Production of Prolonged Arterial Hypertension in Dogs by Chronic Stimulation of the Nervous System

Exploration of the Mechanism of Hypertension Accompanying Increased Intracranial Pressure

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We were unable to produce chronic arterial hypertension in dogs by severe cerebral ischemia induced by ligation of blood supply to the brain. Combining cerebral ischemia with the mechanical effect of a wire in the floor of the fourth ventricle and the thermal stimulus of heat generated in this wire by short wave diathermy resulted in hypertension that lasted as long as 10 months. Experiments are described which indicate that the arterial hypertension which accompanies increased cerebrospinal fluid pressure is in part the result of pressure on the brain and not entirely due to cerebral anemia.

In 1947 we described a method for the production in dogs of arterial hypertension of neurogenic origin which lasted several hours. It depended upon heating with short wave diathermy a wire embedded in the floor of the fourth ventricle. However, attempts to establish permanent hypertension by prolonged and repeated stimulation were not successful, apparently because glial tissue about the wire effectively insulated the pressor areas against heat generated within the wire.

The present study was undertaken because of the observation that 2 of the dogs with wire implanted in the medulla, subjected to progressive ligation of the arteries supplying the brain, developed arterial hypertension which lasted 8 to 10 months while otherwise normal dogs having similar operations to produce cerebral ischemia either had normal blood pressures or were hypertensive for two weeks or less. Several groups of experiments are reported which confirm the view that the combination of cerebral anemia and stimulation of pressor areas of the brain produce more marked and longer lasting hypertension than either one alone.

METHODS

Experiments were carried out on 165 mongrel dogs. For surgical operations and treatment with diathermy the animals were anesthetized with pentobarbital, 35 mg. per Kg. of body weight given by intravenous injection. Operative procedures were carried out with sterile technic. Short-wave diathermy was applied to animals' heads with an ordinary clinical diathermy apparatus. The heads were wrapped with toweling so that three to four inches separated the coils of the apparatus from the skin. Blood pressures were measured with a mercury manometer after puncture of a femoral artery.

The blood vessels supplying the brain were ligated through a midline incision low in the neck. By means of blunt dissection, adequate retraction, and traction upon the carotid arteries, it was possible to deliver into view the origins of the carotid, vertebral, thyrocervical trunk, costocervical, and internal mammary arteries. Vessels were doubly ligated and a 0.5 to 1.0 cm. segment was resected from between the ligatures.

If only the vertebral and carotid arteries were to be served this was done at a one stage operation. If all the vessels were to be interrupted, all save a single carotid were cut during the first stage. The remaining carotid was ligated under local anesthesia three to six days later. Hereafter "ligation of vessels" refers to the two stage operation unless otherwise indicated. This technic gave a high mortality rate. However, less drastic measures were ineffective in producing even transient hypertension. If gradual occlusion of the remaining carotid was accomplished in stages by tightening a Goldblatt clamp on it, no elevation of pressure occurred.

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For exposure of the floor of the fourth ventricle, dogs were placed in a prone position with the head in a holder which extended the neck from the body and flexed the head on the neck. A midline incision which extended downward from the occipital protuberance exposed the lower edge of the occipital bone. A 2 cm. square portion of the occipital bone was removed with a ronguer. Reflection of the dura and upward retraction of the cerebellum exposed the floor of the fourth ventricle for insertion of a wire or injection of silver nitrate solution. The wires and silver nitrate were placed as near as possible to the pressor areas of the medulla. The areas richest in pressor cells were located by stimulating the ventricular floor with weak faradic current while the dog's femoral artery was attached to a recording mercury manometer. Most sensitive areas were on either side of the median sulcus in the region of the middle one third of the length of the ventricle.

**Experiments and Results**

1. **Simple Ligation of Vessels.** This procedure failed to produce hypertension lasting longer than 15 days.

   A. In 5 animals the carotid and vertebral arteries were ligated at one operation. For several days afterward the animals behaved stupidly. They were dazed, apathetic, and listless, and often not interested in food or drink. Eventually, they recovered without obvious changes in habits or disposition. The blood pressures of these animals were above normal for two to three days (160 to 180 mm. Hg) and then reverted to normal (table 1 and fig. 1).

   B. Forty-nine animals underwent two stage operations. In the first, one carotid, the vertebral, thyrocervical trunk, internal mammary, and costocervical arteries were ligated. The remaining carotid artery was cut three to six days later. Many of these animals were demented for days and often died. Of the 49, 20 died three to four days postoperatively, some without recovering from anesthesia. Of those that lived for a week or more, many had repeated convulsive seizures. Some had to be tube fed. They were untidy and wandered aimlessly about. Twenty-nine animals survived both stages of the operations and by the end of the tenth postoperative day they had resumed what seemed to be normal behavior patterns. Only 7 had significant hypertension which persisted for 8 to 15 days. A representative result is shown in figure 1 and table 1.

   For three to five days the blood pressure was 180 to 200 mm. Hg but thereafter it gradually decreased to become normal within two weeks.

   Third stage operations were done on 10 of these animals in search for vessels large enough to be ligated. None was found. Arteriograms performed by injecting 70 per cent Diodrast into a brachial artery indicated why this was true. Myriad minute vessels coursing cephalad were visualized in the muscles of the neck (fig. 2).

   In 10 animals we attempted to prevent the formation of these vessels or to obliterate them.
by pressure of scar tissue developed in response to bands of silk, cellophane or steel about the muscles of the neck. Bands were placed beneath the skin and included all of the neck tissue, the vagi, external jugular veins, the trachea, and esophagus. In spite of sterile precautions and the use of antibacterial drugs there was considerable tissue reaction with drainage from the operative site. Hence, probably more, rather than fewer, collateral vessels formed since none of these 10 dogs had significant hypertension.

2. Ligation of Vessels Combined with Tantalum Wire Implant in the Floor of the Fourth Ventricle and Diathermy. As mentioned in the introduction, 2 dogs from a previous study developed prolonged hypertension after a combination of tantalum wire implant and 20 to 30 minutes of short-wave diathermy five to six days weekly for two to four weeks followed by ligation of the cerebral blood supply. The tantalum wire was inserted into the floor of the fourth ventricle through a suboccipital craniotomy. The wire was 1 cm. in length and was placed with a small forceps in the median raphe just below the ependymal layer so that it extended over the middle third of the ventricular floor. Twenty dogs were so prepared. Eight died following ligation of the vessels. Seven of the remaining 12 developed hypertension which lasted 2 to 10 months. Counting the 2 original animals, 9 of a total of 14 dogs that were subjected to wire stimulation, diathermy and surgically induced cerebral anemia had hypertension (170 to 180 mm. Hg) that lasted two months or longer (table 1 and fig. 1).

3. Sham Craniotomy Combined with Ligation of Vessels. Inasmuch as the dogs with wires in the fourth ventricle that had received diathermy were more apt to develop hypertension of longer duration than after either operation alone, experiments were performed to determine the more important mechanisms.

Fourteen animals were subjected to cranio-
omy following which the floor of the fourth ventricle was exposed and probed with a needle through the area usually receiving the tantalum wire. After six to eight days the cerebral blood vessels were ligated, following which 4 animals died. Only 2 of the remaining 10 irritant acting in the region of the pressor areas along with ischemia might reproduce the hypertension following heating of a wire imbedded in the fourth ventricle. Twenty-one dogs were used. Suboccipital craniotomy was performed and the ventricular floor exposed. Various concentrations of silver nitrate solution were then injected into the region usually occupied by the tantalum wire. A 25 gage hypodermic needle was inserted below the ependyma much as were the bits of tantalum wire. As the needle was withdrawn, 0.25 cc. of three concentrations of silver nitrate were injected. Nine animals received 0.05 per cent solution; 9 received 0.1 per cent, and 3 received 0.2 per cent solution. However, none of the last 3 lived. At autopsy the brain stem was found to be almost completely destroyed and in a semisolid state. The 18 animals that lived underwent the second stage operation for ligation of the vessels six to eight days after craniotomy. Only 10 of these animals survived and of the 10 only 3 showed elevations of blood pressure (160 to 180 mm. Hg). However, at the end of 17 days all had normal blood pressures.

5. Combination of Wire in Fourth Ventricle and Ligation of Vessels without Diathermy. Neither sham craniotomy nor injection of silver nitrate into the region of the pressor areas before ligation of the vessels gave more significant hypertension than in otherwise normal dogs having surgically induced cerebral anemia. In the present group, the tantalum wire was placed and the cerebral circulation mechanically interrupted but diaphermy was omitted. Twenty-five animals were used, only 12 of which lived. Four of these 12 developed hypertension lasting from one and a half to three months or slightly longer than dogs that had only ligation of the vessels.

6. Ligation of Vessels Combined with Diathermy to the Head without Wire Implantation. This group of experiments was performed to determine whether heating the brain of dogs with short-wave diathermy before, as well as following, restriction of the blood supply to the brain might influence the degree and duration of hypertension.

Twenty-five animals were given short wave diathermy to the head two days weekly two
to three weeks preoperatively and one to two weeks postoperatively.

A. Six dogs had ligation of only the vertebral and carotid arteries. One died. None of the other 5 had significant hypertension.

B. Nineteen dogs had preoperative diathermy and ligation of all the blood vessels arising from the aortic arch and subclavian trunks. Nine of these died after the second operation for ligation of the final carotid artery, 5 had no hypertension but 5 showed moderate elevation of blood pressure (150 to 180 mm Hg) that lasted two to eight months. A representative result is shown in figure 1. In this group, as with those with a wire in the fourth ventricle, hypertension was more sustained than in the previous experiments.

7. Effects of Application of Heat to the Heads of Hypertensive Animals That Had Failed to Develop or Lost Hypertension. In 6 animals that failed to develop hypertension and in 6 that began to lose their hypertension, heating of the head with short-wave diathermy was used in an attempt to induce or prolong hypertension. Although it was continued for four to eight weeks, the blood pressure remained within normal limits.

These experiments, which indicate that the combined effects of ischemia of the brain and mechanical and thermal stimulation of the medullary pressor areas often produce moderately prolonged neurogenic hypertension in dogs, made us wonder whether another type of neurogenic hypertension, that which accompanies elevation of intracranial pressure, was due entirely to pressure induced anemia as suggested by Cushing.3 It seemed possible that in addition to anemia the mere pressure of the cerebrospinal fluid on the vasopressor areas might participate in inducing the peripheral arterial hypertension which accompanies cerebrospinal fluid hypertension. Two further groups of experiments were performed to explore this thesis.

8. Ligation of All Vessels to the Brain Combined with Acute Cerebrospinal Fluid Hypertension. Five animals were subjected to two stage ligation of the cerebral vessels. However, instead of ligating the second carotid, the vessel was simply exposed and clamped so that it could be released during subsequent studies.

Three of these dogs had normal blood pressures, 1 had a control pressure of 178 mm. Hg, and the remaining dog had a pressure of 204 mm. Hg.

The cerebrospinal fluid pressure was now elevated by forcing saline with air pressure from a reservoir through a 15 gage needle, the tip of which was placed in the subarachnoid space by cisternal puncture. The pressure attained was measured by a mercury manometer connected into this system. The intracranial pressure (CSFP) was increased by increments of 10 to 20 mm. Hg. After the maximum elevation of pressure was noted the cerebrospinal fluid pressure was released and allowed to return to normal.

The rise of arterial blood pressure which occurred following elevation of cerebrospinal fluid pressure in dogs with cerebral ischemia was roughly proportional to the pressure applied to the brain. However, it varied widely from dog to dog and in the same animal at different times. Cerebrospinal fluid pressure of less than 60 mm. Hg had no effect. Cerebrospinal fluid pressure from 60 to 100 mm. Hg caused the arterial pressure to rise from 8 to 56 mm. Hg; pressure from 100 to 150 mm. Hg elevated arterial pressure from 50 to 128; pressure from 150 to 200 elevated arterial pressure 70 to 138 mm. Hg; and pressure from 200 to 250 produced a rise from 100 to 150 mm. Hg. Results of a typical experiment are shown in table 2.

If the intact carotid artery which had been clamped previous to the above experiments was released while the animals were hypertensive due to increased cerebrospinal fluid pressure, the blood pressure fell but not to the control levels. For instance, when the arterial pressure had been elevated from 144 to 238 mm. Hg by increasing the cerebrospinal fluid pressure to 150 mm. Hg, the release of the clamped carotid artery caused the blood pressure to fall to 190 mm. Hg. Reocclusion of the artery caused the blood pressure to rise to 228 mm. Hg.

The brains of these dogs had no major arterial blood supply, yet increased cerebrospinal fluid pressure caused a further elevation of arterial blood pressure. Although these data
suggest that the hypertension of increased intracranial pressure is due to both mechanical and anoxic stimulation of the pressor areas, we could not be certain the increased cerebrospinal fluid pressure was not simply obliterating the small vessels which kept the brain alive in spite of ligation of the larger vessels. To clarify this facet of the problem, four further experiments were performed.

9. Effects of Cerebral Anemia and Increased Cerebrospinal Fluid Pressure in Animals with the Circulation of the Head Completely Isolated from That of the Body. Four animals were pre-

par ed by a technic we describe in a forthcoming paper so that the circulation of the brain was completely isolated from that of the body, the brain being perfused with the blood of a donor dog. In these animals the effects of complete cerebral anemia induced by clamping the donor arteries upon the arterial pressure of the body were compared with the effects of increased cerebrospinal fluid pressure.

When the perfusing artery was clamped, arterial pressure of the bodies of these 4 dogs rose sharply from control levels of 50, 54, 54 and 66 respectively* to a plateau at 80, 90, 184, and 194 mm. Hg. While the arteries were still clamped the cerebrospinal fluid pressure in the head was increased to 200 mm. Hg and the arterial pressure rose further to 120, 184, 208, and 234. Similar degrees of hypertension resulted when the cerebrospinal fluid pressure was elevated before clamping the donor arteries. If the arteries were not occluded no further rise in pressure occurred.

**DISCUSSION**

These experiments demonstrate that the additive pressor effects of ischemia of the brain and mechanical and thermal stimulation of the vasopressor areas of the medulla cause more prolonged arterial hypertension in a greater number of dogs than does any one of these procedures acting alone. Further, we have shown that the acute hypertension that attends elevation of cerebrospinal fluid pressure is not entirely due to ischemia of the brain resulting from pressure. Rather, the mechanical effect of high cerebrospinal fluid pressure contributes in part to the systemic arterial hypertension which occurs.

Although these 165 experiments used, simultaneously, three agents each known to produce arterial hypertension of neurogenic origin of short duration, we have been unable to induce chronic elevation of blood pressure for longer than 10 months. The capacity of the dog to form collateral circulation rapidly counteracts ischemia of the brain while glial tissue soon

* The control blood pressures were low because the preparations had been used for several hours for other studies.
nullifies the mechanical stimulation arising from a wire in the medulla and insulates the pressor areas from heat generated in the wire by diathermy.

Since only 64 per cent of the animals prepared by combining all three methods developed hypertension, which lasted for periods varying from 2 to 10 months, the preparation has little value for chronic experimentation. This erratic behavior of the blood pressure of dogs receiving neurogenic pressor stimuli may well account for the observations made by Nowak and Walker following ligation of the vertebral and carotid arteries, and by Fishback, Dutra and MacCamy following progressive ligation of all arteries supplying the head. They all reported that such operations produced "chronic neurogenic hypertension." However, they used only a few animals and followed them for short periods of time. Likewise, the hypertension which Dixon and Heller produced by injection of kaolin into the cisterna magna of rabbits was unimpressive and of very short duration. Indeed, many doubt that chronic hypertension can be produced by this method.

Regardless of the difficulties involved in the production of experimental neurogenic hypertension, it is evident that it can be induced so that it lasts nearly a year and might well continue indefinitely if the resourcefulness of nature did not compensate for the meddling of man.

**Summary**

One hundred and sixty-five dogs were used in a series of experiments designed to produce chronic hypertension of neurogenic origin. Surgically induced cerebral ischemia, which was severe enough to cause death in 41 per cent of the animals, induced arterial hypertension in only 24 per cent of those that lived and this lasted only 7 to 15 days.

If the effects of cerebral ischemia were augmented by the stimulation of a tantalum wire in the floor of the fourth ventricle heated by short wave diathermy, 64 per cent of the dogs developed hypertension (160 to 200 mm. Hg) which lasted 2 to 10 months.

Ischemia of the brain combined with the wire implant but without diathermy caused hypertension in 33 per cent of dogs which lasted 45 to 90 days. Ischemia plus diathermy to the head but without the wire implant caused hypertension in 50 per cent which lasted two to eight months.

The additive effects of cerebral anemia and mechanical stimulation were further demonstrated in animals with isolated, perfused brains in which total cerebral anemia could be produced by clamping a perfusing artery. In these animals the mechanical effects of increased cerebrospinal fluid pressure (150 to 200 mm. Hg) caused the systemic blood pressure which had previously risen maximally in response to complete anemia to become further elevated.

**REFERENCES**


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