Cerebral Blood Flow in Man at High Altitude

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

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ABSTRACT

Cerebral blood flow was determined by an N_2O 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 N_2O analyzer was used both to measure end-tidal P_{N_2O} so that it could be kept constant for 15 min and to determine blood N_2O, for which a simple gas extraction method was devised. In addition, acute changes in cerebral blood flow were estimated from cerebral A-V O_2 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 P_{CO_2} had fallen from 41 to 30 mm Hg. Acute correction of hypoxia restored cerebral blood flow to control while mean P_{CO_2} was still 31 mm Hg. Addition of O_2 and CO_2 to inspired air raised cerebral blood flow 34% above control at $P_{aO_2} = 170$, $P_{aCO_2} = 35$ mm Hg. Values obtained by extrapolation suggest that if arterial P_{CO_2} 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 P_{aCO_2}, 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 N_2O determination blood brain barrier hypocarbia 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.[1] 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 P_{CO_2} 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 P_{CO_2} of 30 mm Hg, and a P_{O_2} of 52 mm Hg, whereas man acutely exposed to the same inspired oxygen tension will have a P_{CO_2} of 38 and P_{O_2} 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 P_{CO_2} falls, or to hypoxia, or to both. When an acclimatized man is given sufficient oxygen to restore arterial blood P_{O_2} to normal, his P_{CO_2} rises only 1 to 2 mm Hg immediately, and after several

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A preliminary report of this investigation was presented in the International Symposium on Regional Cerebral Circulation, Lund, Sweden, March 1965.[22]

This work was supported in part by USPHS grants 5-K6-HE-19; HE-06285; 5R01 HE-07946; and 5T1-GM-63.

Accepted for publication March 4, 1966.

hours begins a slow return toward normal which is completed only after several weeks. Under these circumstances (subnormal P_{CO_2} and normal P_{O_2}), cerebral vessels should constrict. However, certain considerations led us to suspect that these predictions might be incorrect. The hyperventilation that persists after removal of the hypoxia appears to be due to a "resetting" of a central medullary respiratory chemoreceptor. In this resetting process, the concentration of the bicarbonate ion of cerebrospinal fluid is reduced, probably by an active transport process across the blood-cerebrospinal fluid barrier, in proportion to the reduction in P_{CO_2} such that cerebrospinal fluid pH remains normal.[2] The following investigation suggests that the regulation of cerebral blood flow is similarly reset and is normal at a low P_{CO_2} if hypoxia is temporarily relieved.

Methods

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 N_2O method of Kety and Schmidt[3] was modified to attempt to (a) provide constant alveolar P_{O_2} at whatever level existed in the subject's alveolar gas at either sea level or high altitude, and (b) maintain alveolar N_2O concentration constant during the 15 min test period so that poorly perfused components of the brain come closer to arterial P_{N_2O} than they do when inspired N_2O concentration is kept constant. End tidal N_2O was observed continually using a rapidly responding infrared N_2O analyzer (Beckman Spinco) and the N_2O flow into the inspired air stream was adjusted to keep $P_{A_{N_2O}}$ constant. End tidal O_2 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 P_{O_2} during the N_2O test. Since cerebral blood flow measured by the N_2O method (N_2O 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 O_2 difference, as will be outlined. During the 15-min equilibration period on N_2O, 3 to 5 arterial and 8 to 12 jugular venous blood samples were obtained. Since it was found possible to raise the alveolar N_2O 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 N_2O 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.[4] The values are comparable to those (mean 42 ml per 100 g per min) obtained by extrapolation to infinity[4] of the curves obtained in the usual technique.

N_2O 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% N_2O, 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_2O method only when the subjects breathed 21% O_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_2O inhalation period; (b) while the subjects breathed air without a mask before or after the N_2O period; (c) after 10 min of breathing about 30% O_2; and (d) after 10 min of breathing an air-O_2-CO_2 mixture.

pH, P_{CO_2}, and P_{O_2} were determined using electrodes, and oxygen saturation was calculated from P_{O_2} and pH.[5] 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_2 was computed for each subject from his two or three measurements of N_2O cerebral blood flow and the associated arteriovenous oxygen differences. Cerebral blood flow was then estimated from additional A-V O_2 differences using this mean value of cerebral metabolic rate for O_2.[6, 7]

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[2] except that cerebrospinal fluid P_{O_2} was also measured in the electrode. For this, the electrode was equilibrated in advance with a gas having a P_{O_2} 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_2 difference and the mean cerebral metabolic rate for O_2 for each subject, was 41.6 ± 1.8 (SE). Cerebral metabolic rate for O_2 averaged 2.99 ± 0.13 ml O_2 per 100 g per min. The flow increased 24% after 6 to 12 hr at altitude, and 13% after 3 to 5 days, but cerebral metabolic rate for O_2 was unaltered at altitude (table 1). The N_2O 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_2 was 10% and 18% above sea level controls. Excluding these two subjects, N_2O 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_2 (from 2 or 3 N_2O cerebral blood flow determinations) and the A-V O_2 differences, calculations showed that cerebral blood flow was restored to normal when hypoxia was relieved, and did not fall below normal although P_{CO_2} 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_{CO_2} decreased by 4.8 mm Hg; P_{CO_2} increased 3.1 and 4.9 mm Hg in the other two subjects. During inhalation of O_2 after 3 to 5 days at 3810 m, P_{CO_2} increased in all four subjects (mean 2.0 mm Hg); Jo responded normally at this time.

In four subjects, both CO_2 and oxygen were added to the inspired gas after 3 to 5 days at altitude. Arterial blood P_{O_2} averaged 170 mm Hg and P_{CO_2} was 6.2 mm Hg greater than when breathing air at 3810 m; the average P_{CO_2} was 35.2, which was still 5.5 mm Hg below their P_{CO_2} 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_{CO_2}[7, 8] suggest that if the P_{CO_2} 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_3^-, calculated from pH and P_{CO_2}, 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

degree of respiratory alkalosis would require the base to fall to − 4.6 meq per L.

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 O_2 does not change appreciably in man exposed to mild hypoxia. Likewise total body metabolism is not altered in man at moderately high altitude.[9]

Lassen and Munck have shown the desirability of extending the usual 10-min N_2O 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 ($\lambda = 0.46$), N_2O 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 N_2O concentration constant, the poorly perfused tissues are brought nearer to equilibrium with the P_{N_2O} 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% O_2 with added N_2O causes a rise in alveolar P_{O_2} due to N_2O uptake, an effect which is exaggerated at high altitude where a constant N_2O partial pressure (80 mm Hg) is a higher percentage of the total gas. This condition also added to our difficulty of maintaining P_{aO_2} constant.

Our method of determining blood N_2O 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 N_2O. This N_2O 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 N_2O escapes, the P_{N_2O} 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 N_2O 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 P_{aO_2} from 43.5 to 51.2 mm Hg, or by the fall of P_{aCO_2} 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 P_{aO_2} to within normal limits (75 to 100 mm Hg) disclosed

TABLE 1

Cerebral Blood Flow in Man at Sea Level and at High Altitude

Subj.	Hr	Hct	Hb	pH_a	Pa_{CO_2}	Pa_{O_2}	pH_c	Pc_{CO_2}	On N_2O CBF N_2O	On N_2O A-V ΔO_2	CMR, O_2	Off N_2O A-V ΔO_2	Off N_2O CBF O_2	Off N_2O Mean CMR, O_2
						1. SEA LEVEL								
Se		43	14.2	7.434	40.3	81.5	7.327	50.1	46.6	7.19	3.35	7.96	37.2	2.96
Ho		43	14.1	7.418	44.2	82.2			38.0	7.13	2.71	7.08	35.6	2.54
Jo		46	15.3	7.403	38.1	86.8			37.1	8.05	2.98	8.05	38.4	3.09
Mu		41	13.4	7.420	40.6	83.6			45.3	6.01	2.72	6.78	46.0	2.76
Le		46		7.405	42.7	91.0	7.327	49.8	47.2	6.05	2.85	6.05	47.2	2.85
Ro		44		7.407	39.2	89.5	7.295	51.6	50.4	7.16	3.61	7.16	46.3	3.32
La		44		7.409	40.5	82.0	7.319	46.5	37.9	7.16	2.71	7.16	40.4	2.89
Mean		44		7.414	40.8	85.2	7.317	49.5	43.2	6.96	2.99	7.18	41.6	2.92
SE		0.7		0.005	0.8	1.5	0.007	1.0	2.0	0.28	0.13	0.27	1.8	0.10
						2. 3810 METERS, 6 to 12 HR								CBF % of control
Ho	8	44.5	14.4	7.472	33.8	45.4			42.0	6.1	2.57	6.7	38.0	106.0
Jo	7	44.1	15.1	7.468	37.0	37.2			74.5	4.4	3.28	5.8	53.3	139.0
Mu	11	41.2	13.5	7.480	31.4	42.5			74.2	4.3	3.22	4.9	56.3	122.0
Le	6			7.444	37.3	42.7	7.328	45.8						
Ro	7	40.6	15.2	7.419	35.3	45.0	7.321	43.2	50.2	5.7	2.87	5.7	58.1	126.0
La	8	40.5	14.5	7.437	35.4	48.0	7.301	44.1	47.0	6.0	2.82	6.0	48.2	127.0
Mean	8	42.2	14.5	7.453	35.0	43.5	7.317	44.4	57.6	5.3	2.95	5.8	50.7	124.0
SE	0.7	0.9	0.5	0.01	0.9	1.4	0.01	0.7	7.0	0.4	0.13	0.3	4.0	5.0
Breathing added O_2 for 10 min														
Ho	8			7.434	36.9	82.5						6.95	36.6	103.0
Jo	7			7.502	32.2	77.0						8.7	35.5	92.0
Mu	11			7.437	36.3	80.0						5.8	47.6	104.0

Se	72	46.4	15.6	7.494	28.9	51.1	7.352	37.0	37.5	6.8	2.56	7.5	46.0	124.0
Ho	72	45.2	14.7	7.460	30.0	52.9			32.0	7.35	2.35	7.35	34.6	97.0
Jo	69	45.1	15.1	7.462	27.9	53.7			47.0	6.44	3.02	6.52	46.5	121.0
Mu	73	41.0	12.8	7.489	29.2	44.5			52.4	4.46	2.34	4.74	59.4	129.0
Le	120	46.4		7.456	32.9	50.5	7.297	43.7	54.6	5.21	2.85	5.21	54.7	116.0
Ro	113	44.6		7.439	31.1	52.0	7.305	40.9	50.6	6.88	3.48	6.88	48.2	104.0
La	120	46.3		7.467	28.0	54.0	7.278	41.6	44.8	6.99	3.13	6.99	41.4	102.0
Mean	91	45.0		7.467	29.7	51.2	7.308	40.8	45.6	6.30	2.82	6.46	47.2	113.0
SE	10	0.7		0.007	0.7	1.3	0.013	1.3	3.0	0.40	0.17	0.40	2.8	5.5
Breathing added O_2 for 10 min														
Se				7.427	31.3	97.5						7.10	41.8	112.0
Ho				7.439	32.8	92.1						7.60	33.4	94.0
Jo				7.466	28.9	96.7						7.39	41.8	109.0
Mu				7.470	30.8	95.5						5.36	51.5	112.0
Mean				7.450	30.9	95.5						6.86	42.0	107.0
SE				0.01	0.8	1.0						0.5	3.0	4.4
Breathing added O_2 and CO_2 for 10 min														
Se				7.432	35.0	155						5.50	53.9	145.0
Ho				7.409	36.8	157						5.93	42.9	120.0
Jo				7.429	32.7	190						6.39	48.4	126.0
Mu				7.440	36.4	179						4.14	66.8	145.0
Mean				7.428	35.2	170						5.49	53.0	133.8
SE				0.006	0.9	10						0.50	4.5	6.6

Abbreviations and units: Hr, hours at 3810 meters; Hct, hematocrit %; Hb, hemoglobin, g per 100 ml; pH_a, arterial pH; $Paco_2$, arterial CO_2 tension, mm Hg; Pao_2, arterial oxygen tension, mm Hg; pH_c, cerebrospinal fluid pH; $Pcco_2$, cerebrospinal fluid CO_2 tension; CBF, cerebral blood flow; A-V ΔO_2, arterial minus jugular venous oxygen content, ml per 100 ml; CMR, O_2, cerebral metabolic rate for oxygen, ml O_2 per 100 g brain per min; CBF O_2, (100 × mean CMR)/A-V ΔO_2.

what appeared to be a regulating mechanism that reset cerebral blood flow, so that flow was normal (+7%) while $Paco_2$ was 10 mm Hg below normal. This 10 mm Hg reduction in $Paco_2$, if produced acutely, would be expected to reduce cerebral blood flow by 22%.[6, 7] 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 Pco_2 may be related to the normalization of cerebrospinal fluid pH which occurs at about the same time. An acute reduction of $Paco_2$ from 40 to 30 mm Hg reduces cerebrospinal fluid Pco_2 about the same amount and should elevate cerebrospinal fluid pH about 0.09 unit. The hyperventilation and

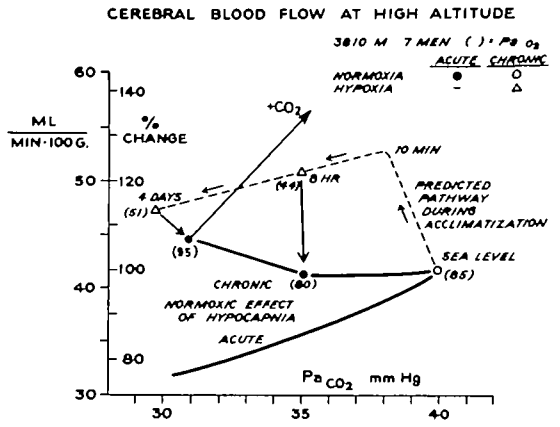

FIGURE 1

The relationship of cerebral blood flow to arterial Pco_2. The lower line is the predicted effect of acute hyperventilation derived from data of Wasserman and Pattersen[6] and Reivich.[7] No attempt was made to accurately predict the cerebral blood flow (CBF) at 10 min, when hypoxia is maximal and hyperventilation has reduced Pco_2 by an average of only 2 mm Hg at an equivalent altitude of 3810 m. The triangles indicate the observed CBF mean in these subjects after 8 hr and 4 days at 3810 m, using the values calculated from the A-V O_2 differences. The correction of the hypoxia by 10 min of breathing gas with high Po_2 decreased CBF to values represented by the solid circles. In the 4th day experiments, addition of CO_2 to the inspired gas of normoxic subjects increased Pco_2 and CBF along the line shown with $+CO_2$. The mean arterial Po_2 values are shown by each point in parentheses. No significance is attributed to the increased slope of the Pco_2 vs CBF curve at high altitude since only 4 of the 7 subjects were tested.

hypocapnia that occur during acclimatization to high altitude did not, however, produce much rise in cerebrospinal fluid pH, either in this or previous studies,[2, 11] although arterial pH remained elevated for many days. Cerebrospinal fluid HCO_3^- falls gradually during acclimatization, in proportion to the Pco_2 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.[12] 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 Lambertsen et al.[13] and Schieve and Wilson[14] that acute arterial acidosis at constant $Paco_2$ did not influence cerebral blood flow in man. Others have shown that weak vasodilation occurs during acidosis and constriction during alkalosis in animals.[8] Mitchell et al.[15] 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 HCO_3^-, do not freely cross the blood-brain barrier, diffuse readily through brain from ventricular or pial surfaces.[16, 17] Diffusion of certain substances appears to determine, in part, the composition of cerebrospinal fluid in the cerebral ventricles.[18] Both these diffu-

sion experiments and recent electron microscopic evidence derived from brain frozen rapidly at death[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_2 and (b) the effect of intracellular pH, controlled by P_{CO_2}. Little evidence can be adduced regarding either of these possibilities, but evidence obtained in other systems make them unlikely; for example, the molecular effects of CO_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.[20] CO_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 P_{CO_2}, albeit less than will extracellular pH because of the protein buffers in the cell water. This concept would explain why CO_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_3^-.

If cerebral vessels are reset to normal tone at the prevailing P_{CO_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[6]) 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.[21]

Acknowledgment

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

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