The Rate of Oxygen Turnover in Cerebrospinal Fluid

Mark B. Ravin, M.D.*

The changes in P_{ao_2}, $P\bar{v}_{o_2}$, and cisternal CSF P_{o_2} were followed in eight goats after abruptly changing the F_{Io_2} from 1.0 to 0.21 during a period of constant hyperventilation (Pa_{CO_2} 30 torr). The half times ($t_{\frac{1}{2}}$'s) for oxygen content in the arterial, venous, and cisternal compartments were 0.57, 1.01, and 3.60 minutes, respectively; the oxygen stores of the CSF were shown to be extremely labile and limited in nature. (Key words: CSF oxygen tension; Hypocarbia; Oxygen turnover rate for arterial, venous and cisternal compartments.)

IN THE 26 YEARS since Kety and Schmidt[1] developed a method for measurement of cerebral blood flow (CBF), the factors controlling CBF have been studied extensively.[2–4] However, we are usually more interested in the oxygenation of the brain tissue, per se, than in the CBF. A direct-reading nontraumatic tissue oxygen electrode would be an ideal method of measuring cerebral P_{o_2}. Unfortunately, the spatial resolution of oxygen electrodes in current use is such that the absolute values obtained from cerebral tissue vary with electrode position relative to blood vessels, movement, and variations in electrode pressure.[5]

An analysis of fluid in equilibrium with cerebral tissue is one approach to the measurement of brain P_{o_2}. After Bering[6] indicated that there is a rapid water exchange between cerebrospinal fluid (CSF) and brain tissue, Bloor et al.[7] suggested that the ventricular CSF P_{o_2} approximates the mean oxygen tension of cerebral tissue.

This study was undertaken to explore the relationship between P_{o_2} in the cisternal fluid and P_{o_2} in arterial and venous blood during a period of constant hyperventilation after an abrupt change of F_{Io_2} from 1.0 to 0.21. Goats

were chosen as the experimental animal since their respiratory and cerebrovascular responses to alteration of Pa_{CO_2} are similar to those of man.[8,9]

Methods

Eight adult, female goats averaging 28 kg in weight (range 20–36 kg) were anesthetized with sodium pentobarbital, 15 mg/kg iv. The trachea of each goat was intubated with a cuffed endotracheal tube and its ventilation was controlled with a constant-volume ventilator. The goat was paralyzed with an intravenous drip of 0.1 per cent succinylcholine in 5 per cent dextrose and water (0.5 mg/min) to eliminate shivering, muscle movement, and spontaneous respiratory effort. Approximately 400 ml/hour of Ringer's lactate solution containing 20 mEq/l of sodium bicarbonate were infused intravenously to replace the volume of sampled fluid and blood and to prevent metabolic acidosis from loss of sodium in the copious salivary secretions. Esophageal temperature was maintained within 0.5 C of its initial value by intermittent use of an electric blanket.

Teflon catheters were inserted into a femoral and/or carotid artery and the right heart via the jugular vein to permit blood sampling and pressure measurement. An 18-gauge spinal needle was inserted percutaneously into the cisterna magna.

The goats were hyperventilated with 100 per cent oxygen (15 ml/kg body weight at a frequency of 16/min) for 90 minutes in preparation for the study. The absence of any significant change (less than 2 per cent) in Pa_{CO_2} or pH_a in three successive samples 3 minutes apart indicated that the animal had achieved a steady state of ventilation. Arterial, mixed venous, and cisternal CSF samples were obtained simultaneously. The inspired mixture was switched to air, and additional arterial, venous, and CSF samples were obtained simultaneously 1, 2, 3, 10, 20, and 30 minutes after the beginning of breathing air. Arterial samples were also obtained at 0.5 minutes. Blood samples were drawn into
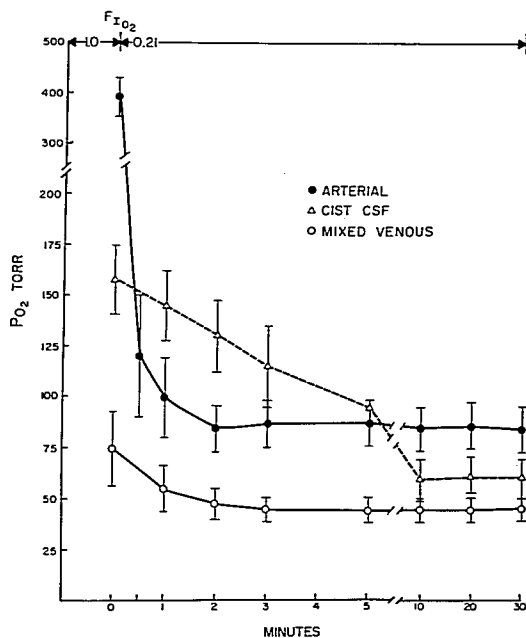
FIG. 1. Relationship between Pa_{O_2}, cisternal CSF P_{O_2} and $P\bar{v}_{O_2}$ after changing F_{IO_2} from 1.0 to 0.21. Plotted points represent mean ± SD of eight goats.

heparinized syringes and immediately analyzed for pH, P_{CO_2}, and P_{O_2} with direct-reading electrodes. The CSF samples were obtained anaerobically; the oxygen electrode was flushed with deoxygenated saline solution prior to the introduction of the CSF sample to avoid the oxygen gradient which exists from air to CSF. Appropriate nomograms[10] were used to correct measured blood gases for animal–electrode temperature differences.

Blood P_{O_2} was corrected for the electrode blood–gas difference by tonometry at 37 C using a sample of the animal's blood.[11] A polypropylene membrane was used to keep the relationship of electrode response to gas and blood of the same P_{O_2} relatively constant. In this study, mixed venous oxygen tensions ranged from 30 to 75 torr, and in this range of blood P_{O_2} values the gas–blood correction factor was 1.02 ± 0.004 (mean ± SE). Hemoglobin concentration was determined by spec-

trophotometry from the first and last arterial samples.

Calculations

Hellegers' nomogram for goats[12] was used to derive hemoglobin oxygen saturation from the corrected values of measured P_{O_2} and pH. The oxygen content of the blood was calculated as $(C_{O_2}) = $ (hemoglobin oxygen saturation × oxygen capacity) + (dissolved oxygen): where dissolved oxygen equals $P_{O_2} \times 0.0031$. The same Bunsen coefficient was used for cerebrospinal fluid.[13]

During the period of oxygen washout the changes in Ca_{O_2}, $C\bar{v}_{O_2}$ and cisternal CSF O_2 content were analyzed in terms of the rate at which each approached its new equilibrium value. A means of expressing the rate of change is the half-time, or the time for the variable in question to achieve 50 per cent of its overall change, expressed in minutes.

Results

Blood hemoglobin concentrations averaged 10.8 ± 1.6 g/100 ml (mean ± SD), with no significant change between the 0-minute and 30-minute samples ($P > 0.10$). Esophageal temperatures averaged 37.8 ± 0.9 C and remained stable during the experiment. Arterial carbon dioxide tensions averaged 30.2 ± 5.5 and 32.0 ± 5.1 torr; pH values averaged 7.52 ± 0.04 and 7.51 ± 0.03 after 90 minutes of ventilation with 100 per cent oxygen and 30 minutes of breathing air, respectively.

Pa_{O_2} and $P\bar{v}_{O_2}$ decreased abruptly when the goat was switched from oxygen to air breathing, and reached their new equilibrium values within two to three minutes. The cisternal CSF P_{O_2} decreased gradually in 10 minutes (fig. 1). The changes in Ca_{O_2} and $C\bar{v}_{O_2}$, as represented by the half-times, were found to be 0.57 and 1.01 minutes, respectively, while the change in C_{CisO_2} proceeded more slowly, with a half-time of 3.6 minutes (fig. 2). Thus, after a change from an F_{IO_2} of 1.0 to an F_{IO_2} of 0.21, arterial equilibration occurred approximately twice as fast as that in the venous pool, and six times as fast as that in the cisternal fluid.

Discussion

Hyperventilation with 100 per cent oxygen has been shown to produce an increased cerebral concentration of lactic acid in dogs.[14] This paradox of apparent tissue hypoxia caused by hyperventilation and hyperoxemia is explained by: 1) the decreased dissociation of oxygen from hemoglobin during the alkalosis that accompanies such hyperventilation; and 2) the limitations of cerebral oxygen transport imposed by increased cerebrovascular resistance. It has been suggested[15,16] that cerebral hypoxia caused by hyperventilation may be significant during anesthesia.

This study suggests that cerebral tissue hypoxia, as reflected by cisternal P_{O_2}, does not develop after the mild hypocarbia (Pa_{CO_2} 30 torr) and alkalosis (pH 7.52) accompanying hyperventilation with 100 per cent oxygen. Our findings are similar to those of Kety and Schmidt (Pa_{CO_2} 24 torr)[17] and Michenfelder and Theye (Pa_{CO_2} 13 torr),[18] who found no change in cerebral oxygen consumption in hypocapnic young men and dogs. Recently, Geha *et al.*[19] also examined the effects on CSF lactate production of nonpulsatile, normo-
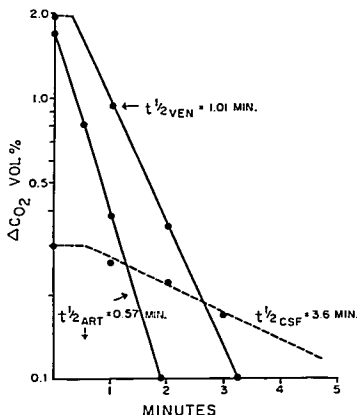

FIG. 2. Plot of calculated $t_{1/2}$'s of changes in oxygen content of arterial blood, venous blood, and cisternal fluid following change in F_{IO_2} from 1.0 to 0.21. Each point represents the mean of eight samples.

thermic, high-flow cardiopulmonary bypass in dogs, and failed to demonstrate cerebral hypoxia with respiratory alkalosis (Pa_{CO_2} 12–27 torr).

The CSF P_{O_2} at any given site is primarily determined by two factors: 1) the P_{O_2} of the neural tissue in proximity to the CSF which, in turn, is reflected by the P_{O_2} of venous blood draining that tissue[20]; and 2) the proximity of the sampling site to the areas where there is a direct transfer of oxygen from the arterial blood to the CSF.[14]

Contemporary investigators[14,15,21] consider the oxygen tension of neural tissue to be the major determinant of CSF P_{O_2}, since cerebrospinal fluid has been looked upon as an extension of the extracellular fluid of cerebral tissue.[15] Factors which affect cerebral oxygen tension should, therefore, influence the CSF P_{O_2}. However, due to the direct transfer of some oxygen from the arterial blood to the CSF, the latter has a higher P_{O_2} than blood draining from the brain. Therefore, P_{CSFO_2} is probably not an accurate indicator of the P_{O_2} of cerebral tissue.

In fact, the CSF P_{O_2} is highest in the ventricles, and the oxygen tension falls along a ventriculo-lumbar axis.[12,14,15] The ventricular P_{O_2} is higher than the cisternal P_{O_2}[15] because

this oxygen transfer between blood and spinal fluid takes place mostly at the ventricular level through the choroid plexus. These structures are thin mesenchymal webs, extremely vascular and, because of a high blood flow in relation to their mass, the blood in their capillaries remains arterialized.[22] Oxygen transfer may also take place at other sites, such as the pial vessels, in a manner similar to the exchange of water between neural tissue and CSF.[7,9] The oxygen gradient in the CSF cannot be explained on the basis of oxygen consumption in the fluid itself since the CSF is essentially acellular. Furthermore, although CSF and brain extracellular fluid have "free exchange," the cisternal CSF is a pool (of relatively large size) which has a slow turnover time itself.

In this study, during the adjustment from oxygen to air breathing, mixed venous oxygen tension decreased an average of 29 torr, which represented a change of 1.97 vol per cent. If we assume a goat blood volume equal to 8 per cent of body weight and a venous volume equal to 75 per cent of the total blood volume, then there would be 60 ml of venous blood/kg of body weight. This would represent a change of 1.18 ml O_2/kg when changing from oxygen to air breathing (1.97×0.60). When the plotted rate of change in venous blood (fig. 2) is extrapolated to the initial concentration, the intercept is at zero time plus 0.32 minutes. This is interpreted to mean that, on the average, the initial change in mixed venous oxygen content takes about 0.32 minutes following the alveolar change, and presumably represents the average circulation time. Similarly, it takes about 0.5 minutes before a change in F_{IO_2} is reflected in the oxygen content of the cisternal fluid.

If we assume that CSF volume in the goat is 1 ml/kg body weight, and that venous blood volume is equal to 75 per cent of the total blood volume, then the amount of oxygen stored in the CSF represents less than 2 per cent of that stored in the venous blood and is negligible in considering total body O_2 stores. P_{CSFO_2} is determined by several factors, including Pa_{O_2}, cerebral blood flow, site of CSF sampling, and P_{O_2} of cerebral tissue. Consequently, P_{CSFO_2} cannot be taken for an acceptable approximation of the P_{O_2} of cerebral tissue.[15]

References

1. Kety SS, Schmidt CF: The determination of cerebral blood flow in man by the use of nitrous oxide in low concentrations. Am J Physiol 143:53–66, 1945
2. Lassen NA: Cerebral blood flow and oxygen consumption in man. Physiol Rev 39:183–238, 1959
3. Harper AM: Physiology of cerebral blood flow. Br J Anaesth 37:225–235, 1965
4. Sokoloff L: The action of drugs on the cerebral circulation. Pharmacol Rev 11:1–85, 1959
5. Bloor BM, Floyd RD, Hall KD, et al: A study of critical oxygen tension during induced hypotension. Arch Surg 77:65–74, 1958
6. Bering EA Jr: Water exchange of central nervous system and cerebrospinal fluid. J Neurosurg 9:275–287, 1952
7. Bloor BM, Fricker J, Hellinger F, et al: A study of cerebrospinal fluid oxygen tension. Arch Neurol 4:49–58, 1961
8. Marshall BE, Gleaton HE, Hedden M, et al: Adaptation of the goat cerebral blood flow during sustained hypocarbia and hypoxia. Fed Proc 26:661, 1967
9. Smith AL, Pender JW, Alexander SC: Effects of Pco_2 on spinal cord blood flow. Am J Physiol 216:1158–1163, 1969
10. Severinghaus JW: Blood gas calculator. J Appl Physiol 21:1108–1116, 1966
11. Ravin MB, Briscoe WA: Blood-gas transfer, hemolysis, and diffusing capacity in a bubble tonometer. J Appl Physiol 19:784–790, 1964
12. Hellegers AE, Meschia G, Prystowsky H, et al: A comparison of the oxygen dissociation curves of the bloods of maternal and fetal goats at various pH's. Q J Exp Physiol 44:215–221, 1959
13. Christoforides C, Laasberg LH, Hedley-Whyte J: Effect of temperature on solubility of O_2 in human plasma. J Appl Physiol 26:56–60, 1969
14. Kazemi H, Klein RC, Turner FN, et al: Dynamics of oxygen transfer in the cerebrospinal fluid. Resp Physiol 4:24–31, 1968
15. Dunkin RS, Bondurant S: The determinants of cerebrospinal fluid P_{O_2}. The effects of oxygen and carbon dioxide breathing in patients with chronic lung disease. Ann Intern Med 64:71–80, 1966
16. Halmagyi DFJ, Gillett DJ: Cerebrospinal fluid oxygen tension at different levels of oxygenation. Resp Physiol 2:207–212, 1967
17. Kety SS, Schmidt CF: The effects of active and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, cardiac output, and blood pressure of normal young men. J Clin Invest 25:107–119, 1946
18. Michenfelder JD, Theye RA: The effects of profound hypocapnia and dilutional anemia on canine cerebral metabolism and blood flow. ANESTHESIOLOGY 31:449–457, 1969
19. Geha AS, Malt SH, Nara Y, et al: Effect of cardiopulmonary bypass on cerebral metabolism. J Thorac Cardiovasc Surg 61:200–211, 1971

20. Mithoefer JC, Kazemi H: Gas exchange during rebreathing. Ann NY Acad Sci 109:743–755, 1963

21. Jamieson D, Van Den Brenk HAS: Measurement of oxygen tensions in cerebral tissues of rats exposed to high pressures of oxygen. J Appl Physiol 18:869–876, 1963

22. Welch K: Secretion of cerebrospinal fluid by choroid plexus of the rabbit. Am J Physiol 205:617–624, 1963

23. Fisher VJ, Christianson LC: Cerebrospinal fluid acid–base balance during a changing ventilatory state in man. J Appl Physiol 18:712–716, 1963

Respiration

ALVEOLAR HYPOXIA AND SITE OF PULMONARY VASOCONSTRICTION

Pulmonary vasoconstriction secondary to alveolar hypoxia is of much clinical interest. The results of attempts to define the site of change in vascular resistance have been contradictory. The site has been variously ascribed to arteries, capillaries, and veins; the reason for the discrepancies lies in difficulties inherent in direct measurement of changes in pulmonary vascular dimensions. The authors have devised a technique for histologic evaluation of erythrocyte counts in alveolar capillaries in dog lungs rapidly frozen after perfusion either from artery to vein or from vein to artery. Changes in the cross-sectional capillary erythrocyte concentrations during the experiment were equated with changes in vascular resistance upstream from the capillaries. Capillary erythrocyte concentrations were measured under zone II conditions in isolated dog lungs rapidly frozen after perfusion from artery to vein or from vein to artery, following inhalation of normal and hypoxic gas mixtures and during infusion of serotonin or histamine. Alveolar hypoxia caused a significant decrease in capillary erythrocyte concentration during forward perfusion, but no change from control values during reverse perfusion. Serotonin infusion was followed by a decrease in erythrocyte concentration during forward perfusion, comparable to that of hypoxia, and a small but significant decrease during reverse perfusion. Histamine produced no change in erythrocyte concentration during forward perfusion, but a large decrease during reverse perfusion. The authors conclude that vasoconstriction occurs: a) exclusively in arteries during alveolar hypoxia; b) predominantly in arteries and to a small extent in veins during serotonin infusion; c) exclusively in veins during histamine infusion. The major source of error in these experiments involved changes in vessel caliber downstream from the collapse point. When pulmonary arterial pressure exceeds alveolar pressure, but alveolar pressure is greater than pulmonary venous pressure (zone II), increasing venous pressure will not affect arterial pressure until venous pressure exceeds alveolar pressure. The authors found that the capillary erythrocyte concentration was greatest when venous pressure exceeded alveolar pressure (zone III). Therefore, if during forward perfusion with alveolar hypoxia or serotonin infusion the increase in pulmonary arterial pressure was owing to venoconstriction sufficient to raise venous pressure above alveolar pressure and passive elevation of arterial pressure, then the capillary erythrocyte concentration should have been greater than in the control situation (these capillaries are now in zone III rather than zone II). However, the erythrocyte concentration was considerably less than under control conditions, indicating that the increase in pulmonary arterial pressure was the result of arterial constriction proximal to the capillaries. (*Glazier, J. B., and Murray, J. F.: Sites of Pulmonary Vasomotor Reactivity in the Dog during Alveolar Hypoxia and Serotonin and Histamine Infusion, J. Clin. Invest. 50: 2550–2558, 1971.*)