# The Physiologic and Pathologic Effects of Localized Cerebral Hypothermia *

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INTEREST in a localized and measurable cerebral circulation stemmed from a six-year study of factors involved in cerebral hemodynamics that were concerned with the clinical problem of acute subarachnoid hemorrhage. These factors included intravascular pressures in various parts of the carotid arterial tree and in arteriovenous anomalies, cortical oxygen tension, cortical oxygen consumption and cortical electroactivity. Studies were made in normal animals and humans, and in various disturbed states such as vascular occlusion and hypotension induced by hemorrhage or chemical blocking agents.[3, 13, 16] With the developing interest in hypothermia, an experimental situation was sought whereby these parameters of study, and others, could be applied to the normothermic and hypothermic brain under conditions simulating those of an extracorporeal circulation.

Previous efforts in this field have had in common either total isolation of the perfused head, as described by Malmejac [10] for instance, or irrigation of the brain with cooled blood through the carotid arteries with an unimpeded efferent flow into the systemic circulation. In several experimental applications of this latter procedure,[1, 2, 6, 7, 9, 11] and in one instance of its clinical trial,[8] a significant lowering of body temperature has been noted, there has been a high incidence of cardiac arrhythmias and there has existed complete brainbody circulatory mixing. In order to explore the effects of localized brain cooling with minimal but measurable systemic changes, the pattern of the present study includes an intact peripheral or systemic circulation and a localized extracorporeal cerebral circulation whose afferent and efferent channels are controlled through both carotid arteries and jugular veins by a dual channel independently variable, torque conversion Sigma motor pump.

## Materials and Methods

The heat-exchangers are made from siliconized Monel metal coils and are placed in ice baths to cool the blood. The oxygenator is a Baxter-DeWall type 500 cc. volume bubble oxygenator into which blood and 100 per cent oxygen are pumped. Stainless steel filters are included in the circuit to remove fibrin clots. An electromagnetic Rotameter is used to measure perfusion flow and perfusion pressure is measured by a Sanborn electromanometer. The systemic blood pressure is measured on a Statham strain gauge. Bead thermistors are used for temperature gradients. These parameters, and the EEG and EKG, are recorded on an Offner Polygraph and a Sanborn Polyviso. Systemic venous pressure is measured directly on a water manometer. Hematocrit, clotting -time and arteriovenous blood oxygen samples are obtained from appropriate areas of both circulations.

Mongrel dogs have been used in 45 stud-

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ies lasting from four to nine hours each. Each animal, with an average body weight of 15 Kg., was anesthetized lightly with nembutal, 20 mgm. per Kg. of body weight. An endotracheal tube was inserted and the animal placed on a Palmer respirator giving 400 cc. of 100 per cent oxygen per minute. The vertex of the head, the anterior cervical region and both femoral areas were shaved and prepared in succession as sterile fields. One femoral artery and vein were catheterized for the continuous measuring of systemic arterial and venous pressures. The opposite femoral artery and vein were used for obtaining blood samples. Inflow and outflow valves were available on the extracorporeal circulation circuit for obtaining comparable blood samples.

Through a midline scalp incision, and after subperiosteal retraction of the musculature, bilateral frontal and parietal trephines were made for the introduction of paired silver EEG electrodes. In one of these trephine openings, a bead thermistor was also placed. Standard EKG leads were inserted intramuscularly. Thermistors or thermometers were always placed in the rectum, heat -exchanger and arterial side of the extracorporeal circulation and variably in the esophagus, nasopharynx and adjacent to the carotid arteries.

Through two lateral and one midline anterior cervical incisions, both external jugular veins and carotid arteries were isolated and prepared for cannulation. The extracorporeal circulation unit, thoroughly washed, was primed with 1,500 cc. of donor blood secured by exsanguination 24 hours prior to each experiment and preserved at icebox temperatures. According to the dictates of the individual study, the donor blood was warmed through a closed extracorporeal circulation to a temperature of 37° C. or pre-cooled to a temperature of 15° C., using the heat exchanger for both purposes. The external jugular veins were then cannulated in sequence and connected by gravitational flow to the venous reservoir. One carotid artery was cannulated distally, connected to the arterial component of the extracorporeal pump-oxygenator and the perfusion started. The opposite carotid artery was then cannulated and by a Y tube added to the perfusion. The perfusion was controlled at indicated flows and pressures by varying the pump cycle and the venous return from the head collected in the venous reservoir was pumped in turn through the oxygenator. By shifting the position of the oxygenator in respect to that of the heat exchanger, either the venous return from the head directly or blood cooled by the heat exchanger could be oxygenated. Each animal received 25 mgm. of heparin intravenously prior to perfusion.

At the end of the perfusion period, ranging from 40 minutes to three hours and 55 minutes, the jugular veins were ligated, the carotid arteries repaired and the animal's brain rewarmed by means of its systemic circulation. Antibiotics were given and the extradural electrodes left in place. EEG tracings were secured at survival periods from five to 33 days, the animals sacrificed and their brains studied by standard neuropathologic methods.

## Results

In all experiments, the localized cooling of the brain possessed the properties of rapid induction and ready reversibility (Fig. 1). The results obtained were reproducible in all animals in the designated areas of study within the limits of technical errors. These errors included gross air emboli from defects in the perfusion system, cerebral anoxia from pumping chamber difficulties, faulty cannulation of vessels and transfusion reactions from old blood. At perfusion flows of 10 cc./min./Kg., brain temperatures dropped an average of 10° C. during the first 30 minutes of perfusion and attained the desired level of cooling in these studies of 21 to 20° C. after 45 to 60 minutes of perfusion.

The effect of cooling upon electrocortical activity has been demonstrated repeatedly in states of generalized hypothermia [12] and in states of hibernation.[5] The changes noted in localized cerebral hypothermia were identical (Fig. 2, 3 and 8). Slow wave activity became apparent after cooling the brain to 32° C. There was a concomitant fall in amplitude as the temperature was reduced and the recordings became flat at 21 to 20° C. The cortex remained electrically silent below this temperature and when the gradient was reversed, small bursts of low amplitude activity reappeared at 21 to 23° C. At 30° C., fast activity dominated the EEG pattern and the record became normal again at the pre-cooling level. No abnormal change was noted in surviving animals.

During most of these experiments, the $AVO_2$ differences of the cerebral and systemic circulations were determined. There was little change in the systemic circulation in this respect unless the animal's body temperature at the stage of rewarming fell below a level of 34° C. The $AVO_2$ difference of the perfusion blood of the cerebral

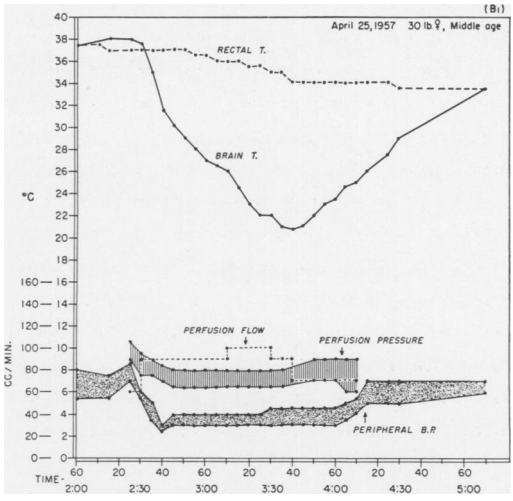


FIG. 1. Rapid induction and ready reversibility of usual state of localized cerebral hypothermia attained in this study. Note brain temperature fall to 20° C. within 60 minutes at perfusion flows ranging between 60 and 100 cc./min. in a 13.6 Kg. animal, relative systemic hypotension and body temperature.

circulation fell in a linear fashion with decrease in brain temperature and reached 0.0 at a brain temperature of 21 to 20° C. (Fig. 2 and 3). With rewarming, the $AVO_2$ difference rose progressively and stabilized

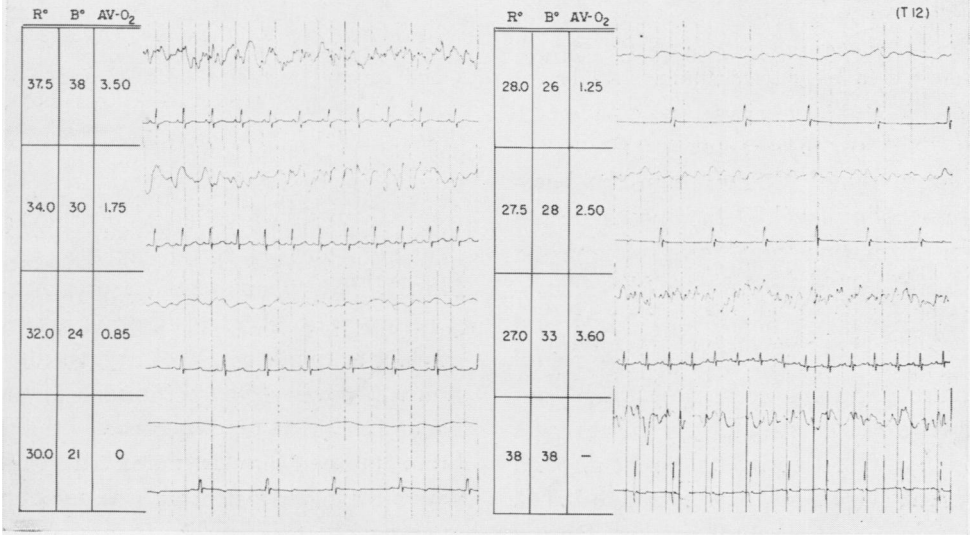


FIG. 2. Characteristic abolition of cortical electroactivity as 21 to 20° C. brain temperature with linear decrease in arteriovenous differences.

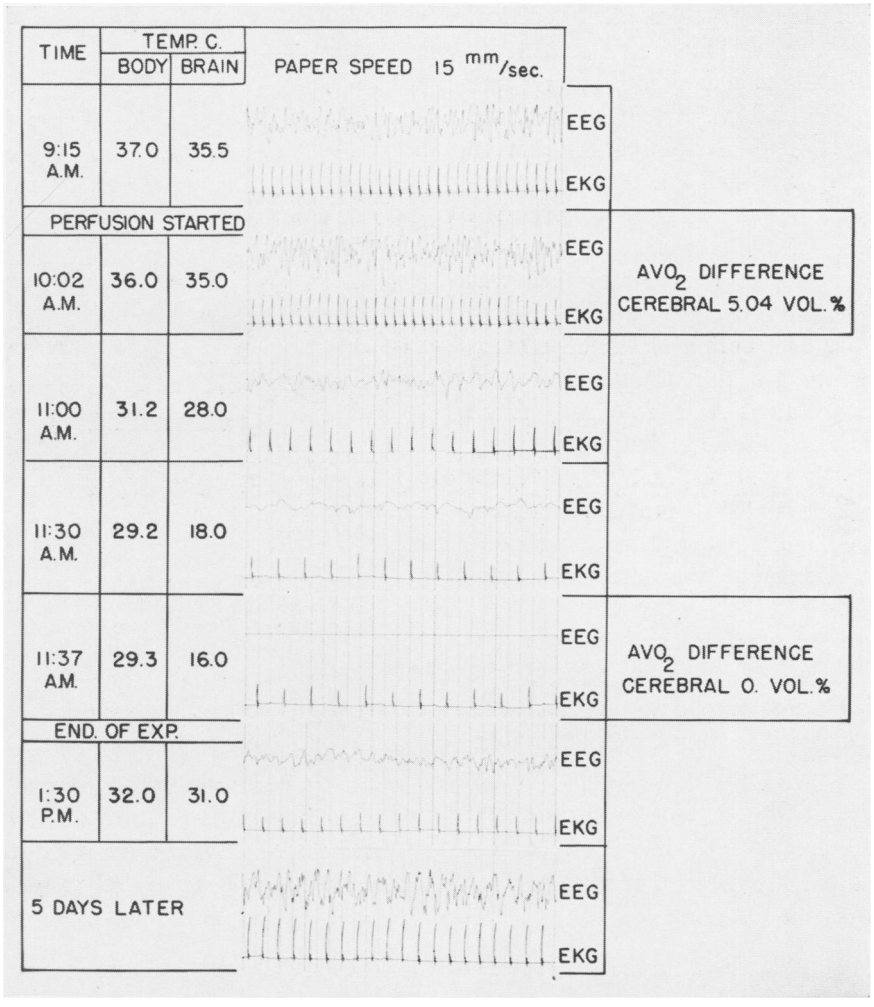


FIG. 3. Electrical silence of cortex at 18 to 16° C. brain temperature and unusual fall in body temperature. Note bradycardia, and survival recording of EEG and EKG, $T_9$.

at a figure slightly higher than the baseline, pre-cooling level. Data concerned with oxygen saturation and oxygen capacity, hematocrit and hemoglobin in the normothermic animal are noted in Table 1 and the perfusion rate and pressure are found in Figure 4. In the second of three consecutive experiments, the perfusate was cooled in a closed perfusion circuit through the heat exchanger and oxygenated to 15° C. prior to localized cerebral cooling. During a perfusion period of two hours and one minute, with brain temperatures falling from 37 to 20° C., the $AVO_2$ differences began at a low level and remained so (Table 2). This phenomenon represents oxygen supersaturation of the perfusate according to the principle of oxygen dissociation with lowered temperatures.[4] The usual linear fall in $AVO_2$ difference with fall in brain temperature is noted in Table 3 where the blood perfusate was commenced at a temperature of 37° C. and was oxygenated prior to circulation through the

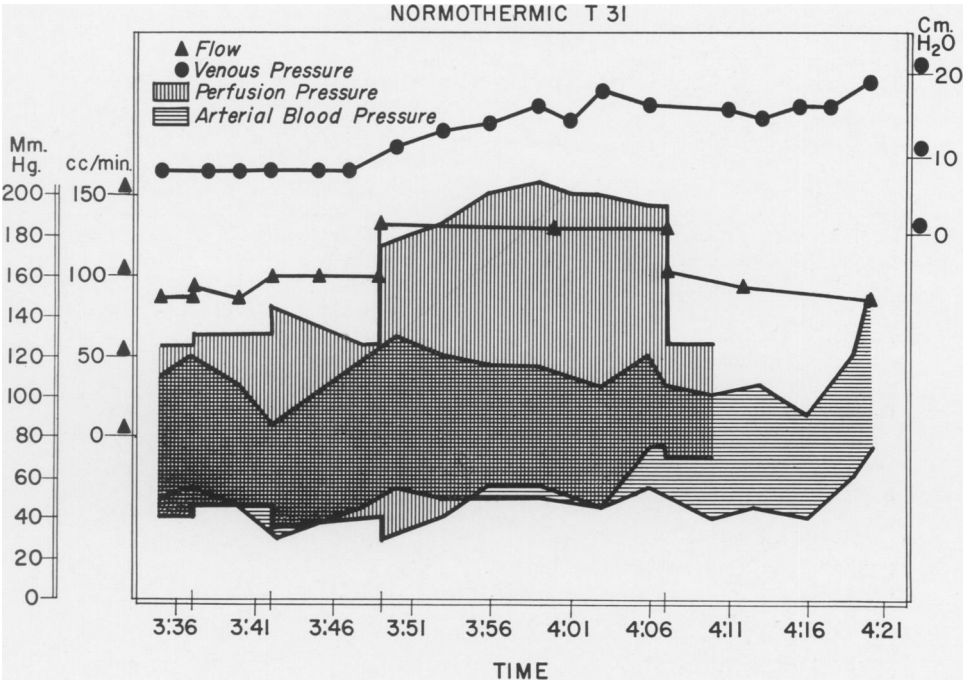


FIG. 4. Isolated cerebral circulation in hypothermic state with blood perfusate at 37.0° C. Note elevated venous pressure with increase in perfusion flow and perfusion pressure—failure to survive.

cooling coils of the heat exchanger. The perfusion flow and pressure in this animal may be noted in Figure 6.

The principal finding in the electrocardiogram was a relative bradycardia that developed with progressive brain cooling. The average cardiac rate at the beginning of an experiment was 156 and averaged 88

TABLE 1. *Oxygen Consumption Data of Normothermic Brain During Localized Perfusion Over Time Period of One Hour and 18 Minutes. Refer to Figure 4 for perfusion flow rates and perfusion pressure.*

| | % Sat. $O_2$ | $O_2$ Cap. (Vols. %) | Hct. (%) | Hgb. (Gm. %) | $AVO_2$ Difference (Vols. %) |
|---|---|---|---|---|---|
| $CA_1$ | 100 | 13.54 | 19 | 10.1 | 0 |
| $CA_2$ | 99.0 | 15.12 | 21 | 11.2 | 7.60 |
| $CV_2$ | 55.9 | 8.52 | 28 | | |
| $CA_3$ | 98.8 | 16.32 | 18 (hem.) | 12.2 | 7.58 |
| $CV_3$ | 53.0 | 8.71 | | | |
| $BA_1$ | 98.1 | 19.15 | 27 | 14.2 | 2.81 |
| $BV_1$ | 78.5 | 16.34 | 23 | | |
| $BA_2$ | 97.1 | 18.76 | 29 | 14.0 | 7.48 |
| $BV_2$ | 58.4 | 11.28 | 17 | | |
| $BA_3$ | 97.3 | 18.45 | 25 | 13.7 | 6.39 |
| $BV_3$ | 63.6 | 12.06 | 25 | | |

C = Cerebral circulation
B = Systemic circulation

Time
Sample 1—2:45 p.m.
Sample 2—3:35 p.m.
Sample 3—4:07 p.m.
Pump on—3:11 p.m.
Pump off—4:29 p.m.

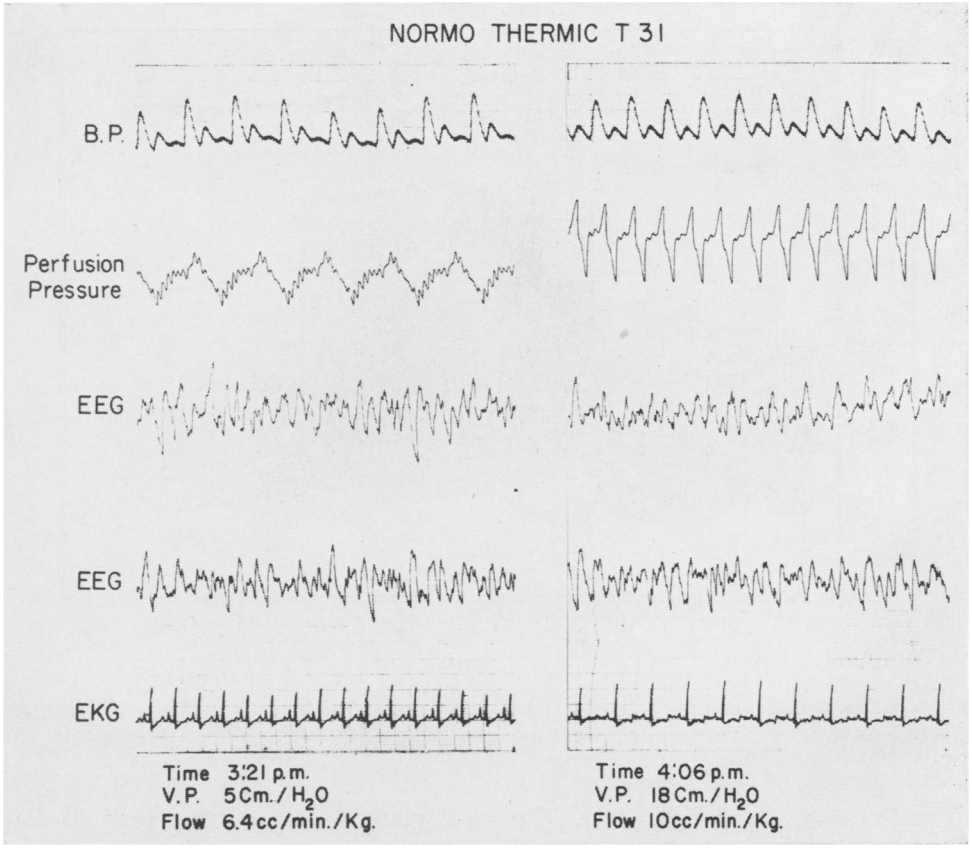


FIG. 5. Recording data in normothermic animal—elevated perfusion pressure on right with subsequent rise in systemic venous pressure—persisting coma and failure to survive 24 hours post-perfusion.

when electrocortical activity ceased. This sequence was reversed with rewarming. Associated with the decrease in rate, the QT interval was prolonged from a pre-cooling average of .23 seconds to an average of .43 seconds when the EEG was flat. There was usually some decrease in the over-all amplitude of the tracing, noticeable in the QRS complex and in the T wave. On several occasions, the T wave became inverted but returned to normal upon rewarming. In two animals, the PR interval was prolonged 0.1 and 0.8 seconds. There were no instances of ventricular fibrillation or other cardiac arrhythmias (Fig. 2, 3 and 8).

There was a linear relationship apparent between systemic arterial pressure and the degree of brain cooling. With brain temperatures at 20° C. or somewhat below this point, the systemic arterial pressure might range between 30 and 50 mm. of mercury. The systolic pressure fell an average of 53 points and the diastolic pressure 42 points when, in these studies, the brain was cooled to 20° C. The pulse pressure, therefore, tended to narrow at low brain temperatures (Fig. 1, 6 and 7).

The perfusion flow was chosen arbitrarily during the early phases of this study which were concerned largely with the technical feasibility of localized hypothermia. In the further course of this study, it became apparent that perfusion flow, or perfusion pressure, was the single important factor in terms of survival and that hypothermic preparations withstood higher flow levels

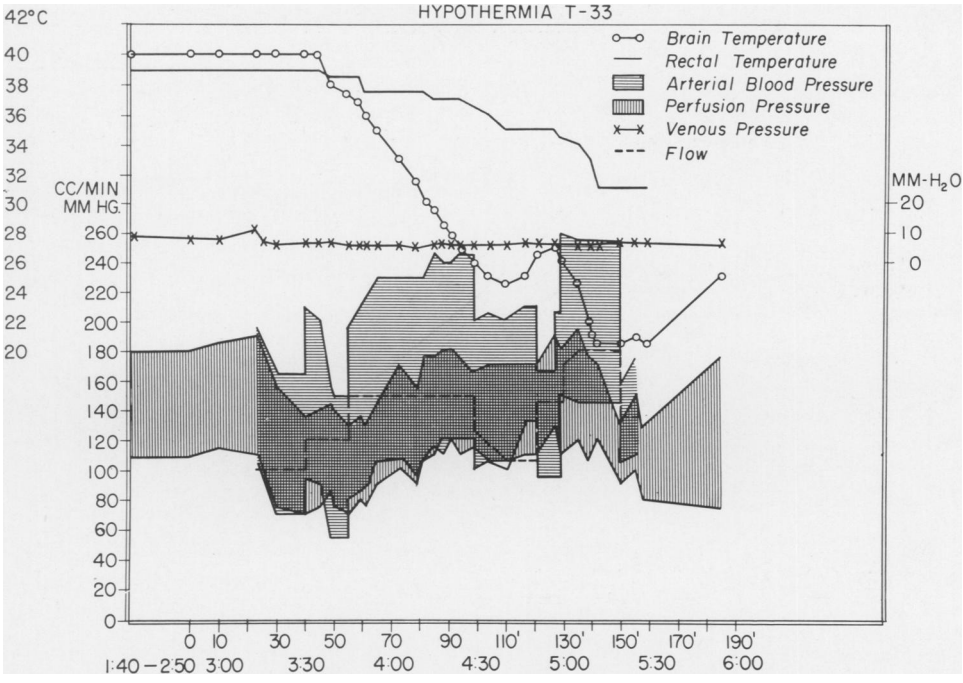


FIG. 6. Comparison with Figure 5, Exp. T 31—hypothermic preparation with relatively high perfusion pressure, static systemic venous pressure and uneventful survival.

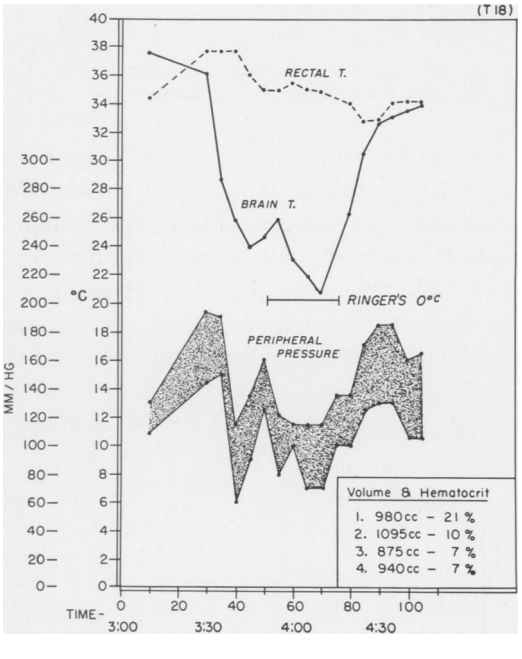


FIG. 7. Brain-body circulatory mixing demonstrated by perfusion of Ringer's solution in hypothermic state and evaluation of hematocrits of return or venous cerebral circulation.

much more readily than did the normothermic brain. Figure 4 and 5 show respectively the graphic representation of perfusion flow and pressure and the actual recording data in a normothermic animal with a localized cerebral circulation with the blood perfusate at body temperature. In this animal, flow values of 10 cc./min./Kg. caused death within 24 hours with autopsy evidence of cerebral edema, even though this perfusion rate was reduced after a period of 30 minutes to lower values. The normal venous pressure, in both normothermic and hypothermic animals, was maintained at a level of five to 10 cm./water. With high perfusion flows, as in this animal, it might rise to levels of 15 to 20 cm./water. In the localized hypothermic state, flow values in the order of 10 to 15 cc./min./Kg. allowed the perfusion pressure in the carotid circulation to approximate or rise somewhat above the peripheral arterial pressure and these ani-

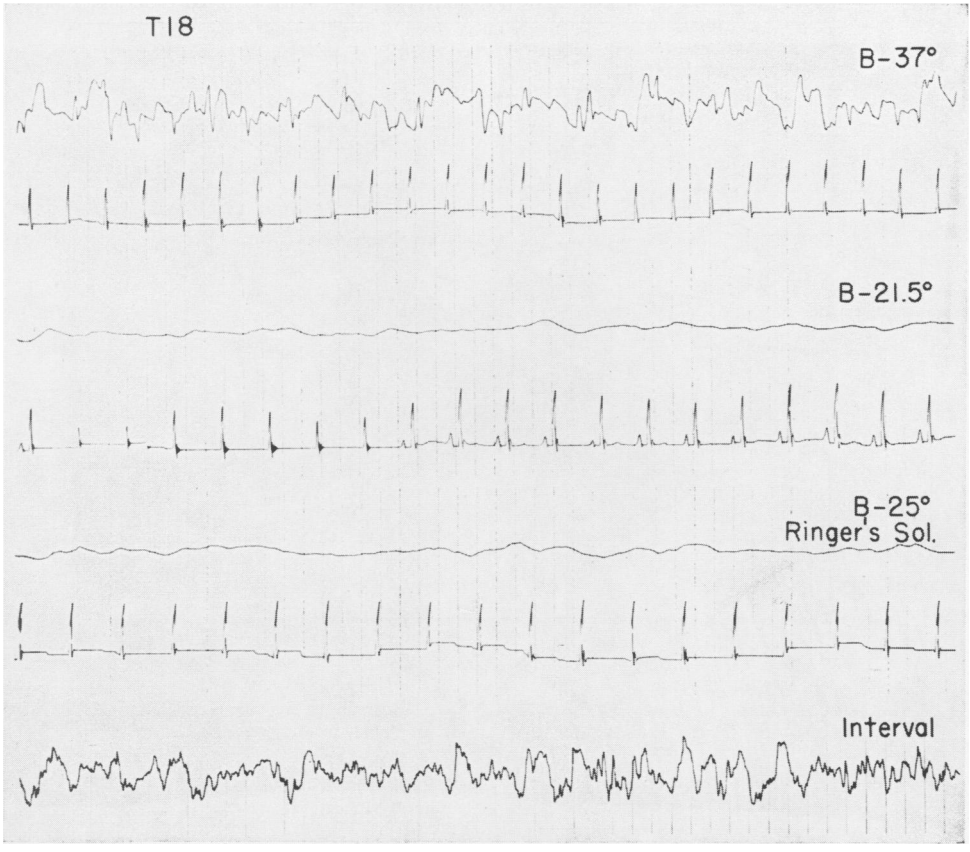


FIG. 8. Maintenance of cerebral electrical silence during 30 minute period of perfusion of Ringer's solution during localized cerebral hypothermia. Note survival EEG.

mals did well (Fig. 1, 6). When flow values were elevated in the hypothermic brain to levels above 20 cc./min./Kg., the peripheral venous pressure began to rise and cardiac failure ensued. At autopsy, evidence of cerebral edema was present in such animals. In the later stages of localized hypothermia, at static flow rates, the perfusion pressure tended to follow the fall in systemic arterial pressure (Fig. 6).

The cerebral circulation of the canine brain is well known. No effort was made to isolate this circulation in terms of the carotid arteries and external jugular veins. The concept of some collateral circulation was accepted, on the other hand, since this concept would be important in any clinical application of a localized cerebral circulation. Emphasis has been placed, therefore, upon terms of measurement of brain-body circulatory mixing. As already noted, with perfusion pressures far above the systemic arterial pressure, the systemic venous pressure always rose, implicit evidence of brain-body circulatory mixing, and if these perfusion pressures were sustained, the animal succumbed. In six animals at a brain temperature of 20° C. and at normal body temperatures, the blood perfusate was abruptly replaced by Ringer's solution through the medium of a second perfusion unit. For 30 minutes, the venous return hematocrits were measured at five minute intervals (Fig. 7, 8). With a constant perfusion pressure, the venous return hematocrits fell steadily from levels of 14 per cent to levels of five per cent during the final

TABLE 2. *Oxygen Consumption Data of Hypothermic Brain During Localized Perfusion Over Time Period of Two Hours and One Minute with Perfusate Blood Initially Oxygenated at 15° C. with Initial Brain Temperature of 37.0° C.*

| | % Sat. $O_2$ | $O_2$ Cap. (Vols. %) | Hct. (%) | Hgb. (Gm. %) | $AVO_2$ Difference (Vols. %) |
|---|---|---|---|---|---|
| $CA_1$ | 100 | 9.66 | 19 | 7.2 | 0 |
| $CA_2$ | 99.0 | 7.01 | | 5.2 | .30 |
| $CV_2$ | 95.5 | 6.71 | | | |
| $CA_3$ | 100 | 11.40 | (hem.) | 8.5 | .08 |
| $CV_3$ | 99.3 | 11.32 | | | |
| $BA_1$ | 97.6 | 14.60 | 37 | 10.8 | 4.28 |
| $BV_1$ | 69.0 | 10.32 | | | |
| $BA_2$ | 95.8 | 15.87 | 31 | 11 | 9.61 |
| $BV_2$ | 37.8 | 6.26 | | | |
| $BA_3$ | 98.9 | 17.40 | 24 | 12.9 | 5.25 |
| $BV_3$ | 69.1 | 12.15 | 28 | | |

C = Cerebral circulation
B = Systemic circulation

Time
Sample 1—1:00 p.m.
Sample 2—1:50 p.m.
Sample 3—3:30 p.m.
Pump on—1:38 p.m.
Pump off—3:39 p.m.

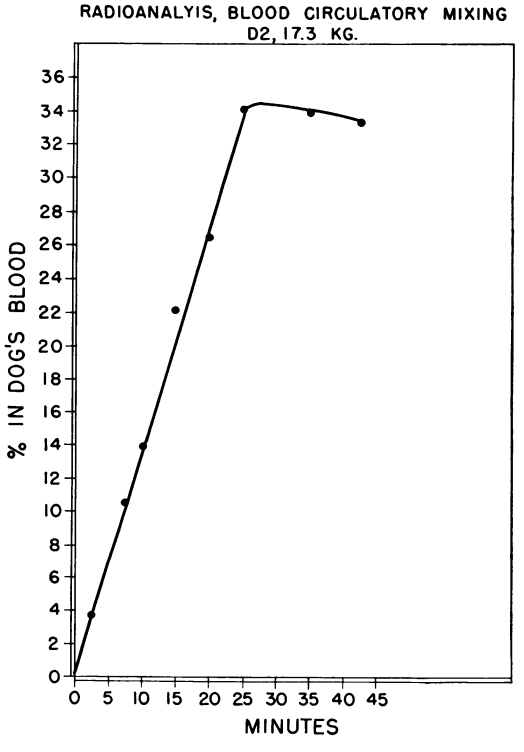


FIG. 9. Instance of radioanalysis of brain-body circulatory mixing in localized cerebral circulation.

five minute period. The normal dog hematocrit measures 45 to 48 per cent and these studies suggested a circulatory mixing of perhaps 15 per cent. It is of some interest that three of the six animals survived the use of this unphysiologic perfusate and showed normal EEG records during their survival periods.

Brain-body circulatory mixing could also be demonstrated by the addition of 30 millicuries of radio-iodine labeled serum albumen in the blood volume to be circulated through the brain. By conventional radioanalysis technics, the percentage of circulatory mixing from brain perfusate to body blood volume could be determined. In three animals, this measured between 22 and 34 per cent over a perfusion period of 30 minutes and the circulatory mixing tended to remain constant thereafter (Fig. 9). In all probability, this method of measuring circulatory mixing is accurate for the individual animal.

TABLE 3. *Oxygen Consumption Data of Hypothermic Brain During Localized Perfusion Over Time Period of Two Hours and 20 Minutes with Perfusate Blood Initially Oxygenated at 37.0° C. and Initial Brain Temperature of 37.0° C. Refer to Figure 6 for perfusion flow rates and perfusion pressure.*

| | % Sat. $O_2$ | $O_2$ Cap. (Vols. %) | Hct. (%) | Hgb. (Gm. %) | $AVO_2$ Difference (Vols. %) |
|---|---|---|---|---|---|
| $CA_1$ | 100 | 16.24 | 24 | 12.12 | 0 |
| $CA_2$ | 100 | 17.79 | 34 | 13.28 | 8.26 |
| $CV_2$ | 53.5 | 9.53 | | | |
| $CA_3$ | 100 | 16.91 | 34 | 12.62 | 4.27 |
| $CV_3$ | 74.8 | 12.64 | | | |
| $CA_4$ | 100 | 18.07 | 34 | 13.49 | 2.02 |
| $CV_4$ | 88.8 | 16.05 | | | |
| $CA_5$ | 100 | 17.42 | 33 | 13.00 | 2.18 |
| $CV_5$ | 87.5 | 15.24 | | | |
| $CA_6$ | 100 | 14.32 | 27 | 10.69 | 0 |
| $CV_6$ | 100 | 14.32 | | | |
| $BA_1$ | 100 | 18.18 | 42 | 13.57 | 7.79 |
| $BV_1$ | 57.0 | 10.39 | | | |
| $BA_2$ | 100 | 17.89 | 37 | 13.43 | 9.27 |
| $BV_2$ | 48.5 | 8.62 | | | |
| $BA_3$ | 100 | 16.64 | 37 | 12.42 | 12.03 |
| $BV_3$ | 27.8 | 4.61 | | | |
| $BA_4$ | 100 | 18.96 | 38 | 14.15 | 10.83 |
| $BV_4$ | 43.0 | 8.13 | | | |
| $BA_5$ | 100 | 17.89 | 36 | 13.43 | 10.24 |
| $BV_5$ | 43.0 | 7.65 | | | |
| $BA_6$ | 100 | 16.52 | 33 | 12.33 | 4.66 |
| $BV_6$ | 71.8 | 11.86 | | | |

Time

C = Cerebral circulation
B = Systemic circulation

Sample 1—3:00 p.m.
Sample 2—3:25 p.m.
Sample 3—3:55 p.m.
Sample 4—4:12 p.m.
Sample 5—4:40 p.m.
Sample 6—5:10 p.m.
Pump on—3:08 p.m.
Pump off—5:28 p.m.

## Conclusion

Localized cerebral hypothermia has been produced in the dog by an extracorporeal circulation utilizing the carotid arteries and external jugular veins. During the acute stage of perfusion, various parameters of study have been recorded and in general, these results are in accord with those noted in states of generalized hypothermia. Survival is predicated upon low perfusion flows and the development of a perfusion pressure closely aligned with the systemic arterial pressure. Such long-term survivals allow the further investigation of the effect of various drugs and chemical substances upon the normothermic and hypothermic brain whose circulation is isolated in a measurable manner from the systemic circulation.

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## Discussion

Dr. James C. Drye: As a general surgeon I feel somewhat impertinent in discussing a paper in the neurological field. However, I have had some experience in perfusing dogs' brains. I got into this as a preliminary part of a study on gastric secretion. I was interested in the effect of hypoglycemia on secretion—did it act directly on vagal nuclei, or was the hypoglycemia effect due to the effect on the whole dog, particularly the adrenals? We attempted to keep the dogs' brains at a normal level of glucose concentration while putting the rest of the dog into insulin shock. We gave large doses of insulin and then perfused glucose into the carotid artery and drew samples of blood from the femoral vein, from the jugular vein, for glucose determinations. After running a number of dogs, we became aware of many difficulties. Under nembutal anesthesia we were able to produce a nice differential between jugular vein fluid and femoral vein blood as far as glucose concentrations went, but the nembutal stopped all gastric secretion. Under other anesthetic agents, such as ether cyclopropane, nitrous oxide with morphine, etc., we were unable to produce any hypoglycemia.

During the course of these studies we happened to dissect out the carotid artery and jugular veins. To our surprise we found that the carotid artery broken into a small number of small twigs at the foramen, and supplied the brain hardly at all, but chiefly the skin and the muscles of the face and jaws. Apparently the dog's brain is supplied chiefly by the vertebral and spinal arteries. In the dog the internal jugular vein seems to empty immediately into the external jugular as it leaves the brain, so that samples taken out of the neck are of venous blood, partly from the brain but mostly from the jaws and face.

I just do not understand Dr. Woodhall's observation. He was perfusing the carotids which do not supply the brain. I am not clear as to how he was measuring the brain temperature. If he were taking temperatures from the venous blood, he was not getting anything related to the brain, as most of this blood comes from the exterior of the skull. I am just a little confused about this paper.

Dr. Barnes Woodhall: (closing) I am aware that the carotid artery of the dog supplies other head structures as well as the brain, and that the brain further obtains its blood supply from the vertebral arteries and the spinal artery. These are demonstrated facts, however, that perfusion of the carotid artery with cooled, oxygenated blood lowers brain temperature, abolishes cerebral electroactivity and reduces the AVO differences of the perfusate to zero at 21 to 20° C.