Alteration of the Blood-Brain Barrier with Hyperventilation*

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Hyperventilation produces a reduction in brain volume through a well-documented sequence of events, the first of which is a lowering of the alveolar carbon dioxide tension. In response to the hypocapnia, the cerebral arterioles constrict, causing a decrease in cerebral blood flow\(^7,10\) and ultimately a reduction in cerebral blood volume.\(^16\)

The reduction in brain bulk is used clinically in neurosurgical operations to minimize the cerebral trauma due to manipulation and retraction of the brain. It also diminishes the risk of outward herniation of a tight brain when the dura is opened. Hayes\(^8\) has reported its successful application in 325 operations.

However, in addition to its beneficial effect on cerebral volume, the cerebral ischemia may also give rise to an undesirable side effect, cerebral hypoxia.\(^7,13\) The light-headedness, impaired psychomotor performance, transient unconsciousness, and electroencephalographic slow-wave activity following hyperventilation\(^6\)–\(^15\) have been correlated to the hypoxic interval. During hyperventilation, cortical oxygen tension (PO\(_2\)) diminishes to hypoxic levels,\(^15,18\) as does jugular oxygen tension (PO\(_2\)) and oxygen saturation.\(^7\)

Although the hypoxia secondary to hyperventilation may produce transient clinical, metabolic, and electrical alterations, it has never been observed to cause any structural alterations of brain substance. However, it seemed possible that hypoxia severe enough to produce functional impairment of the brain, if prolonged or intense enough, could eventually produce architectural changes. The present study was undertaken to explore that possibility.

Methods

Nineteen cats were selected for hyperventilation. Under pentobarbital anesthesia, a cannula was inserted into the trachea, tightly secured, and connected to a variable speed-stroke Harvard Respirator; room air was employed for ventilation. A non-re-breathing valve was used to minimize dead space and expiratory airway resistance. A Wright Spirometer was used to record the tidal volume before and during hyperventilation. A PE 160 catheter was inserted into the femoral artery to permit drawing of serial blood samples for the determination of carbon dioxide tension (PCO\(_2\)), oxygen tension (PO\(_2\)), and hydrogen ion concentration (pH) on an Instrumentation Laboratory blood gas analyzer, and to allow a continuous recording of the blood pressure by a Statham transducer connected to a Grass direct-writing polygraph.

Initially, the stroke volume of the respirator was set at a level to provide a full expansion of the chest. This required a tidal volume of 3 to 5 times the resting value. Since the normal tidal volume was 12 to 15 ml, the tidal volume maintained by the respirator was 45 to 60 ml. The respiratory rate was maintained at 20 per minute. Hyperventilation was considered adequate when the arterial PCO\(_2\) was brought below 20 mm Hg. The stroke volume was altered to keep the arterial PCO\(_2\) at the desired level. It was decreased on several occasions to prevent hypotension. Hyperventilation was maintained for 5 hours.

Nine animals were kept as controls. They were anesthetized with equivalent doses of pentobarbital but were not hyperventilated. The same blood-gas and blood-pressure determinations were performed.

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Thirty minutes before the end of the experiment, 5 ml of 5% fluorescein were injected through the femoral catheter. The animals were sacrificed with rapid craniectomy and medullary transection. Care was taken to keep the hyperventilated animals on the respirator during craniectomy until the medulla was severed to prevent any agonal changes in the blood-brain barrier (BBB). Photographs of the whole brains and coronal sections of the brain at the level of the optic chiasm were taken under regular and ultraviolet light with Kodachrome II A film. The wave length of the ultraviolet light was 366.3 mμ. A Kodak No. 2B Wratten filter excluded all reflected ultraviolet light and allowed only the fluorescence from the specimen to be transmitted through the lens. Time exposures under ultraviolet light were kept constant at 90 seconds.

Results

Nineteen animals satisfied the criteria for hyperventilation. Nine other were used as controls. Animals were excluded from either group if the arterial carbon dioxide tension (PCO₂) could not be maintained at the desired level. They were also excluded if hypoxia from another mechanism, such as systemic hypotension or airway obstruction, inadvertently occurred during the experiment.

Eight of the nine cats in the control series did not reveal any fluorescence except in the mammillary bodies, ependymal surface, and the area postrema (Fig. 1A); these areas stain normally due to the absence of a blood-brain barrier (BBB). In one control specimen there was an area of questionable staining in the white matter. However, that cat had a tachypnea for reasons which were not clear and maintained an arterial PCO₂ of 28 mm Hg during the 5-hour experiment.

There was abnormal fluorescein uptake in the brains of 14 (73%) of the hyperventilated animals, primarily in the subcortical white matter. Staining took the form of discrete, irregularly-shaped patches located throughout the entire length and diameter of the brain (Fig. 1B). Although the parasagittal area fluoresced well in almost every brain, each area of white matter was stained at least once in one of the brains. The patches often extended in an arc from the medullary substance of one gyrus to that of an adjacent gyrus. The number of gyri involved varied between 1 to 4. No correlation existed between the number of gyri involved and the intensity of staining. Deeply fluorescing areas were present when either single or multiple gyri were involved. In addition to the discrete patches, the other major change was a diffuse uptake of fluorescein throughout both the white and gray matter so as to produce a generalized glow of the entire brain (compare Figs. 2A and B).

The brain of one cat which was hyperventilated for 5 hours and sacrificed 24 hours
later showed a pattern of staining similar to the other hyperventilated specimens which were sacrificed immediately. Although this is only a single observation, it suggests that the disruption in the blood-brain barrier (BBB) is not reversed immediately.

Discussion

In spite of the fact that neither cortical nor jugular venous oxygen tensions (PO2) were obtained in these experiments, the state of cerebral oxygenation could be correctly assessed from the arterial carbon dioxide tension (PCO2).19 There is a good correlation between arterial PCO2 and cerebral blood flow (CBF).11 Since the cerebral metabolic rate remains constant,14 a direct correlation also exists between cerebral blood flow and tissue oxygenation. Therefore, there is a relationship between arterial PCO2 and cerebral tissue oxygenation.15

Cerebral symptoms begin to appear when the CBF drops to 70% of normal.10 At that level, cerebral perfusion can no longer oxygenate the tissues adequately. If damage to neural elements is to occur from ischemic hypoxia, it is assumed that CBF must be maintained at 70% or below. When compared to Wasserman and Patterson’s figures for CBF derived from arterial PCO2 levels,19 the CBF in these experiments remained at 60 to 64% of normal, well below the critical value.

The preliminary report of these experiments17 suggested that prolonged hyperventilation may disrupt the blood-brain barrier (BBB). These results confirm that observation, but its mechanism and significance are not clear because the precise nature of the BBB itself is not known. Considerable doubt exists as to whether BBB represents an actual physical entity, a physiological process of negative active transport, or a combination of both. An analysis of the events accompanying hyperventilation, such as the reduced arterial PCO2, cerebral arteriolar vasoconstriction, diminished blood flow, and lowered cortical oxygen tension, suggests that ischemic hypoxia in the central nervous system is responsible for the EEG slowing and the cerebral symptomatology. It is conceivable, therefore, that prolonged ischemic hypoxia might also be responsible for the disruption of the blood-brain barrier.

Previous investigators have obtained contradictory results in studying the effect of ischemic hypoxia on the blood-brain barrier. The effect apparently depends upon three factors:

1. The substance used to test the integrity of the BBB
2. The method used to produce hypoxia
3. The presence or absence of hypercapnia.

Hodges, et al.,9 found fluorescein useful in detecting hypoxic disruption of the BBB during extracorporeal perfusion. Backer and Quadbeck2 used ultraviolet FF and found BBB breakdown in hypoxia induced in a high altitude chamber and by carbon mon-
oxide poisoning. Bakay and Bendixen,1 in evaluating the effect of varying concentrations of oxygen and carbon dioxide on the BBB, found an increase in Na+ and P2 in cerebral tissue in hypercapnic hypoxia but not in pure hypoxia of hypercapnia. Broman3 could detect no BBB permeability to trypan blue in cats after complete occlusion of the cerebral circulation. Insulin and sucrose did not cross the BBB in severe hypoxia.5

It may be concluded that some substances are better than others in detecting subtle changes in the BBB, and hypoxic damage to the BBB is made worse with hypercapnia.

Two objections may be raised in transferring these experimental results to the clinical situation. The first is that only room air was used in these experiments to ventilate the animals, while high concentrations of oxygen are commonly employed in neurosurgical operations. Although an increase in alveolar PO2 does cause a rise in arterial PO2, the concomitant cerebral arteriolar vasoconstriction from hypcapnia still reduces cerebral perfusion to ischemic levels. In animals hyperventilated with 100% oxygen, Sugioka and Davis3,4 found the cortical oxygen tension to be at hypoxic levels. Gotoh and Meyer7 described EEG-slowing in patients hyperventilated with 100% oxygen. High concentrations of oxygen in the inspired air offer no immunity to the hypoxia of hyperventilation. In addition, oxygen itself has a mild vasoconstrictor effect.12

The second objection is that the degree of hyperventilation used in these experiments greatly exceeds that employed in the operating room. However, a relatively small initial change in pulmonary ventilation produces a significant lowering of arterial PCO2. Clinically, Hayes used a 50% increase in tidal volume. Based on Comroe's calculations,4 the arterial PCO2 would be lowered to approximately 28 mm Hg. A further increase in ventilation produces relatively less alteration of the PCO2, so that in our experiments a tidal volume of 3 to 5 times normal lowered the PCO2 only to 10–18 mm Hg.

Cerebral blood flow also reacts in the same way to alterations in the arterial PO2, with an initial rapid drop.19 An arterial PCO2 of 28 mm Hg, such as that employed clinically, would lead to a CBF of 70% of normal,19 the level at which syncope occurs.6 As PCO2 decreases further, there is a decreasing response of vasoconstriction per unit of diminution in arterial PCO2. A reduction of PCO2 below 25 mm Hg produces very little additional vasoconstrictor response. The CBF will not be reduced below 60% of normal by any degree of hyperventilation. Although the PCO2 in our experiments remained below 20 mm Hg, the CBF was actually calculated to be 60 to 64% of normal,19 quite close to the level used clinically. There appears to be no gross difference in the CBF from the moderate degree of hyperventilation in the operating room and the marked degree of hyperventilation used in these experiments.

Summary and Conclusions

We have found that prolonged hyperventilation produced a disruption of the blood-brain barrier in 73% of 19 experimental animals tested. This disruption appears to be secondary to the ischemic hypoxia resulting from hypcapnic arteriolar vasoconstriction.

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