Experimental Ischemic Brain Swelling*

HOWARD A. ZAREN, B.SC., JAMES D. WEINSTEIN, M.D., AND THOMAS W. LANGFITT, M.D.

Section of Neurosurgery, Pennsylvania Hospital, and Division of Neurosurgery,
University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

There is little clinical information on the incidence of brain swelling and intracranial hypertension in patients following a period of profound shock or cardiac arrest, although frequently the patient is treated with steroids, hypothermia, or hypertonic solutions, on the premise that brain swelling is a significant problem. Also, few experimental studies have been designed to define the incidence and magnitude of ischemic brain swelling, and there has not been agreement on the cause of the swelling in successful experiments. The brain swelling may be due to anoxia,21 or to anoxia only when combined with hypercapnia. It may be the result of tissue necrosis,12 or occur without necrosis and without increased blood-brain barrier permeability to protein.1

The effects of anoxia on brain circulation and metabolism have been studied intensively in recent years, in experimental animals and man.9,14 Cerebral autoregulation, the property of the resistance vessels of the brain that maintains blood flow constant during changes in systemic arterial pressure, is disturbed by hypoxia and hypercapnia.5,6 Recently we found that elevation of the blood pressure following a period of cerebral ischemia, or during hypercapnia, caused acute swelling of the exposed brain in the cat.11 We postulated that the hypoxia or hypercapnia caused loss of autoregulation, and when the blood pressure was then elevated, the arterioles failed to constrict. Cerebral blood flow increased, and, in addition, the arterial pressure head was released downstream into the capillary and venous bed causing an outpouring of fluid from the intravascular space into the extracellular space of the brain.

The purposes of the present experiments were to determine the incidence of brain swelling and increased intracranial pressure in cats, with the skull intact, following a period of ischemia, and to obtain information on the cause of the brain swelling by measuring cerebral blood volume and the status of the blood-brain barrier to serum protein. Transient occlusion of the arterial blood supply to the brain rather than systemic shock was used as the anoxic ischemic insult.

Materials and Methods

Adult cats were anesthetized with pentobarbital sodium (Diabutal), 30 mg/kg injected intraperitoneally. A tracheostomy was performed, and the animal was placed on a respirator. Catheters were placed in the femoral vein for administration of fluid and drugs and in the femoral artery for recording systemic arterial pressure. The common carotid, the subclavian, and the origin of the vertebral artery were exposed bilaterally. In the first few experiments, the vertebral arteries were ligated. In subsequent experiments both subclavian arteries, proximal to the origin of the vertebrals, and large branches of the distal subclavian arteries were also ligated. Clamping the ascending aorta is a more certain method of producing total cerebral ischemia. However, we desired some preparations with the same surgical procedures but without clinical signs of ischemia to serve as controls.

The head was fixed in a stereotaxic headholder and the scalp reflected. The skull was marked in coronal planes 10 mm anterior and 20 mm posterior to the interaural line. A small balloon containing 0.2 ml water was inserted through a trephine hole into the right frontal extradural space for recording intracranial pressure, and the hole was sealed with polymethylmethacrylate. The electrocorticogram (ECG) was recorded from four stainless steel electrodes inserted through twist drill holes into the extradural space over the frontal and parietal lobes bilaterally. Sodium fluorescein isothiocyanate was injected into the femoral vein approxi-
mately 1 hour prior to occlusion of the carotid arteries. Protein-bound fluorescein, 2.0 ml of a 5% solution per 5 lbs body weight, or free sodium fluorescein isothiocyanate 0.5 ml of a 5% solution per 5 lbs body weight, were used.

The carotid arteries were occluded for varying lengths of time. The time from carotid occlusion to loss of the corneal reflex, maximum pupillary dilatation and loss of the light reflex, and flattening of the ECG were recorded. In most preparations it was necessary to maintain blood pressure during the period of carotid occlusion with an infusion of norepinephrine or whole cat blood. The clamps were then removed from the carotid arteries, and several minutes later the animal's head was immersed in liquid nitrogen while the systemic arterial pressure was maintained at either normotensive or hypertensive levels. The head was then removed and placed in a freezer overnight.

The following day the frozen head was sectioned with a band saw in coronal planes at the predetermined positions. The most posterior of the three blocks, containing the occipital lobes and posterior fossa structures, was sectioned in the midsagittal plane. These sections were photographed to assess transitentorial and foramen magnum herniation. The distance from the middle of the free edge of the tentorium to the tip of the inferior colliculus was measured as an index of caudal displacement of the brain stem. The remaining coronal sections were also photographed.

The amount of fluorescein in the brain was evaluated macroscopically by photographing the specimens under a high intensity Woods lamp using a Nikon F camera with a filter system consisting of three gelatin filters (magenta 10, UV 16, and yellow 50) at an exposure time of 3 seconds. The frozen coronal sections of brain can be manually "punched out" from the surrounding skull, and the plane of cleavage is always through the subarachnoid space. The cortical vascular architecture was well preserved in all specimens, and the cortical surfaces were photographed.

Each coronal specimen and the posterior fossa sagittal sections were cut in a cryostat, and alternate sections at 2 mm intervals were used for ultraviolet microscopy and routine histology. The latter were stained with methylene blue or H & E. Fluorescence photomicrography was performed with a combination of a primary and secondary filter system. The primary (barrier) filters transmit UV light up to 400 μ, and filter out visible illumination and heat. The secondary system consists of a yellow-green filter operated with a bright ground condenser. The system gives a practical excitation range of 320 to 400 μ. Cerebral blood volume was measured in 12 animals using 51Cr-labeled red blood cells. The technique has been described elsewhere.

**Results**

A slight arterial pressor response and transient dilatation of the pupils occurred in a few animals after vertebral-subclavian ligations, but persistent signs of brain ischemia were never observed. Prior to occlusion of the carotid arteries, norepinephrine (0.02 to 0.06 μg) was administered intravenously to compare the effects of arterial hypertension on intracranial pressure in the control period and following brain ischemia (Fig. 1). When the two pressures had stabilized, the common carotid arteries were clamped. This was followed by a rise in arterial pressure, then a gradual fall toward shock levels. Throughout the remainder of the experiment the pressure was maintained with norepinephrine or infusion of blood. At the end of the predetermined time of occlusion, the carotid artery clamps were removed. Arterial pressure initially fell, then began to rise spontaneously. Intracranial pressure increased abruptly on release of the carotids, then gradually declined with the developing arterial hypotension. At this time the same dose of norepinephrine administered during the control period was injected. The two pressures rose rapidly, and when they had stabilized the animal was sacrificed. Four cats were sacrificed without terminal administration of the vasopressor agent.

Observations in 19 animals are presented in Table 1; the animals are grouped according to the clinical evidence of cerebral ischemia during temporary occlusion of the carotid arteries. In Group A, slowing of the ECG and pupillary dilatation were observed shortly following carotid occlusion, but these signs disappeared within a few minutes. In