EFFECT OF HYPOTHERMIA AND HYPERTONIC UREA ON DISTRIBUTION OF INTRACRANIAL CONTENTS*

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(Received for publication April 4, 1961)

MORE than forty years ago, Weed and his associates reported a series of experiments describing "the alteration of brain bulk by hypertonic solutions." These studies demonstrated that the intravenous administration of hypertonic solutions rapidly lowered intracranial pressure to levels below zero. It was inferred that the reduction in pressure was the result of a decrease in brain volume, but no actual determinations of brain volume were made. The cranial cavity was described as being completely filled by brain, cerebrospinal fluid, and blood. It was postulated that variations in any one of the three elements induced compensatory alterations in the volume of one or both of the remaining elements. The hypothesis of Monro and Kellie was declared valid; the central nervous system was enclosed in a rigid system of bony coverings which served as a closed box of fixed volume.

There followed two additional observations of note. Forbes and Nason reported that the pial vessels dilated during the administration of hypertonic solutions. Bullock and his associates observed a "rebound" rise in cerebrospinal fluid pressure above the initial pressure once the effect of the hypertonic agent had become dissipated. As a consequence of the latter, the use of hypertonic dehydrating agents fell into disrepute until revived by Smythe and associates and Javid and Settlage.

In 1955, another mode of reducing brain volume and cerebrospinal fluid pressure was reported by Rosomoff and Gilbert. These investigators demonstrated that there was a decrease in brain volume of 4.1 per cent during hypothermia of 25°C. Measurements of cerebrospinal fluid pressure and venous pressure indicated there was a parallel decline in both pressures as a function of temperature. Other observations led to the impression that as the brain decreased in size, the subarachnoid space appeared to contain more fluid. The blood vessels seemed to be constricted; this was confirmed by experiments in which a 50 per cent increase in cerebral vascular resistance was demonstrated at 25°C. However, it could not be stated whether there was an actual reduction in the intracranial blood volume.

Thus, two methods have been demonstrated which produce a decline in cerebrospinal fluid pressure, one the administration of hypertonic solutions, the other, the application of the physical effect of cold. For neither has there been advanced a reliable quantitative description of events of water transfer or mode of action. In order to investigate accurately volumetric dynamics of the nervous system, it is necessary to determine simultaneously all component units of the intracranial contents. These are blood, cerebrospinal fluid, the amount of water in brain substance, and brain solids. The current study presents the results obtained with a new technique which measured simultaneously intracranial blood volume, cerebrospinal fluid volume, brain water, and brain solids. In these experiments the method was applied following the induction of hypothermia or the administration of hypertonic urea.

* This study was supported by Research Grant B-2469 from the National Institute of Neurological Diseases and Blindness, Public Health Service, Bethesda, Maryland.
METHODS

The experimental animal was the dog, unselected as to age and sex. The animals were anesthetized with sodium pentobarbital. Those dogs that were to be made hypothermic were intubated, attached to a positive-negative phase respirator, and placed in an ice-water bath. The body temperature was lowered to 25°C according to the technique described in detail elsewhere. Those dogs that were to receive urea were allowed to breathe room air spontaneously and the urea was given intravenously in the form of Urevert,* 6 gm./kg. at 60 drops per min. The method for the simultaneous determination of intracranial contents, to be described below, was applied when the animal to be studied had been stabilized at a body temperature of 25°C for 80 min. or when the nadir of the curve of cerebrospinal fluid pressure had been reached following the administration of urea.

One hundred microeuries of RISA were given intravenously and 15-20 min. were allowed for the equilibration. Ten ml. of blood were removed from the femoral artery, the dog’s head was plunged into liquid nitrogen, and cardiac action was stopped by an overdose of sodium pentobarbital injected into the heart. The head and neck were packed in dry ice for 1-4 hours to assure solid freezing of the intracranial contents. The dog was decapitated and the head was split in the midsagittal plane.

The frozen intracranial contents were removed in the cold room to preserve their solid state. The tissue was divided into two portions. One portion contained 5-10 ml. of tissue from representative sections of all areas of the brain. Care was taken not to include cerebrospinal fluid from the subarachnoid space or ventricles in this sample—sample B. The remaining brain, together with the intracranial cerebrospinal fluid down to the level at the foramen magnum, was set aside in the second portion. This sample contained also the leptomeninges and blood from the superior sagittal sinus—sample S.

Both portions were placed in individual glass-metal tissue homogenizers. A measured amount of water was added to each homogenizer. Following homogenization, the contents were transferred to volumetric flasks. Each flask was brought to the volumetric mark with a measured amount of water. The difference between the calibrated volume of the volumetric flask and the amount of water added to the sample and flask represented the volume of intracranial contents in the flask.

\[
\text{Volume intracranial contents} = \text{volume of flask} - \text{volume water added.}
\]

\[
\text{Volume water} = \text{weight full flask} - \text{weight dried flask} - \text{volume water added.}
\]

\[
\%_{w,o} = \frac{\text{volume water}}{\text{volume intracranial contents}}
\]

Blood volume (BV)

\[
\text{RISA count/ml, plasma} = \frac{\text{RISA count/ml, homogenate} \times 200 + 100 - \text{hematocrit} + \text{total intracranial volume}}{100 - \text{ (%HS, S) - %HS, B}} \times (100 - \text{vol. S})
\]

CSF volume (CSFV) = \[
\frac{(\%_{w,o} S - \%_{w,o} B)}{100 + \frac{(100 - \text{vol. S})}{100}}
\]

Brain water volume = 100

\[
-(\text{CSFV + BV}) \times \%_{w,o} B
\]

Brain solids volume = 100 - (CSFV + BV) \times (100 - \%_{w,o} B)

\[
\text{S.D.} = \frac{(x - \bar{x})^2}{n}, \quad \text{S.E.} = \frac{\text{S.D.}}{n}
\]

Cerebrospinal fluid pressure was measured from the cisterna magna through a No. 18 gauge spinal needle or catheter. Venous pressure was obtained from a catheter in the superior sagittal sinus. Both pressure systems were attached to water manometers and observations were recorded every 2 min. All measurements of pressure were made with the animal in the lateral recumbent position. In most experiments, systemic blood pressure was recorded on a mercury manometer from a catheter threaded through the femoral artery into the aorta.

* Urevert is a 30 per cent solution of urea in 10 per cent invert sugar. The Urevert used in these experiments was supplied by the Baxter Laboratories, Morton Grove, Illinois.