Cerebral Blood Flow in Man at High Altitude

ROLE OF CEREBROSPINAL FLUID pH IN NORMALIZATION OF FLOW IN CHRONIC HYPOCAPNIA

By John W. Severinghaus, M.D., Hugo Chiodi, M.D., E. I. Eger II, M.D., Bernard Brandstater, M.D., and Thomas F. Hornbein, M.D.

ABSTRACT

Cerebral blood flow was determined by an N₂O method in 7 normal men at sea level and after 6 to 12 hr and 3 to 5 days at 3810 m altitude. An infrared N₂O analyzer was used both to measure end-tidal PN₂O SO that it could be kept constant for 15 min and to determine blood N₂O, for which a simple gas extraction method was devised. In addition, acute changes in cerebral blood flow were estimated from cerebral A-V O₂ differences. Control cerebral blood flow was 43 ml per 100 g per min; it increased 24% at 6 to 12 hours and 13% at 3 to 5 days at altitude. After 3 to 5 days, pH of cerebrospinal fluid was normal (7.31) in four subjects while arterial blood pH was alkaline (7.47); arterial blood Pco₂ had fallen from 41 to 30 mm Hg. Acute correction of hypoxia restored cerebral blood flow to control while mean Pco₂ was still 31 mm Hg. Addition of O₂ and CO₂ to inspired air raised cerebral blood flow 34% above control at Pao₂ = 170, Paco₂ = 35 mm Hg. Values obtained by extrapolation suggest that if arterial Pco₂ was raised to control (41 mm Hg), cerebral blood flow would have been 60% above control. Cerebral blood flow thus appears to return to normal at the prevailing Paco₂, probably because the pH of cerebrospinal fluid and of the extracellular fluid of cerebral vascular smooth muscle is kept normal by active transport across the 'blood-brain' barrier. It is postulated that an ion-impermeable barrier separates the blood stream from extracellular fluid of the smooth muscle of cerebral arterioles.

ADDITIONAL KEY WORDS cerebrospinal fluid pH hypoxia blood N₂O determination blood brain barrier hypocapnia acclimatization smooth muscle tone and pH cerebral extracellular fluid pH

Acute hypoxia increases cerebral blood flow, overriding the vasoconstrictive effect of the associated hyperventilation and hypocapnia. The balance between these conflicting effects may be expected to alter during the process of acclimatization to high altitude, since a gradual increase in ventilation over several days produces a further fall in Pco₂ and an amelioration of the hypoxia. For example, normal man acclimatized for more than a week at about 4000 m altitude will have an arterial Pco₂ of 30 mm Hg, and a Po₂ of 52 mm Hg, whereas man acutely exposed to the same inspired oxygen tension will have a Pco₂ of 38 and Po₂ of 43 mm Hg. The arterial oxygen saturation after acclimatization is about 90%, but only about 80% during brief periods at 4000 m.

The process of acclimatization is often accompanied by headache, nausea and other symptoms which might be due either to a decreasing cerebral blood flow as Pco₂ falls, or to hypoxia, or to both. When an acclimatized man is given sufficient oxygen to restore arterial blood Po₂ to normal, his Pco₂ rises only 1 to 2 mm Hg immediately, and after several
CFB AND CEREBROSPINAL FLUID pH

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sired level of about 80 mm Hg within 30 sec, and hold it approximately constant, and since the alveolar level was continuously recorded, only a few arterial samples were needed to define the relationship between the continuous alveolar curve and the arterial concentration. The method using 15-min equilibration and constant N2O concentration, yielded a lower normal figure for cerebral blood flow, since it more correctly esti-
imated the contribution of the poorly perfused regions of the brain, as described by Lassen and Klee. The values are comparable to those (mean 42 ml per 100 g per min) obtained by extrapolation to infinity4 of the curves obtained in the usual technique.

Cerebral blood flow was determined in 7 healthy men at sea level and after 6 to 12 hr and 3 to 5 days residence at the Barcroft Laboratory on White Mountain, Calif., at 3810 m altitude. The N2O method of Kety and Schmidt was modified to attempt to (a) provide constant al-
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tration constant during the 15 min test period so that poorly perfused components of the brain come closer to arterial PN2O than they do when inspired N2O concentration is kept constant. End tidal N2O was observed continually using a rapidly responding infrared N2O analyzer (Beckman Spinco) and the N2O flow into the inspired air stream was adjusted to keep PN2O constant.

End tidal O2 was monitored by drawing gas samples from the mouthpiece into a syringe and im-
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Methods

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End tidal O2 was monitored by drawing gas samples from the mouthpiece into a syringe and immediately transferring these to either an oxygen electrode or a paramagnetic analyzer. The delay and occasional sampling errors resulted in some variations in Po2 during the N2O test. Since cerebral blood flow measured by the N2O method (N2O cerebral blood flow) could not be assumed to represent exactly the cerebral blood flow in a steady state breathing air, additional estimations were obtained from the A-V O2 difference, as will be outlined. During the 15-min equilibration period on N2O, 3 to 5 arterial and 8 to 12 jugular venous blood samples were obtained. Since it was found possible to raise the

alveolar N2O concentration from zero to the desired level of about 80 mm Hg within 30 sec, and hold it approximately constant, and since the alveolar level was continuously recorded, only a few arterial samples were needed to define the relationship between the continuous alveolar curve and the arterial concentration. The method using 15-min equilibration and constant N2O concentration, yielded a lower normal figure for cerebral blood flow, since it more correctly estimated the contribution of the poorly perfused regions of the brain, as described by Lassen and Klee. The values are comparable to those (mean 42 ml per 100 g per min) obtained by extrapolation to infinity4 of the curves obtained in the usual technique.

N2O concentration in the blood samples was determined in the following way: 2-ml calibrated glass syringes containing heparin in the dead space were filled with about 2.5 ml of blood from the indwelling needles. A three-way stopcock was placed on the syringe and the plunger advanced to exactly 2.00 ml. The stopcock was then closed to the syringe and the other lumen cleared of blood. A 10-ml syringe with an oiled plunger was then attached to the three-way stopcock; the syringe contained a drop of caprylic alcohol, but had no free oil in the dead space. The two syringes were connected and the 2.00 ml of blood pushed into the 10-ml syringe and stopcock dead space. The stopcock of the 10-ml syringe was turned to the open lumen, and the dead space blood and 6 ml of air drawn in. The stopcock was then turned to occlude the 10-ml syringe. Its plunger was withdrawn to the 10-ml mark and held there using lucite half cylinders cut to fit each syringe and held onto the exposed plunger with rubber bands. The syringes containing all of the arterial and venous samples were rotated simultaneously at room temperature for 15 min. The stopcocks were momentarily opened to admit air to equalize the syringe and ambient pressures, the syringes were shaken briefly to mix the fresh air with the gas in the syringe and then connected to the sample cell of the infrared analyzer through a blood trap consisting of a 3-cm-long piece of pipe cleaner in the inlet plastic tubing. The gas was pushed slowly through the sample cell and the analyzer output recorded with a direct pen writer. Analyzer zero and calibration were recorded between each sample. Full scale was set to about 1.5% N2O, using standard gas mixtures from a cylinder. All concentrations were expressed as a fraction of the final arterial concentration, and the arterial and venous curves were plotted on a dimensionless ordinate scale from 0 to 1. Cerebral blood flow then was directly computed as 100 divided by the area between the curves.
Cerebral blood flow was measured by the N\textsubscript{2}O method only when the subjects breathed 21\% O\textsubscript{2} at ambient barometric pressure, attempting to keep alveolar oxygen tension constant. In four subjects, additional information was sought by determining cerebral arteriovenous oxygen difference under the following conditions: (a) during the N\textsubscript{2}O inhalation period; (b) while the subjects breathed air without a mask before or after the N\textsubscript{2}O period; (c) after 10 min of breathing about 30\% O\textsubscript{2}; and (d) after 10 min of breathing an air-O\textsubscript{2}-CO\textsubscript{2} mixture.

pH, P\textsubscript{co2}, and P\textsubscript{o2} were determined using electrodes, and oxygen saturation was calculated from P\textsubscript{o2} and pH. Saturation was also determined in some samples manometrically (Van Slyke) and spectrophotometrically (Nahas cuvette) at sea level, and spectrophotometrically (American Optical reflectance oximeter) at altitude. Oxygen capacity was calculated from hemoglobin or hematocrit or both. A mean cerebral metabolic rate for O\textsubscript{2} was computed for each subject from his two or three measurements of N\textsubscript{2}O cerebral blood flow and the associated arteriovenous oxygen differences. Cerebral blood flow was then estimated from additional A-V O\textsubscript{2} differences using this mean value of cerebral metabolic rate for O\textsubscript{2}. Cerebrospinal fluid was sampled from three subjects during this sojourn at high altitude, and data from these and from the fourth subject, obtained 1 yr previously under identical conditions, are included. Techniques of sampling and measurement were as previously described except that cerebrospinal fluid P\textsubscript{o2} was also measured in the electrode. For this, the electrode was equilibrated in advance with a gas having a P\textsubscript{o2} of about 40 mm Hg and the electrode was flushed with three successive 0.5-ml samples, without disconnecting the syringe, thereby obtaining duplicate readings on at least the last two aliquots.

**Results**

Mean cerebral blood flow at sea level, estimated from the A-V O\textsubscript{2} difference and the mean cerebral metabolic rate for O\textsubscript{2} for each subject, was 41.6 ± 1.8 (SE). Cerebral blood flow was increased 24\% after 6 to 12 hr at altitude, and 13\% after 3 to 5 days, but cerebral metabolic rate for O\textsubscript{2} was unaltered at altitude (table 1). The N\textsubscript{2}O cerebral blood flow was increased 33\% in the 6 subjects at 6 to 12 hr, including values obtained in two men who became more hypoxic than intended. In these two more severely hypoxic subjects, cerebral blood flow was 64\% and 100\% above the sea level value and their cerebral metabolic rate for O\textsubscript{2} was 10\% and 18\% above sea level controls. Excluding these two subjects, N\textsubscript{2}O cerebral blood flow was increased 12\% at this time.

The effect of restoring alveolar oxygen tension to sea level values was studied in three subjects after 6 to 12 hr and in four after 3 to 5 days. Again using each subject's mean cerebral metabolic rate for O\textsubscript{2} (from 2 or 3 N\textsubscript{2}O cerebral blood flow determinations) and the A-V O\textsubscript{2} differences, calculations showed that cerebral blood flow was restored to normal when hypoxia was relieved, and did not fall below normal although P\textsubscript{co2} remained below normal, averaging 35.1 and 30.9 at the two high altitude test periods. At 6 to 12 hr, subject Jo hyperventilated (for no apparent reason) when given oxygen, and his P\textsubscript{co2} decreased by 4.8 mm Hg; P\textsubscript{co2} increased 31\% and 4.9 mm Hg in the other two subjects. During inhalation of O\textsubscript{2} after 3 to 5 days at 3810 m, P\textsubscript{co2} increased in all four subjects (mean 2.0 mm Hg); Jo responded normally at this time.

In four subjects, both CO\textsubscript{2} and oxygen were added to the inspired gas after 3 to 5 days at altitude. Arterial blood P\textsubscript{o2} averaged 170 mm Hg and P\textsubscript{co2} was 6.2 mm Hg greater than when breathing air at 3810 m; the average P\textsubscript{co2} was 35.2, which was still 5.5 mm Hg below their P\textsubscript{co2} at sea level. In spite of this continued hypocapnia, cerebral blood flow was 34 ± 7\% above the sea level control. Values obtained from extrapolating along a curve relating cerebral blood flow to P\textsubscript{co2} suggest that if the P\textsubscript{co2} of an acclimatized subject were returned to normal and hypoxia were relieved, cerebral blood flow would be about 60\% higher than normal.

Cerebrospinal fluid pH was normal at both 6 to 12 hr and 3 to 5 days. Cerebrospinal fluid HCO\textsubscript{3}−, calculated from pH and P\textsubscript{co2}, decreased from 24.3 to 19.5 meq per L. Arterial blood pH increased from 7.41 to 7.47 and, by the third to fifth day, base excess had fallen from +1 to −1.5 (base deficit of 1.5). Complete renal compensation for this...
Discussion

Much of our data reported here is based on the assumption that cerebral metabolic rate in each individual is not appreciably altered under the conditions of these experiments. While this has been widely documented under a variety of conditions at sea level,8 it has not been specifically studied at high altitude. The mean values obtained in this study were 2.99 ml per 100 g per min at sea level, 2.95 after 6 to 12 hr, and 2.93 after 3.5 days, supporting the assumption that cerebral metabolic rate for O2 does not change appreciably in man exposed to mild hypoxia. Likewise total body metabolism is not altered in man at moderately high altitude.8

Lassen and Munck have shown the desirability of extending the usual 10-min N2O breathing period to permit extrapolation to infinity of the arterial and venous curves, to avoid overestimating cerebral blood flow in the Kety method due to heterogeneous cerebral perfusion.10 Lassen and Klee have shown that the overestimation, usually no more than 10%, will be increased if cerebral blood flow is low.4 Because of its high solubility (λ = 0.46), N2O continues to be absorbed from the alveolar gas into the blood for many hours, and the rising arterial concentration is therefore less than 90% of the inspired concentration after 10 min. This makes the extrapolation procedure difficult and less accurate than in the present method. By keeping the alveolar and arterial N2O concentration constant, the poorly perfused tissues are brought nearer to equilibrium with the PN2O of arterial blood and, in most cases, after 15 min there remained no measurable difference between arterial and venous curves. The inhalation of a gas mixture containing 21% O2 with added N2O causes a rise in alveolar PO2 due to N2O uptake, an effect which is exaggerated at high altitude where a constant N2O partial pressure (80 mm Hg) is a higher percentage of the total gas. This condition also added to our difficulty of maintaining Pao2 constant.

Our method of determining blood N2O does not yield absolute values, but rather relative concentrations in which one blood concentration, the last arterial sample, is set equal to unity. In the usual method the concentration units cancel in the calculation, and the actual values are of course, irrelevant. In the syringe equilibration procedure, a gas space of 8 ml, containing air at reduced pressure, is equilibrated with 2 ml of blood containing the unknown concentration of N2O. This N2O distributes itself between the blood and gas according to its partition coefficient at room temperature, so it is important that all the samples be equilibrated simultaneously at the same temperature. After the equilibration, which is complete in 15 min, air is admitted to bring the total pressure to ambient pressure. Since the gas space remains 8 ml and no N2O escapes, the PN2O is unchanged by the addition of air and does not require further equilibration. The newly admitted air, however, must be completely mixed with the equilibrated gas, and for this reason caprylic alcohol is added to prevent any bubbles which would sequester gas. The amount of N2O in the equilibrated 8-ml gas sample amounts to 0 to 1%. The response of the infrared analyzer is linear over this range. The noise level is about 0.02%. The cuvette volume is less than 1 ml. The reproducibility of the method was shown to be ±5% in 20 identical blood aliquots. The analysis of the 12 to 16 samples used per study was completed in about 45 min including time for loading of the syringes, equilibration, and reading.

As anticipated, cerebral blood flow was higher early in the acclimatization process than it was after 3 to 5 days. Because this could be explained either by the rise of Pao2 from 43.5 to 51.2 mm Hg, or by the fall of Paco2 from 35.0 to 29.7 mm Hg as acclimatization progressed, this evidence alone would not be incompatible with a continuation of the normal responses of the cerebral vessels. However, the temporary administration of sufficient oxygen to restore Pao2 to within normal limits (75 to 100 mm Hg) disclosed...
### Cerebral Blood Flow in Man at Sea Level and at High Altitude

**TABLE 1**

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**1. SEA LEVEL**

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<tr>
<td>Breathing added O_{2} for 10 min</td>
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The table represents the data on cerebral blood flow and other parameters measured in a study of man at sea level and at high altitude. The values in the table are averages of measurements taken under specified conditions.

2. 3810 METERS, 6 to 12 HR

The data for 3810 meters altitude shows similar trends with slight variations in the values compared to sea level conditions.

Breathing added O_{2} for 10 min

- Ho: 7.434 36.9 82.5
- Jo: 7.502 32.2 77.0
- Mu: 7.437 36.3 80.0

These values indicate the effects of breathing increased levels of O_{2} for 10 minutes on the measured parameters.
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**Breathing added O₂ for 10 min**

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<td>0.5</td>
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**Breathing added O₂ and CO₂ for 10 min**

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Abbreviations and units: Hr, hours at 3810 meters; Hct, hematocrit %; Hb, hemoglobin, g per 100 ml; pHa, arterial pH; Paco₂, arterial CO₂ tension, mm Hg; PaO₂, arterial oxygen tension, mm Hg; pHe, cerebrospinal fluid pH; Pcco₂, cerebrospinal fluid CO₂ tension; CBF, cerebral blood flow; A-V ΔO₂, arterial minus jugular venous oxygen content, ml per 100 ml; CMR, O₂, cerebral metabolic rate for oxygen, ml O₂ per 100 g brain per min; CBF O₂, (100 × mean CMR)/A-V ΔO₂.
what appeared to be a regulating mechanism that reset cerebral blood flow, so that flow was normal (+7%) while Paco₂ was 10 mm Hg below normal. This 10 mm Hg reduction in Paco₂, if produced acutely, would be expected to reduce cerebral blood flow by 22.6. The discrepancy between the acute and chronic effect of hypocapnia is illustrated in figure 1.

This return to normal cerebral blood flow at a low Pco₂ may be related to the normalization of cerebrospinal fluid pH which occurs at about the same time. An acute reduction of Paco₂ from 40 to 30 mm Hg reduces cerebrospinal fluid Pco₂ about the same amount and should elevate cerebrospinal fluid pH about 0.09 unit. The hyperventilation and hypocapnia that occur during acclimatization to high altitude did not, however, produce much rise in cerebrospinal fluid pH, either in this or previous studies. Although arterial pH remained elevated for many days. Cerebrospinal fluid HCO₃⁻ falls gradually during acclimatization, in proportion to the Pco₂ reduction, permitting hypocapnia to occur without depression of the medullary respiratory chemoreceptors by an increased pH. Mitchell's experiments suggest that these receptors are largely responsive to changes in pH of cerebrospinal fluid of the extracellular fluid of the brain in a specialized area overlying the ventral medulla. One interpretation of the present experiments is that the tone of the smooth muscle of cerebral arterioles is regulated (in part) by the pH of its own extracellular fluid, that this pH resembles that of cerebrospinal fluid, and that the blood-brain or blood-cerebrospinal fluid barrier separates the extracellular fluid of the arteriolar smooth muscle from the blood stream. Such separation would be required to explain the findings of Lamberthson et al. and Schieve and Wilson that acute arterial acidosis at constant Paco₂ did not influence cerebral blood flow in man. Others have shown that weak vasodilation occurs during acidosis and constriction during alkalosis in animals. Mitchell et al. reviewed the abundant evidence that the pH of cerebrospinal fluid is stable under a variety of conditions when the pH of arterial blood is abnormal. In the present study, arterial blood pH remained alkaline even at 3 to 5 days, while the pH of cerebrospinal fluid was normal.

Until recently, the existence of extracellular fluid in brain has been in dispute, and a theory about the pH of the extracellular fluid of arteriolar smooth muscle would have been unsupportable. However, it is now known that inulin and sucrose, which, like H⁺ and HCO₃⁻, do not freely cross the blood-brain barrier, diffuse readily through brain from ventricular or pial surfaces. Diffusion of certain substances appears to determine, in part, the composition of cerebrospinal fluid in the cerebral ventricles. Both these diffu-
CBF AND CEREBROSPINAL FLUID pH

sion experiments and recent electron microscopic evidence derived from brain frozen rapidly at death\textsuperscript{19} support the presence of significant amounts of extracellular fluid throughout the brain.

While the results seem consistent with the hypothesis that cerebral arteriolar tone is controlled by the pH of the extracellular fluid of smooth muscle, two alternate possibilities should be considered. These are (a) a direct effect of molecular CO\textsubscript{2} and (b) the effect of intracellular pH, controlled by Pco\textsubscript{2}. Little evidence can be adduced regarding either of these possibilities, but evidence obtained in other systems makes them unlikely; for example, the molecular effects of CO\textsubscript{2} acting as an inert gas in the body are (a) the anesthetic effect, or a part of it, and (b) the combination with proteins, notably hemoglobin as carbamino hemoglobin. Some anesthetics such as halothane slightly dilate cerebral and all other blood vessels when in anesthetic concentrations.\textsuperscript{20} CO\textsubscript{2} has profound effects on cerebral vessels in concentrations having no anesthetic effect. A direct protein-binding effect, perhaps modified by the local hydrogen ion concentration, remains a possibility. Intracellular pH, or perhaps more specifically, pH of the aqueous film along the inside of the depolarizable membrane of the cell certainly will be affected by Pco\textsubscript{2}, albeit less than will extracellular pH because of the protein buffers in the cell water. This concept would explain why CO\textsubscript{2} has a greater effect than arterial acidosis, without invoking the blood-brain barrier as interposed between the arteriolar lumen and the extracellular fluid of smooth muscle. Although this intracellular pH cannot be measured at present, it will be of interest to determine such things as the time constant for resetting the cerebral vessels, in comparison to the time constant for readjustment of cerebrospinal fluid HCO\textsubscript{3}\textsuperscript{-}.

If cerebral vessels are reset to normal tone at the prevailing Pco\textsubscript{2}, as these data suggest, by either of the above mechanisms, the dire results predicted to occur in patients with prolonged hyperventilation (who presumably had cerebral vasoconstriction and cerebral under-perfusion\textsuperscript{8}) need be less feared. At high altitude, certainly, the cerebral blood flow does not fall below normal, and none of the symptoms can be attributed to an effect of hyperventilation on cerebral blood flow. A corollary is that efforts to increase ventilation at altitude will improve oxygenation without limiting oxygen delivery to the brain, which may provide an explanation for the beneficial effects attributed to acidosis induced by inhibition of carbonic anhydrase.\textsuperscript{21}

Acknowledgment

We are pleased to acknowledge the assistance of Dr. John Adams.

References


Cerebral Blood Flow In Man at High Altitude: Role of Cerebrospinal Fluid pH in Normalization of Flow in Chronic Hypocapnia

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Circ Res. 1966;19:274-282
doi: 10.1161/01.RES.19.2.274

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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