Edema of the Brain Following Circulatory Arrest

C. G. GUNN, M.D., G. R. WILLIAMS, M.D., AND I. T. PARKER, M.D.,
The University of Oklahoma Medical Center

Rational attempts to minimize or treat brain injury following circulatory arrest depend upon knowledge of the pathophysiology of this type of injury. Although swelling of the brain has been considered a characteristic and important feature of many types of brain injury, its presence has not been conclusively demonstrated after circulatory arrest. The availability of agents which reduce brain volume under certain circumstances has made it important to determine whether the brain swells following circulatory arrest and what part the swelling may play in the total injury. The following experiments were undertaken to investigate the effect of circulatory arrest on brain volume.

METHOD

Mongrel dogs without prior treatment were anesthetized with pentobarbital, intubated and placed on a simple piston respirator using room air. Through a short, right fourth interspace thoracotomy, the azygos vein was ligated and tapes placed about the venae cavae and ascending aorta. Circulatory arrest was produced by cross-clamping the venae cavae and the aorta about 2 cm. above the aortic valve. During the period of arrest, 2.0 ml. of dilute heparin in saline was injected into the right atrium at two or three minute intervals to maintain pulmonary and coronary flow. All clamps were released after ten minutes and the chest was closed with sealed drainage. The respirator was stopped immediately after chest closure and the animal allowed to breathe spontaneously. In the postoperative period, 10 per cent glucose totaling 30 cc./kg., was given intravenously over an eight hour period. EEG, EKG, arterial blood pressure and rectal temperature were monitored during some experiments.

The experimental preparation was very little modified from that reported by others. A high operative mortality from aortic rupture at the site of cross-clamping was greatly reduced by use of the Muller-Markham coarctation clamps. An occasional animal exhibited ventricular fibrillation at the time circulation was restored or died before the end of the eight hour observation period. These animals were not included in the present series.

Surviving animals were exsanguinated eight hours after the period of circulatory arrest. Cerebral water content was measured by the method of Elliott and Jasper. The brains were removed intact immediately after sacrifice and sagittally sectioned in the midline. Cerebrospinal fluid was blotted away and the wet brain halves weighed in tared beakers with cover and mace. Five milliliters of acetone was added to each brain half and the brains were macerated to paste and evenly spread about the sides and bottom of the beaker. The beakers were then dried in an oven for 48 hours at 100°C and, after cooling to room temperature, were reweighed. The differences between wet and dry weights of the brain were considered to be water content.

Control animals were matched in sex and weight to the circulatory arrest animals and were treated in exactly the same way except that the great vessels were not clamped during the sham operation.

RESULTS

Data derived from eight matched pairs of animals are tabulated in Table I. Statistical consideration of the figures for water content of the brain in the two groups of animals reveals a significant increase in water content in the brains

* V. Mueller and Company.
of animals subjected to circulatory arrest (P greater than .001 and less than .01, T test for paired controls).

There was a striking behavioral difference in the animals subjected to circulatory arrest when compared with the control animals. Those animals in whom the great vessels were clamped for ten minutes remained unconscious and developed extensor rigidity. The control animals were awake, responsive, and showed no neurological or behavioral abnormalities at the time of sacrifice, eight hours after temporary circulatory arrest.

**DISCUSSION**

There is some confusion regarding the terms "swelling of the brain" and "edema of the brain," or "cerebral edema." Swelling of the brain is defined simply as an increase in brain volume. Total brain volume includes intravascular fluid volume, brain tissue volume and cerebrospinal fluid volume. Edema of the brain or cerebral edema properly refers only to an increase in extravascular fluid volume without regard to intravascular and cerebrospinal fluid volumes. The nature of the extravascular space in the brain is a controversy not pertinent to the present discussion. All authors have not made the distinctions outlined above and may have used the terms swelling and edema interchangeably. It is clear that swelling of the brain can occur without cerebral edema, a phenomenon familiar to neurosurgeons and easily demonstrable in the laboratory by administering vasoressors to an animal with the cortex exposed. It is also possible that mild degrees of cerebral edema may occur without swelling of the brain if the other components of total brain volume are reduced.

The role of cerebrospinal fluid in brain swelling or cerebral edema is not entirely clear. As mentioned previously, increased intraventricular spinal fluid volume produces gross brain swelling. Ordinarily, however, total cerebrospinal fluid volume decreases as the brain swells. When clinical or experimental data involves measurement of cerebrospinal fluid pressures as an indication of brain swelling or cerebral edema, the volume of cerebrospinal fluid is of obvious importance. Experimental demonstration of brain swelling is difficult and most methods reported to date depend upon measurements or observations made with the skull of the experimental animal open or after sacrifice of the animal. There is good evidence that the response of the brain to injury differs in the closed and open skull preparations. Furthermore, simple exposure of the cortex results in brain swelling in some instances. Experiments that depend upon observation of the exposed brain are, therefore, subject to criticism. After sacrifice of the experimental animal, the contribution of both intravascular and spinal fluid components to total brain volume is rapidly altered, rendering postmortem observations invalid as a measure of total swelling. Determination of cisternal or subarachnoid cerebrospinal fluid pressures has not been a reliable method of demonstrating acute brain swelling.

Cerebral edema has been produced and measured experimentally by a number of workers. Weed and McKibben first demonstrated a rise in spinal fluid pressure and an increase in brain bulk after administration of hypotonic solutions and their work has been amplified and clarified recently by Stern. White et al. measured brain volume by immersion and fluid displacement techniques. Comparison of this figure with
measured skull volume established a 10 per cent difference between brain volume and skull capacity in the normal animal sacrificed by exsanguination. Cerebral edema induced by hypoxia reduced this figure to 5 per cent. These investigators further showed that intracerebral blood volume is unchanged by hypoxia but greatly increased by hypercarbia. Elliott and Jasper reported the method of determining cerebral edema used in the present investigation. Edema was produced in rabbits by intravenous administration of hypotonic solution and results were expressed in percentage dry weight which was compared with a known average for normal rabbit brains. Similar methods have been reported by others. The technique of Elliott and Jasper is handicapped by the fact that the relative dry weight of the brain varies from animal to animal, and, therefore, the determination of an increase in percentage dry weight in an individual animal has little significance.

In the experiments reported in this communication, water content of the brain of animals subjected to circulatory arrest is compared with the same determination made in a sham operation control dog matched in sex and weight. This method of control is far from ideal but statistically the difference in water content of the brain in the several pairs is valid.

The data derived from these experiments appear to show that cerebral edema follows circulatory arrest in the dog. If it can be assumed that the intravascular and intraventricular fluid volumes are unchanged or at least not reduced, the cerebral edema demonstrated is also manifested as brain swelling. Though no data relative to these values has been obtained, this seems to be a reasonable assumption based on the work of others. The demonstration that cerebral edema or brain swelling occurs following circulatory arrest in no way clarifies a more fundamental question regarding the importance of such swelling in the course of an animal or patient with brain injury following an ischemic episode. It has been inferred that cerebral edema is of minor importance in the total picture of neurologic damage following cardiac arrest. However, it seems most reasonable that edema may be a significant secondary factor in further compromising metabolic processes in neuronal populations damaged by anoxia.

REFERENCES