gases:pH



## Arterial blood Gases: Carbon dioxide



## Arterial blood Gases: Oxygen



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

Values are means $\pm$ 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 $Pa_{O_2}$ at both altitudes ($P < 0.01$) and a rise in $Pa_{CO_2}$ at 150 m ($P < 0.01$). Compared with BL1, 35% $O_2$ resulted in an increase in pulse oximetry ($P < 0.0001$) and $Pa_{O_2}$ ($P < 0.0001$) 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 $Pa_{O_2}$ at 150 m ($P < 0.01$) and at 3459 m ($P < 0.001$), and an increase in $Pa_{CO_2}$ at 150 m ($P < 0.01$).

**Table 3   Changes in MCAV and rSo₂ at the end of each 5 min period of supplementary gas breathing**

MCAV and $rS_{O_2}$ 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) |
| $rS_{O_2}$ (%) | | | | | |
| 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 $\sim 8800$ 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,
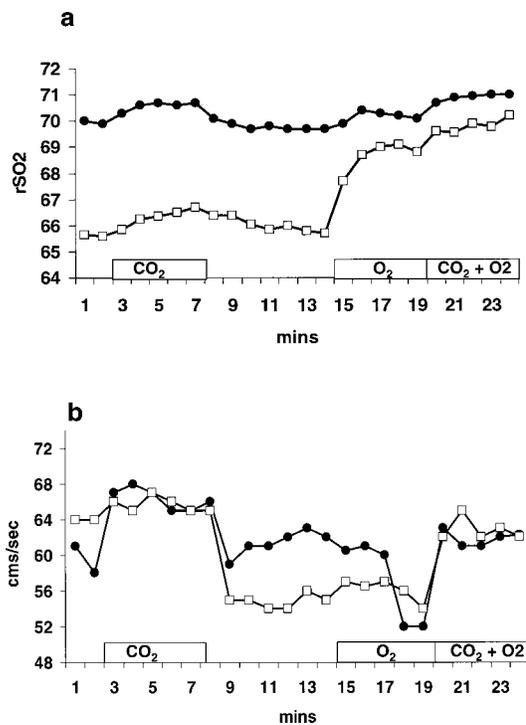
**Figure 2   Sequential measurements of $rSo_2$ (a) and MCAV (b) during inhalation of 3% $CO_2$, 35% $O_2$ or 3% $CO_2$/35% $O_2$ in ambient air at 150 m (●) and 3459 m (□)**

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 $P_{iCO_2}$ 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), $P_{iCO_2}$ 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 pro-found 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

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