Distribution of Intracranial Contents with Controlled Hyperventilation: Implications for Neuroanesthesia

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DURING the past 40 years, reports have appeared periodically describing the reduction of intracranial pressure by chemical or physical means. For 30 of these years, the only available chemical agents were the osmotic dehydrating solutions, hypertonic sodium chloride, glucose, or sucrose.[1-4] Their application was limited by development of intravascular hemolysis and a "rebound" rise in cerebrospinal fluid pressure.[6] In 1950, urea was refined and reintroduced for clinical use; a few years later, hypertonic mannitol was also found to be a good dehydrating substance.[6] Urea and mannitol are now utilized widely and both appear to be effective and well tolerated.[7-8]

During the last decade, hypothermia has been developed as a physical method for lowering intracranial tension, this technique becoming routine in many institutions.[9] Recently, controlled hyperventilation was reported as another means of reducing intracranial pressure and brain volume.[10-12] With the exception of hypothermia, however, the proponents of these techniques have not produced acceptable data on reduction in brain volume, although statments have appeared claiming this effect. In this respect, observation of a reduction in cerebrospinal fluid pressure does not constitute proof that brain volume is diminished. Nor is it justified to conclude that the brain is smaller because it "appears to be slack" at the time of craniotomy. Examples can be cited in which there is no correlation between brain size and cerebrospinal fluid pressure, and the human eye has often been found incapable of distinguishing between apparent and real change.[13] Objective, quantitative measurements are required, therefore, in which all component units comprising the intracranial cavity are considered, to establish the true state of volumetric dynamics. No such method was available until 1961; since then, it has been possible to measure the distribution of the intracranial blood volume, cerebrospinal fluid volume, brain water, and brain solids under various experimental conditions.[14] With this technique, both 30 per cent urea, as a representative hypertonic solution, and hypothermia have been found to decrease brain water, *i.e.*, brain volume.[13] This is a report in which the effect of controlled hyperventilation was studied in the same series of experiments.

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Methods

The experimental animal was the dog, unselected as to age and sex. The animals were anesthetized with sodium pentobarbital, 30 mg./kg., and a cuffed endotracheal catheter was inserted. A sample of femoral arterial blood was obtained for the determination of pre-ventilatory *p*H and P_{CO_2}. A standard glass electrode and an Instrumentation Laboratory *p*H meter were used to determine the hydrogen ion concentration anaerobically. Carbon dioxide tension was measured directly by means of a Severinghaus electrode.[15]

The endotracheal tube was attached to the spirometer bellows of an automatic positive-negative pressure respirator and the resting tidal exchange measured. The ventilator was then started utilizing 100 per cent oxygen and the resting tidal exchange increasing the rate to 24 respirations/minute. This required a positive pressure of 7–11 mm. of mercury with

a negative phase of 1–4 mm. of mercury. It had been determined previously that maximum blood *p*H and P_{CO_2} changes were attained with this technique during the first 30 minutes of hyperventilation. Accordingly, the present experiments were conducted through a 30-minute period at the end of which femoral arterial blood was drawn for the determination of the final *p*H and P_{CO_2}. Repeated runs with the same technique on the same animal demonstrated almost identical chemical results with each period of hyperventilation. It was necessary to establish this point since the distribution of intracranial contents could not be determined during the same period as the determination of the blood chemistries, owing to the use of radioactive isotopes in the distribution technique. The animals, therefore, were anesthetized and hyperventilated to obtain the blood gas data in one experiment. They were allowed to recover, were reanesthetized and hyperventilated on another day for the intracranial distribution study. In the latter circumstances, radio-iodinated serum albumin was given at or about the start of the hyperventilation period, and the distribution technique was carried out at the end of 30 minutes according to the method described.

Distribution of the intracranial contents was determined in the following manner. One hundred microcuries of radio-iodinated serum albumin were given intravenously and 15–30 minutes were allowed for the equilibration. Ten milliliters of blood were then removed from the femoral artery, the dog's head was plunged into liquid nitrogen, and cardiac action stopped by an overdose of sodium pentobarbital injected into the heart. The head and neck were packed in dry ice for 12–24 hours to assure solid freezing of the intracranial contents. The dog was decapitated and the head split in the mid-sagittal plane.

The frozen intracranial contents were removed in a 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 also contained the leptomeninges and blood from the superior sagittal sinus—sample S.

TABLE 1. Distribution of Intracranial Contents in 10 Eucapneic Dogs

Dog No.	Blood Volume	CSF Volume	Brain Water	Total Fluid	Total Solids
1	2.21	8.93	63.98	75.12	24.88
2	2.00	9.47	62.75	74.22	25.78
3	2.06	8.56	64.91	75.53	24.47
4	2.26	10.69	61.81	74.76	25.24
5	2.78	9.25	64.64	76.67	23.33
6	2.05	10.33	63.28	75.66	24.34
7	2.14	8.14	65.71	75.99	24.01
8	2.66	7.45	65.78	75.89	24.11
9	2.45	7.53	66.33	76.31	23.69
10	1.97	8.80	66.51	77.34	22.66
Mean	2.26	8.92	64.58	75.75	24.25
S.D.	±0.27	±1.02	±1.51	±0.87	±0.87
S.E.	±0.08	±0.34	±0.48	±0.27	±0.27

Both portions were placed in individual glassmetal 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.

The blood, taken at the time of sacrifice, was centrifuged at 3500 r.p.m. for 60 minutes to determine the hematocrit. Aliquots of homogenate and plasma from the hematocrit tubes were counted in a well-type scintillation counter. The aliquots of homogenate were returned to their flasks and each flask was weighed to an accuracy of 0.1 g. The flasks were dried to constant weight in an oven at a temperature of 100–105° C. and then reweighed. The difference between the weights of the flasks before and after drying was the weight of water lost from the flask. Since 1 g. of water equals 1 ml. of water, the difference in weight represented the total volume of water in the flask. The following formulas were applied and the volumes of the intracranial compartments calculated.

Volume of cranial contents = volume of flask − volume H_2O added.

Volume H_2O = weight of full flask − weight of dried flask − volume H_2O added.

$$\text{Percentage } H_2O = \frac{\text{volume } H_2O}{\text{volume cranial contents}}$$

$$\text{Blood volume (BV)} = \frac{\text{RISA count/ml. plasma}}{\text{RISA count/ml. homogenate} \times 200} \div 100 - \text{hematocrit value} \div \text{intracranial volume.}$$

$$\text{CSF vol (CSFV)} = (\%\ H_2O\ S - \%\ H_2O\ B) \times \left[\frac{100 + (100 - \text{vol. S})}{100}\right]$$

$$\text{Brain } H_2O \text{ vol.} = [100 - (\text{CSFV} + \text{BV})] \times \%\ H_2O\ B$$

$$\text{Brain solids volume} = 100 - [(\text{CSFV} + \text{BV})] \times (100 - \%\ H_2O\ B)$$

$$\text{S.D.} = \sqrt{\frac{\Sigma\ (x - \bar{x})^2}{n}} \quad \text{S.E.} = \frac{\text{S.D.}}{\sqrt{n}}$$

Cerebrospinal fluid pressures were measured through a no. 18 needle or special catheter placed in the cisterna magna. The measurements were made on a water manometer with the dog in the lateral recumbent position.

Results

Controls. The distribution of the intracranial contents in the eucapneic anesthetized dog breathing room air is presented in table 1. The pre-ventilatory mean arterial *p*H and P_{CO_2} were 7.33 and 41 mm. of mercury, respectively. These distribution data were taken from previous experiments in this series.[14] The mean blood volume was 2.26 per cent of the total intracranial contents. The mean cerebrospinal fluid volume was 8.92 per cent. Brain water, which refers to the combined contributions of the extracellular and intracellular spaces, amounted to 64.58 per cent. Therefore, the mean total fluid content of the cranium was 75.75 per cent. Brain solids comprised 24.25 per cent of the remaining intracranial contents.

Controlled Hyperventilation. The distribution of the intracranial contents following 30 minutes of controlled hyperventilation is shown in table 2. The final blood chemistry values for this group were: *p*H 7.59, P_{CO_2} 20 mm. of mercury. There was a decrease in blood volume from the control of 2.26 to 1.90 per cent in the experimental group. The cerebrospinal fluid volume increased from 8.92 to 9.92 per cent. No significant alterations were found in either brain water or brain solids. Therefore, there was no loss of water from the brain, and there was no net loss of fluid from the cranium. Only a redistribution had occurred between the volumes of blood and cerebrospinal fliud.

Cerebrospinal Fluid Pressure. When the arterial *p*H and P_{CO_2} were normal prior to the onset of controlled hyperventilation, there was little or no change in the cerebrospinal fluid pressure during hyperventilation, despite a 50 per cent decrease in blood P_{CO_2} levels, figure 1.

Discussion

The claim for a decrease in brain volume is based on the following observations: "When the effect of hyperventilation has been well established, an unusual depth of the pia-arachnoid space is observed." Further, "following removal of the cerebrospinal fluid, reduction in the volume of the brain tissue is apparent immediately."[16] The data from the present study corroborate the increase in the size of the subarachnoid space. It is also true that the brain seems to collapse when its supporting lake of cerebrospinal fluid is removed; however, this does not constitute shrinkage of brain tissue. The same effect can be obtained from insertion of a needle into the ventricles with the removal of cerebrospinal fluid

without hyperventilation. The brain collapses from lack of hydraulic support, a fact well recognized and often utilized by the neurosurgeon. Therefore, hyperventilation does not result in an actual decrease in the volume of brain tisssue, but produces instead the illusion of reduction in size due to the increased depth of the subarachnoid space and collapse of the brain by withdrawal of cerebrospinal fluid.

Hyperventilation during thiopental anesthesia does result in an increase in cerebrovascular resistance to three and one half times normal.[17] This is reflected in the present study as a reduction in intracranial blood volume. There is a concomitant decrease in cerebral blood flow to a level 30 per cent of that seen in the normal conscious adult, while cerebral oxygen consumption is reduced 50 per cent.[17] Because of the disproportionate reduction in blood flow as compared to oxygen consumption, concern has been expressed as to the safety of the technique.[18] Studies with an oxygen electrode suggest further the possibility of hypoxia by the demonstration that the P_{O_2} of brain tissue falls from a normal level of 8–15 mm. of mercury to a tension of 3–5 mm. of mercury during hyperventilation.[19] However, the interpretation of this observation may be challenged since brain tissue has been shown to maintain unimpaired respiratory activity down to an oxygen tension of 4 mm. of mercury *in vitro*.[20] Although hyperventilation does produce an increase in arterial hemoglobin saturation, the internal jugular vein saturation falls to 41.6 per cent and P_{O_2} to 20.6 mm. of mercury.[17] At this oxygen tension, unconsciousness may develop in unanesthetized man. Despite these suggestive data, however,

TABLE 2. Distribution of Intracranial Contents Following Hyperventilation

Dog No.	Blood Volume	CSF Volume	Brain Water	Total Fluid	Total Solids
1	1.81	10.43	62.77	75.01	24.99
2	1.68	10.10	62.89	74.67	25.33
3	1.60	10.03	63.33	74.96	25.04
4	2.08	9.96	64.01	76.05	23.95
5	1.95	9.52	64.46	75.93	24.07
6	2.29	9.49	64.22	76.00	24.00
Mean	1.90	9.92	63.61	75.44	24.56
S.D.	±0.24	±0.33	±0.65	±0.57	±0.57
S.E.	±0.10	±0.13	±0.27	±0.23	±0.23
"P"	0.05	0.05	N.S.	N.S.	N.S.

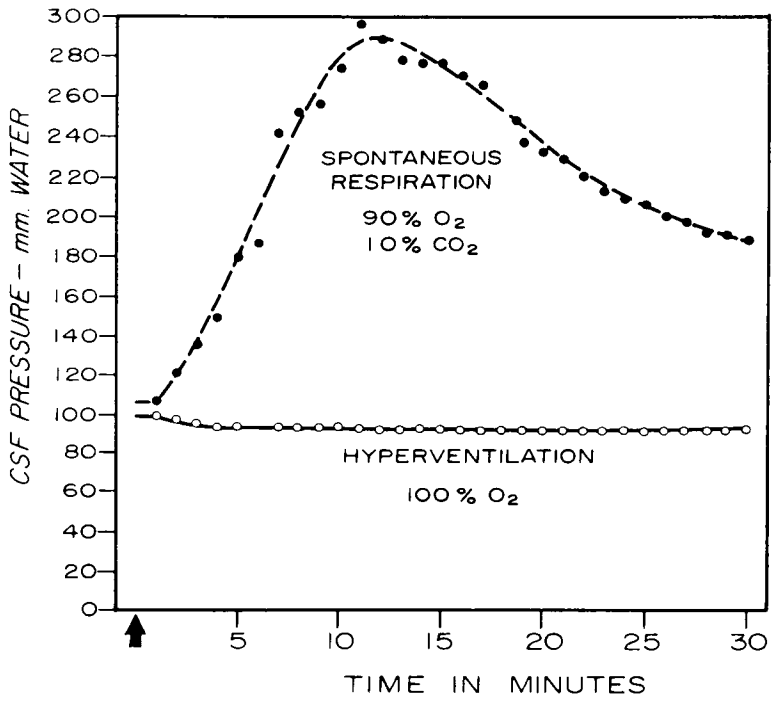

FIG. 1. Cerebrospinal fluid pressure during hypercapnea (90 per cent oxygen, 10 per cent CO_2) and during hypocapnea (hyperventilation).

there has been no report of a deleterious effect of hyperventilation under controlled clinical conditions.

Benefit may be derived from the use of controlled hyperventilation in other ways. A reduction in intracranial tension may be seen if hypercapnea is the starting point rather than eucapnea, figure 1. Hypercapnea will result when underventilation occurs in the anesthetized patient whose respiration is poorly controlled; as a consequence, the cerebrospinal fluid pressure may be lowered with hyperventilation by decreasing the intracranial blood volume, through a reduction of the blood CO_2 tension. The conduct of anesthesia may be more satisfactory during controlled hyperventilation.[21-22] Cyclical inflation of the lungs overstimulates the inhibitory Hering-Breuer reflex prolonging apnea, and apnea is maintained more easily by keeping the CO_2 tension below the respiratory threshold.[23-24] The dosage of thiopental is decreased; and, to a lesser degree, the dosage of other agents such as the muscle relaxants is also diminished.[25]

In the final analysis, the importance of controlled hyperventilation in neuroanesthesia does not result from a dramatic reduction of intracranial pressure or brain volume. Rather, there is insured regular, uninterrupted control of the airway under conditions which minimize the opportunity for coughing and straining, and which prevent deleterious changes in intracranial dynamics mediated through the respiratory gas tensions.

Summary and Conclusions

The distribution of the intracranial contents was determined during controlled hyperventilation to an arterial *p*H of 7.59 and a P_{CO_2} of 20 mm. of mercury. A decrease in intracranial blood volume was found and a compensatory increase in cerebrospinal fluid volume. No change was seen in either brain water or brain solids, nor was there a decline in cerebrospinal fluid pressure. It was concluded that controlled hyperventilation does not reduce the volume of brain tissue, and intracranial pressure is not affected if the blood CO_2 tension is normal prior to the onset of ventilation.

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ARTERIAL INJECTION During measurement of arm-to-lung venous circulation time a small volume of ether was accidentally injected into an artery. The patient developed severe burning pain in his forearm and hand followed by severe edema and tenderness of his upper extremity to a few inches above the elbow. Neither radial nor ulnar arterial pulsations were palpable. Following relaxing incisions in the forearm, there was improvement; but gangrene developed in the hand and amputation was necessary. (*King, H., and Hawtof, D. B.: Accidental Intra-Arterial Injection of Ether, J.A.M.A. 184: 175 (Apr. 20) 1963.*)

CHLOROFORM AND HALOTHANE Chloroform was administered to 215 patients and halothane to 548 patients. Induction concentrations were below 2.5 per cent with halothane and below 1.5 per cent with chloroform. Concentrations of 0.5 per cent chloroform or 0.75 per cent halothane were used during maintenance. Ninety per cent of patients were intubated, most without relaxants. Complications were rare, and relaxants were unnecessary in most cases. Nausea and vomiting during emergence and later were notably less with halothane. In the chloroform group one fatality occurred in which there was prolonged blood loss, hypovolemia, and hypotension induced by trimethaphan. One fatality occurred in the halothane group, due to aspiration pneumonia. One patient with severe liver disease died 15 days postoperatively of diffuse hepatic and renal necrosis. Unfortunately, he received two anesthetics, one halothane and one chloroform, so no conclusions could be drawn. Participating anesthetists in this study were found to be more cautious with choloroform, because of distrust and fear of the drug. However, knowledge acquired with halothane may be utilized for chloroform, particularly accurate control of concentration and attention to avoidance of hypoxia and hypercarbia. Neither drug should be used in patients with liver damage, respiratory disease or induced hypotension. (*McReynolds, E. C., Thorogood, A., and Morris, L. E.: Clinical Comparison of Halothane (Fluothane) and Chloroform, Arch. Surg. 86: 633 (Apr.) 1963.*)