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EFFECT OF CARBON DIOXIDE IN ACUTE MOUNTAIN SICKNESS: A REDISCOVERY

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Summary The effect of adding CO_2 to inhaled air in six subjects with acute mountain sickness was investigated during a medical expedition to 5400 m. 3% CO_2 in ambient air increased ventilation and resulted in a rise in PaO_2 of between 24% and 40%. There was a 9–28% increase in $PaCO_2$ and a reduction of the respiratory alkalosis normally seen at high altitude. Symptoms of acute mountain sickness were rapidly relieved. In three subjects cerebral blood flow increased by 17–39%, so that oxygen delivery to the brain would have been considerably improved. This study confirms earlier suggestions of the beneficial effect of CO_2 inhalation at high altitude.

Introduction

THE behaviour of man exposed to extremes of the physical environment is of considerable scientific interest because the resulting observations frequently cast new light on important physiological mechanisms as well as on pathological processes seen in disease.[1]

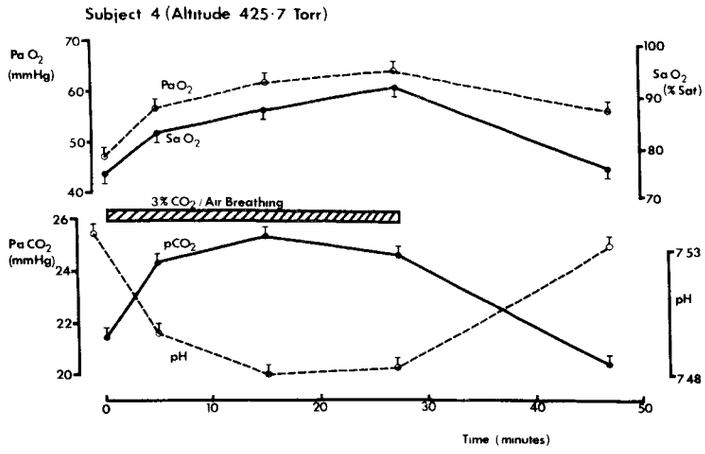
Ascent to high altitude presents interesting physiological questions. Control of respiration[2] and control of cerebral blood flow (CBF)[3] are highly sensitive to changes in carbon dioxide tension ($PaCO_2$) but rather less sensitive to changes in oxygen (PaO_2).[4] On exposure to low barometric pressure, reduced tension of inspired oxygen results in a fall of PaO_2 which eventually becomes severe enough to stimulate respiratory chemoreceptors and increase both depth and rate of ventilation. This increases PaO_2 but at the cost of inducing hypocapnia—a strong inhibitory stimulus to the respiratory centre and a powerful constrictor of mammalian cerebral blood vessels.

These stimuli alternately excite and inhibit the respiratory centre, leading to Cheyne-Stokes respiration.[5] Although this is hardly noticeable during activity at high altitude the effect becomes pronounced during sleep. Severe hypoxia may occur during the apnoeic phase, when the subject may slip from sleep into coma—and from coma into death.[6]

The combination of hypoxia and hypocapnia, also found in carbon monoxide poisoning and various cardiac and respiratory disorders, was recognised in aviators and mountaineers at the end of the last century. Modern clinicians, familiar with lethal hypercapnia and accustomed to treating the anoxia of respiratory failure with oxygen in hospital practice, are apt to think of oxygen as the "vital spirit" and carbon dioxide as a potentially dangerous exhalation. In biological terms, however, carbon dioxide (in appropriate concentration) is no less vital to life than oxygen. Miescher-Rüsch (1885) recognised this in a poetic phrase: "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 not lack air in warm blooded animals whereas skin and muscle may tolerate the ischaemia of a tourniquet for more than half an hour".[7,8]

Angelo Mosso (1898) believed in treating acapnia (he coined the term) and administered CO_2 gas mixtures to relieve hypoxic symptoms in subjects exposed to pressures as low as 250 torr (~8800 m) in a hypobaric chamber.[6] Douglas,[5] Haldane,[9] Henderson,[8] and others re-emphasised the importance of hypocapnia and Childs[10] suggested that inhaled CO_2 might be useful in climbing to great altitudes. Carbon dioxide mixtures were frequently used to stimulate respiration in carbon monoxide asphyxia from the 1920s and there was interest in its use in aviation, pilot anoxia being a major source of casualties in the 1939–49 war.[11-13]

Although the results of these early experiments with CO_2 were encouraging, direct blood gas data were difficult to obtain because of technical limitations; and without such information the therapeutic use of CO_2 was both unsubstantiated and hazardous. Moreover, the hazard of anoxia in aviation—the principal stimulus for this work—was largely eliminated in the 1940s with the introduction of aircraft pressurisation. Most of the interest in



Observations in subject 4.

mountaineering hypoxia in recent years has been concentrated on treatment with drugs and oxygen, and the promising early work on CO_2 seems to have become largely forgotten. The development of electronic instruments has made it possible to conduct blood gas studies and other experiments under the most demanding conditions and we decided to investigate the effect of CO_2 in subjects with acute mountain sickness (AMS) during a medical expedition to Gondokoro (5620 m) in the Karakoram, Baltistan, in 1987.

Subjects and Methods

Six subjects (one at two altitudes) with moderate AMS, defined on the basis of clinical symptoms (headache, vomiting, nausea, ataxia) and assessment by two senior physicians, were studied at altitudes between 3400 and 5400 m (517–392 torr) as they became ill.

Each subject was placed supine on a mattress and spent several minutes breathing air via a non-return valve until a steady state was reached. A 3% CO_2 in ambient air mixture was made up by filling a 500 l Douglas bag (PK Morgan Ltd) with air and adding CO_2 from a cylinder to the appropriate concentration. After the subject became accustomed to the apparatus the valve was opened so that the 3% CO_2/air mixture was inhaled for between 12 and 25 minutes during which time ear-lobe capillary blood samples were obtained.

Analysis of blood and gas samples was made on a BMS 3 analyser (Radiometer) driven off a 1·5 kW generator (Haverhill) especially adapted for high altitude. In three cases continuous oxygen saturation (SaO_2) was recorded with a Biox finger oximeter (Medilog).

CBF was measured in three subjects during inhalation of CO_2, by the radioactive xenon method (Jenson J, Wright AD, Lassen NA, et al, unpublished). ^{133}Xe in saline (~250 MBq) was injected as a bolus into a forearm vein and the 81 keV peak of ^{133}Xe was counted from the γ-spectrum recorded over the brain by an array of six collimated sodium iodide crystal detectors linked to a microcomputer (Scan Detectronic, Denmark).

This experiment was usually done under difficult conditions in a hostile environment, so there were constraints on the number of measurements that could be obtained.

Results

During inhalation of CO_2 there was a striking increase in PaO_2 and SaO_2, a small fall in pH, and a rise in $PaCO_2$ as a consequence of increased ventilation. (Pneumotachograph studies were not recorded on this occasion but inhalation of 3% CO_2-in-air increased ventilation by about 30% in previous experiments at 3475 m; Harvey TC, Winterborn MH, unpublished).

There was a considerable improvement in oxygenation with corresponding clinical benefit. Subjects with headache noted prompt relief, and other subjective features such as nausea, ataxia, drowsiness, and weakness disappeared within a few minutes. This clinical benefit lasted for 30–60 minutes after inhalation of CO_2 but symptoms gradually returned on breathing of ambient air.

The accompanying figure showed results of a typical study, the table gives blood gas data. In three subjects CBF was recorded before and during CO_2 inhalation. In each case there was a prompt rise in CBF (17, 18, and 39%) within 10 minutes, during which time headache disappeared.

Discussion

The accompanying figure shows results of a typical study, the table gives blood gas data. In three subjects CBF was recorded before and during CO_2 inhalation. In each case at sea level and showed that although 5% O_2/95% N_2 rendered subjects unconscious with grossly abnormal changes in the electroencephalogram, addition of 5% CO_2 gas (ie, 5% CO_2 + 5% O_2 + 90% N_2) restored consciousness and returned the EEG to normal.

Gellhorn investigated aspects of cerebral cortical function that were impaired by breathing hypoxic gas mixtures. Abnormalities of visual intensity discrimination[15,16] and hearing[17] were completely reversed by the addition of 3% CO_2 to the inspired hypoxic mixture, and the authors concluded that the effect was due to the circulatory improvement induced by CO_2 in oxygen deficiency.

Lahiri administered CO_2 to subjects at 5400 m on Everest and recorded abolition of Cheyne-Stokes respiration in sleep and an increase in minute ventilation and SaO_2. No mention was made of any effect on AMS.[18,19]

Many of the cerebral symptoms of AMS have been ascribed to actual or incipient cerebral oedema and the condition in its most severe form is often referred to as HACE (High Altitude Cerebral Edema).[20] Post-mortem examination of 58 USAF personnel who died of acute anoxia in high altitude aircraft accidents did show extensive brain swelling[21] but other workers have argued that oedema is secondary to hypoxic neural injury.[22]

Some physicians on our expedition were initially concerned about breathing CO_2 in AMS in case the predicted increase in CBF precipitated acute cerebral

BLOOD GAS DATA: BASAL AND DURING 3% CO_2 INHALATION

Case	Barometric pressure	PaO_2 (torr)*			$PaCO_2$ (torr)			pH	
		Basal	During	Change (%)	Basal	During	Change (%)	Basal	After
1	517	70·0	87·0	+17·0 (+24)	20·5	25·6	+5·1 (+25)	7·365	7 351
2a	517	56 3	77 8	+21·5 (+38)	26 6	28 9	+6·3 (+9)	7·447	7 424
2b	426	49·5	65·5	+16 0 (+32)	21 3	25·7	+4·4 (+21)	7·495	7 469
3	426	50·3	68·6	+18 3 (+31)	20 8	25·3	+4 5 (+22)	7 515	7 450
4	426	47 3	63·7	+16·4 (+35)	21·3	25 3	+4·0 (+19)	7·528	7 482
5	426	57 4	72 3	+14·9 (+26)	20·2	24 9	+4·7 (+28)	7 483	7·472
6	392	41 1	57 4	+16·3 (+40)	18·6	20 9	+2·3 (+12)	7·516	7 480

*1 torr (mm Hg) = 7·5 kPa.

oedema and exacerbated headache, as suggested by Maher.[23] In practice the opposite effect was observed; despite an increase in CBF, there was relief of neurological symptoms within minutes. Oxygen delivery to the brain was probably increased (raised PaO_2 and CBF) and the very rapid response suggested strongly that the cerebral symptoms of AMS were due to hypoxic nervous tissue injury rather than oedema.

Fifty years ago Henderson[8] showed that headache and other acute neurological symptoms in carbon monoxide poisoning were rapidly relieved by breathing a CO_2 mixture and that the benefit achieved by this means was greater than that produced by 100% oxygen alone: the similarity between this condition and AMS is striking.

These observations are complemented by work on the effect of hypocapnia on CBF in the Pekin duck and certain migratory birds.[24,25] The bar-headed goose can fly with ease from sea level to over 11 000 m. In such birds, unlike all mammalian species in which it has been measured, CBF is not reduced by acute hypocapnia, whereas hypercapnia does cause the expected increase in CBF.

The difference, which remains unexplained, is obviously very important to the lifestyle of these birds. Man, lacking this mechanism, is gravely handicapped at high altitude by the limiting effects of hypocapnia. We suggest that inhalation of 3% CO_2 might be a useful emergency treatment for AMS, although prophylactic or longer term therapy might be better achieved by use of a carbonic anhydrase inhibitor to stimulate respiration and CBF by increasing central PCO_2.[26]

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WHAT IS THE BEST PREDICTOR OF THE SEVERITY OF ABO-HAEMOLYTIC DISEASE OF THE NEWBORN?

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Summary In 80 newborn infants ABO-incompatible with their mothers, the lysis-inducing effect of the maternal IgG anti-A or anti-B antibodies in an antibody-dependent cell-mediated cytotoxicity (ADCC) assay and the antigen density of A or B antigens on the red cells of the children were measured. On the basis of the results, the children were divided into two groups—24 children in whom increased haemolysis was to be expected, and 56 children in whom it was not. Signs of haemolysis and serological features of ABO haemolytic disease of the newborn (ABO-HDN) were compared in these two groups and a control group of 120 ABO-compatible infants. The effect of the maternal antibodies in the ADCC assay, the titres of maternal IgG anti-A or anti-B antibodies, the results of the direct antiglobulin test on the red cells in the cord blood, and the titre of IgG anti-A or anti-B antibodies in the serum of the infants were compared for their ability to predict the severity of ABO-HDN. This was also done for the combination of the ADCC assay results plus the A or B antigen density and the direct antiglobulin test plus the titre of maternal IgG anti-A or anti-B antibodies. The ADCC assay with maternal serum was the most sensitive assay to predict ABO-HDN, and the combination of the ADCC assay with A or B antigen density determination the most specific test.

Introduction

ABO haemolytic disease of the newborn (ABO-HDN) was first described by Halbrecht in 1944.[1] Since then, many investigators have tried to find a simple serological test to predict whether the baby will be affected, because in 15% of all pregnancies in White women, the mother has blood group O and her infant blood group A or B.[2] The value of

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