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 and ultimately a reduction in cerebral blood volume. 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 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. The light-headedness, impaired psychomotor performance, transient unconsciousness, and electroencephalographic slow-wave activity following hyperventilation have been correlated to the hypoxic interval. During hyperventilation, cortical oxygen tension (PO$_2$) diminishes to hypoxic levels as does jugular oxygen tension (PO$_2$) and oxygen saturation.

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.

Received for publication November 11, 1966.

* Supported by U. S. Public Health Service Research Grant NBO 6483-02 and by a grant from the Massachusetts Chapter of the American Heart Association. Reprints available from Dr. Roth.

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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 craniecotomy and medullary transection. Care was taken to keep the hyperventilatated animals on the respirator during craniecotomy 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