Profound Selective Hypothermia and Arrest of Arterial Circulation to the Dog Brain*

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To provide circulatory arrest in the brain during intracranial surgery, total body profound hypothermia has been successfully accomplished with extracorporeal circulation in a number of neurosurgical centers throughout the world. Unfortunately, inherent in this technique are at least two major limitations: 1) the necessity of a prolonged period of systemic anticoagulation during the cooling and rewarming phases which causes troublesome bleeding during and after surgery; 2) the complexity of the method itself which requires two well-trained surgical teams and presupposes complete familiarity with the pump-oxygenator-heat exchanger systems.

Since the surgical target of cooling and ischemic arrest is the brain itself and not the body as a whole, we have become interested in overcoming the present limitations of extracorporeally-produced, profound hypothermia. This could be accomplished by selective cerebral cooling via carotid perfusion during temporary arrest of the cerebral circulation by occlusion of the extracranial arterial system.

Utilizing a simple artery to artery extracorporeal circuit to cool the brain alone would avoid cooling of the entire body and would thus eliminate the need for an oxygenator and the mechanically controlled rewarming phase. In addition, the period of anticoagulation would be significantly shortened and with the absence of the oxygenator, additional problems in blood coagulation would be obviated.

While we, as others, have demonstrated the feasibility of differentially reducing the brain temperature in the experimental animal utilizing direct cooling via the carotid arterial system, this method to date has enjoyed only limited clinical application.

The principal objection both experimentally and clinically has been the difficulty of totally arresting circulation to the brain via suitable closures of the major cervical arteries.

We are reporting our experience with selective cooling of the brain in animals which have been so prepared that they provide differential and reversible ischemia of the brain by means of occlusions of the extracranial circulation. The technique of cerebral circulatory arrest was developed within the framework of comparative anatomy so that the carotid arterial ligations utilized in dogs could be related to similar occlusions of the cervical vasculature in man.

Methods and Materials

Twenty-one mongrel dogs weighing 9–15 kg. were used for these experiments. All surgical procedures were performed under sterile conditions. The animals were anesthetized with sodium pentobarbital (25 mg./kg. body weight), intubated with a wire spiral-cuffed endotracheal tube and ventilated with a Harvard respirator and room air when hypothermic perfusion was begun.

Three to 7 days prior to the selective brain cooling and temporary occlusion of the extracranial circulation, each of the 21 animals was subjected to basilar artery ligation in order to eliminate the contribution of the vertebral-anterior spinal artery complex to the cerebral circulation. All 21 dogs underwent temporary cerebral ischemia by means of occlusion of the carotid circulation. The external maxillary, the branches of the external and the internal carotid arteries at the carotid bifurcation as well as both common carotid arteries were exposed and ligatures for later occlusion left in place (Fig. 1). In addition, the thyroid arteries and superficial temporal arteries were permanently ligated. (Previous injection and dissection studies had led us to believe that nearly complete cerebral ischemia in the canine can be achieved by this method of cervical arterial ligation.) Sixteen of the 21 animals so prepared were destined for subsequent perfusion and differential brain cooling. The remaining 5 animals were to be kept

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as normothermic controls, without differential cooling.

Selective cerebral perfusion was performed in 16 dogs by pumping blood from a cannulated femoral artery through a Brown Harrison Pediatric heat-exchanger to 2 metal "T" cannulae, each placed in a common carotid artery (Fig. 1). Prior to arterial cannulation, each animal was given 3 mg. of Heparin/kg. of body weight. The perfusion circuit (priming volume, 150 cc.) was filled with 6 per cent dextran in 5 per cent glucose and slowly circulated into the animal to provide even mixing of the animal's blood with the perfusate and to supply oxygenated blood in the extracorporeal system. Tap water, 10–13°C, followed by ice water 1–3°C, was actively circulated through the heat-exchanger to reduce blood temperature. As perfusion was begun, the carotid arteries were occluded on the cardiac side of the cannulae. Utilizing flow rates ranging from 80–140 cc./min., selective hypothermic perfusion was continued until intracerebral temperatures of 14–19°C were obtained. At this point cerebral ischemia was immediately produced by closing all the cephalic ligatures (Fig. 1); the dog's head was then packed with ice.

In the 5 control animals as well as in the 16 animals undergoing selective hypothermic perfusion, ischemia was maintained for 30 minutes and then terminated by release of the occluded vessels. During the ischemic period, the perfusion cannulae were removed from the femoral and carotid arteries; the femoral artery was ligated and the arteriotomies in the carotid vessels were carefully repaired with 5-0 arterial silk to insure a patent lumen.

Following release of the extracranial occlusions, the brain was rewarmed rapidly via the systemic circulation. Hexadimethrine bromide (Polybrenne), 3 mg./kg. body weight, was given to neutralize the action of Heparin at the time of release of the arterial occlusions. Penicillin, 500,000 U, was administered for 3 days following surgery. Careful neurological and behavioral evaluation was made during the first 2 weeks after surgery.

At the initiation of the experiment, a small perforation had been made in the parietal bone for the introduction of a needle thermistor into the depths of the brain. Esophageal, muscle and rectal thermistors were utilized to monitor the temperature in these areas. The temperature of the blood entering and leaving the heat-exchanger was measured by appropriate thermistors. Using a Statham strain gauge transducer connected to a Grass Polygraph, systemic arterial pressure was measured by a catheter inserted into the aorta via the femoral artery; the perfusion pressure was obtained from a fine polyethylene catheter introduced proximally in one of the carotid "T" cannulae.

**Results**

1. **Control Group (ischemic-normothermic).** In these 5 animals, arrest of circulation to the brain for 30 minutes by temporary occlusion of the carotid circulation was uniformly lethal. In spite of mechanical respiratory support for 2 hours after release of the ligatures, only 2 of the normothermic animals were ever able to breathe on their own; both remained in coma and died within 24 hours.

2. **Experimental Group (ischemic-hypothermic).** During the cooling period, the inflow of cold blood to the head averaged 115 cc. per minute, ranging from 80–140 cc. per minute. At the termination of the hypothermic perfusion, the average deep brain temperature was 14.7°C. (range 13.5–16°C.) with the mean arterial blood pressure approximately 40 mm. Hg (range 35–45 mm. Hg) and the heart rate averaging 60 beats per minute.
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TABLE 1

Average blood pressure, heart rate and differential temperature in 16 animals during cerebral hypothermia

<table>
<thead>
<tr>
<th>Observation</th>
<th>Mean Arterial Blood Pressure (mmHg)</th>
<th>Heart Rate (per min.)</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Brain</td>
</tr>
<tr>
<td>Pre-perfusion</td>
<td>120</td>
<td>200</td>
<td>38.5</td>
</tr>
<tr>
<td>Termination of perfusion</td>
<td>40</td>
<td>60</td>
<td>14.7</td>
</tr>
<tr>
<td>After 30 mins. ischemia</td>
<td>68</td>
<td>150</td>
<td>16.0</td>
</tr>
<tr>
<td>50 mins. after end of ischemia</td>
<td>110</td>
<td>180</td>
<td>33.0</td>
</tr>
</tbody>
</table>

(range 48–65). The average time required to cool the brain to 15°C was 35 minutes; the average rate of cerebral cooling being 0.7°C per minute (Table 1). At the termination of the 30 minute period of ischemic arrest, the brain temperature had risen less than 2.0°C, while the average heart rate rose to 150 and mean arterial blood pressures to 68 mm. Hg (Fig. 2). Within 50 minutes after the termination of ischemia, sufficient rewarming had occurred to bring the average brain temperature to 33.0°C. (rewarming rate of 0.32°C per minute) with heart rates and mean arterial blood pressures nearing pre-perfusion values (Table 1). During the periods of profound selective hypothermic perfusion and ischemic arrest, esophageal, rectal and muscle temperatures never reached levels below 29.0°C. (Fig. 3).

Each of these 16 animals was awake within 5–8 hours following surgery. During the immediate postoperative period, transient weakness of hind limbs, postural instability or minor adverse seizures were noted in some of the animals. Within 12 hours after the procedure, these abnormalities had disappeared except in 2 dogs, in which mild hind leg paresis was permanent. All animals were able to eat and drink on the morning following isolated cerebral hypothermia and ischemia. Neurological examination conducted on a daily basis for 2 weeks after surgery failed to demonstrate any significant

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Fig. 2. Typical changes in temperature, arterial pressure and heart rate in the dog during localized hypothermic cerebral perfusion.
neurological deficits other than the paresis mentioned above.

Discussion

In this experiment we were concerned with the temporary occlusion of the cerebral arterial circulation. Since there are many anastomotic channels linking the intracranial and extracranial arteries in the dog, the temporary elimination of blood flow into the brain, particularly its posterior components, would require a complicated and prolonged surgical procedure. In order to eliminate cerebral arterial flow through the vertebral-basilar system, we therefore elected simply to ligate the basilar artery.

This technique of selective hypothermia after permanent occlusion of the basilar artery, offered a rapid, reliable method for reducing cerebral temperature without significantly reducing general body temperature. Selective cerebral cooling to 14-18°C protected 16 consecutive dogs from an otherwise fatal period of cerebral circulatory arrest. Five control animals undergoing the same degree of cerebral ischemia died immediately if untreated, or within 24 hours if artificial respiration was used.

Despite the relatively minor reductions in the temperature of the body as a whole obtained with this method, marked alterations in systemic blood pressure and heart rate were recorded during cooling periods. Two explanations have previously been advanced for the severe hypotension and bradycardia seen with cerebral cooling: 1) direct cooling of the sino-atrial node by cold venous blood returning to the heart from the jugular, superior vena caval system,11 and 2) the effect of cold on the cardiovascular centers of the brain stem.3 Our experiments were not concerned with the importance of either of these mechanisms since both were operating in our method of isolated cerebral cooling. The relatively moderate hypotension and bradycardia in our cases were probably related to the moderate degree of systemic hypothermia occasioned by the withdrawal of blood from the femoral artery and the dilution of blood with 6 per cent dextran to prime the system.

The absence of any demonstrable neurological damage a few hours after rewarming from the systemic circulation was evidence of the protective effect of hypothermia upon the ischemic brain.

Summary

The brains of 21 dogs were rendered ischemic by permanent ligation and temporary occlusion of the extracranial cerebral circulation. Sixteen of these animals were protected by local cerebral hypothermia of 14.7°C during 30 minutes of brain ischemia. A similar period of cerebral ischemia was lethal for 5 control animals maintained at normal temperatures. Differential brain cooling was produced by a simplified femoral to carotid
arterial perfusion circuit which eliminated the need for an oxygenator and reduced the time of anti-coagulation therapy since the brain was rewarmed via the systemic circulation.

References