Profound Hypothermia for Intracranial Surgery Using a Disposable Bubble Oxygenator*

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Surgeons have long thought that better results might be achieved in the treatment of intracranial aneurysm if surgical repair could be performed without the danger of hemorrhage. Temporary clips placed on the proximal artery are helpful and have been widely employed but their application requires dissection of the cerebral arteries which may contribute to arterial spasm and thrombosis and result in cerebral infarction.15

An advantage of performing aneurysmorrhaphy with hemostasis achieved by temporary arrest of the circulation under deep hypothermia is that extensive dissection of the cerebral vessels is unnecessary. Intracranial operations have been performed in several clinics under these conditions and experience has shown that patients tolerate 30 or more minutes of cerebral ischemia if the temperature of the brain is reduced to about 15°C.5,7,9,11,13,18

In 1962 we reported our laboratory and clinical experiences with the surgery of aneurysms performed at low body temperatures attained by an extracorporeal circuit incorporating a rotating disc oxygenator.13 In many respects the results were gratifying but in others improvement was needed. The disc oxygenator required large amounts of blood for priming and considerable maintenance. Surgery often had to be delayed several days while donors for 4500 to 6000 cc. of fresh blood of the appropriate type were being located. By substituting a disposable bubble oxygenator which requires only saline and dextrose solutions as a prime, maintenance has been simplified and the blood bank relieved of a heavy burden.4 Possibly as a result of diluting the blood, time spent on cardiopulmonary bypass has been almost halved and troublesome venous bleeding from the craniotomy reduced. Laboratory and clinical experiences with this modified technique are described in the following account.

Laboratory Studies

Experiments were performed on 25 mongrel dogs weighing 22 to 45 kg., averaging 26 kg. Anesthesia was induced with thiopentonal sodium, the trachea intubated and methoxyflurane† then administered from a Heidbrink no. 8 ether vaporizer in the efferent line of a Bird Mark VIII respirator. Respirations were controlled at a rate of about 16 per minute except when cardiac asystole or ventricular fibrillation occurred. Anesthetic agent was not usually administered after the esophageal temperature fell below 25°C, unless the dog awakened during the rewarming period. The respiratory gas in all cases was 100 per cent oxygen.

The animals were connected to the extracorporeal circuit by venous cannulas inserted through the right innominate vein into the right atrium and through the femoral vein into the inferior vena cava. The blood drained by gravity into a Travenol disposable bubble oxygenator which was ventilated with 100 per cent oxygen at esophageal temperatures greater than 20°C. and 95 per cent oxygen + 5 per cent carbon dioxide at temperatures lower than 29°C.

A totally occlusive pump propelled the blood from the oxygenator through a Brown-Harrison heat exchanger containing nylon rods and back to the animal by a femoral artery. In later experiments a second heat exchanger was added parallel with the first in order to obtain more efficient cooling and to reduce resistance to the flow of blood.

The extracorporeal circuit was primed with isotonic saline and 5 per cent dextrose in water. Low molecular weight dextran was not employed because of the suspicion that it might contribute to excessive bleeding from the craniotomy during

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the period of rewarming. Drake and Lewis have shown that low molecular weight dextran administered to hypothermic dogs significantly increases the volume of plasma whereas saline and plasma do not. The effect of dextran on the venous pressure of dogs was compared with that of plasma, whole blood, mannitol and isotonic saline (Table 1). The dextran solution resulted in a higher and more sustained elevation of venous pressure than any of the other solutions in the doses employed. Therefore, it was omitted from the priming medium of the extracorporeal circuit when the disposable bubble oxygenator was adapted, and 1000 cc. of isotonic saline and 500 cc. of 5 per cent dextrose in water substituted. More saline was used than might be suitable for a patient with cardiac disease, in order to minimize the risk of inducing cerebral edema by the administration of a solution, such as dextrose in water, which may become hypotonic when the solute is metabolized.

The pH and pCO₂ of arterial blood were determined at intervals during 15 of the experiments. Samples collected from the aorta in heparinized syringes were stored in ice water for 1–3 hours and then agitated at room temperature for several minutes prior to being introduced into two separate pH and pCO₂ meters.* The water bath of one meter was maintained at 37°C, and that of the other at 20°C. Assuming an inverse relationship to temperature, the pH of arterial blood at body temperature, BT (taken as the arithmetic mean of the esophageal and rectal temperatures) was obtained by the formula:

$$pH_{BT} = \frac{pH_{37} - pH_{20}}{17} + (37 - BT) + pH_{37}$$

The pCO₂ of arterial blood at body temperature was calculated from a similar formula assuming that the log pCO₂ varies directly with temperature.

$$\log pCO₂_{BT} = \frac{\log pCO₂_{37} - \log pCO₂_{20}}{17} + (37 - BT) + \log pCO₂_{37}$$

* Instrumentation Laboratory model 113.

TABLE 1

<p>| Effect of various solutions on venous pressure (intravenous administration over 15 minutes to dogs) |</p>
<table>
<thead>
<tr>
<th>No. of Animals</th>
<th>Pressure: Mean Rise mm./Saline</th>
<th>Median Duration in Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 per cent low molecular weight dextran in saline 20 cc./kg.</td>
<td>4</td>
<td>77</td>
</tr>
<tr>
<td>Plasma 90 cc./kg.</td>
<td>3</td>
<td>41</td>
</tr>
<tr>
<td>Whole blood 90 cc./kg.</td>
<td>4</td>
<td>39</td>
</tr>
<tr>
<td>20 per cent solution mannitol 5 gm./kg.</td>
<td>8</td>
<td>34</td>
</tr>
<tr>
<td>Isotonic saline 20 cc./kg.</td>
<td>8</td>
<td>1</td>
</tr>
</tbody>
</table>

Fig. 1. A shift of the pH-pCO₂ line to the left is shown on 2 blood samples taken from a dog before (A) and after (B) a metabolic acidosis has developed. Base excess has fallen from 0 to −5. The pH and pCO₂ on each sample were measured at both 37°C and 20°C to construct the lines.

An alternative way of determining pCO₂ and also some other parameters of acid-base metabolism was employed. The pH and pCO₂ at 37°C and 20°C were plotted on the Sigggaard Andersen graph and connected by a straight line (Fig. 1). The pH at body temperature (which is quickly calculated) was located on the line and the value for pCO₂ read directly from the graph. A shift of the line to the left as determined from successive samples of blood during an experiment is evidence that a metabolic acidosis has developed. A value for base excess may also be read from the graph. Base excess is a measurement of the non-respiratory component of acid-base metabolism introduced by Astrup and his co-workers; it expresses in mEq/L the amount of strong base present in the blood. The normal value for base excess is arbitrarily fixed at zero while metabolic acidosis (a lack of base) is reported in negative values and metabolic alkalosis in positive values.

Management of Perfusion. Partial cardiopulmonary bypass was induced using about 100 cm. of venous drainage by gravity. The return arterial flow was balanced to keep the amount of blood in the extracorporeal circuit constant. Rates of flow initially ranged between 75 and 100 cc./kg./min. and fell somewhat during cooling but usually remained greater than 50 cc./kg./min. Low rates of flow or a fall of the arterial blood pressure much below 50 mm. Hg were corrected by adding 100–300 cc. of 5 per cent dextrose in water to the extracorporeal circuit.

The perfusion was usually continued until the electrocardiogram became iso-electric whether or...
not ventricular fibrillation ensued during cooling. Occasionally the perfusion was stopped before cardiacl standstill occurred if electrical activity of the heart persisted at an unusually low body temperature. Then the dog was exsanguinated through the venous catheters and the blood stored in a reservoir. After 30 minutes of circulatory arrest the perfusion was restarted and the animal rewarmed. When rewarmin was completed and the bypass could be discontinued, approximately $\frac{2}{3}$ of the 1500 cc. of diluted blood remaining in the extracorporeal circuit was transfused into the animal. As a result the venous pressure rose above normal for 5–10 minutes.

In 10 of the early experiments the animal was anticoagulated with 200–300 units/kg. of heparin and in 2 instances when circulation was resumed after the period of arrest, clots blocked the filter in the disposable oxygenator. Massage of the filter kept the clots in suspension in 1 experiment and allowed the perfusion to be completed with survival of the animal, but in the other, even perforation of the filter mesh with a sharp instrument did not restore a satisfactory perfusion and death resulted. Clotting did not occur, however, in 13 experiments in which 300 units/kg. of heparin were administered to the animal and an additional 7000 units added to the priming volume of the extracorporeal circuit.

**Temperatures.** The animals were rapidly cooled by circulating ice water through the heat exchangers thus reducing the temperature of the inflowing arterial blood to below 10°C. Rewarming was started gradually and the temperature of the arterial blood maintained about 10°C, greater than the esophageal temperature until either a well-formed electrocardiogram was obtained or ventricular fibrillation occurred. Then the rate of rewarmin was speeded by the circulation of water at 48°C through the heat exchangers. If necessary, defibrillation of the heart was accomplished by an external electric shock when the esophageal temperature approached 30°C, and when rapid fibrillatory waves of good amplitude were observed on the electrocardiogram. At the termination of the cardiopulmonary bypass the temperature measured in the esophagus was ordi-narily higher than that measured in the rectum but the two temperatures became equal at a value near their arithmetic mean after about 30 minutes. Consequently extracorporeal rewarmin was continued until the mean was 30°C, or greater.

The 25 experimental animals were cooled to a mean esophageal temperature of 7°C and a mean rectal temperature of 12°C, in an average of 25 minutes or at a rate of 1.1°C per minute. Re-warmin occurred at a slightly slower rate (0.94°C./per minute) and an average of 23 min-utes was required to attain a body temperature of about 31°C.

**Results of Animal Experiments**

**Acid-Base Balance.** Base excess was a useful parameter of acid-base equilibrium. The values for pH and pCO$_2$ were difficult to interpret in view of the large changes in temperature and the presence of carbon dioxide in the respiratory gas. The wisdom of using an artificial value such as base excess to de-scribe acid-base balance may properly be questioned. But in practice base excess conveniently identifies the position of the experimentally determined line which connects the values for pH and log pCO$_2$ at 37°C. and 20°C. Brewin et al. and more recently Astrup et al. have emphasized that the position of such a line shifts when a metabolie acidosis or alkalosis develops. Changes in either the temperature or the pCO$_2$ of any sample of blood will not affect the position of the line but will alter the pH: the new values, however, still fall along the same line (Fig. 1).

In all but one of the animals low values for base excess were observed after about 1 hour of anesthesia indicating that a metabolic acidosis was present prior to starting cardiopulmonary bypass (Table 2). Though a metabolic acidosis under anesthesia may be compensatory for a respiratory alkalosis in-duced by hyperventilation, in these experi-ments low values for pCO$_2$ (secondary to hyperventilation) were not correlated with low values for base excess (a metabolic aci-dosis).

The base excess, usually already low prior to the establishment of cardiopulmonary by-pass, fell further during the period of cooling but then usually remained stable during the 30 minutes of circulatory arrest and rewarmin. Ventricular fibrillation occurred in 5 of the 10 animals studied but its occurrence and the number of electrical shocks neces-sary to establish a normal rhythm were not related to the pH, pCO$_2$ or base excess of the blood.

In some animals the acidosis present at the end of the rewarmin period was corrected by
the administration of Tromethamine buffer,* while in 2 others sufficient buffer was added to the priming volume of the extracorporeal circuit to prevent an important degree of acidosis from occurring. The speed and completeness of recovery in animals treated with buffer did not differ from that of the untreated animals in which a significant acidosis had developed.

**Morbidity and Mortality.** In 22 of 25 experiments the animals survived (Table 3). On the 1st and 2nd day after operation many of the animals were lethargic, fed poorly and a few were weak in the hind limbs. Improvement followed thereafter and by the 3rd to 5th day most of the animals were alert and active.

On 3 occasions the perfusion resulted in death of the animal. One succumbed when clots formed in the oxygenator. A 2nd appeared to have distemper prior to the perfusion, never rallied and died 2 days after operation. The last death occurred in a dog which did well at first but died after 4 days from obstruction of the tricuspid valve by a large organized thrombus attached to the base of one of the tricuspid leaflets. Whether or not damage to the endocardium by an intracardiac cannula accounted for the thrombus was not determined.

**Clinical Experience**

The methods developed with experimental animals were applied with certain modifications in operations on 8 patients. The technique of perfusion was unchanged except that gases for the oxygenator were filtered to remove bacteria. Arterial pressure was measured by a catheter passed through a side arm on a cannula in the femoral artery; venous pressure was not monitored.

Anesthesia was induced with thiopental and maintained with diethyl ether or methoxyflurane after tracheal intubation with the aid of a short acting muscle relaxant. The patient lay on a refrigeration blanket which lowered the body temperature several degrees before the perfusion was started. In the first 5 patients venous cannulas for the extracorporeal circuit were inserted through the right jugular vein and a femoral vein. In the last 3 patients the operation was speeded by abandoning the cervical incision and using both femoral veins instead. One cannula reached from the groin to the region of the right atrium while the other remained in the distal portion of the inferior vena cava.

While the intracranial contents and femoral vessels were being exposed, 1.5–2 gm./kg. of mannitol† were administered to shrink the brain and to hasten excretion of any excess water which might increase blood volume and cause venous bleeding from the craniotomy.

The perfusion was continued until cardiac standstill ensued and the temperature of the brain measured with a blunt needle probe fell to 15°C or below. Sometimes temperatures as low as 7°C were obtained, particularly if the head was slightly dependent during the perfusion (Table 4).

In order to shorten the period of circulatory arrest, the operation was planned so that the dura was open when the perfusion was discontinued. Then the patient was partially exsanguinated and the head elevated thus creating a bloodless surgi-

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† Supplied in 20 per cent solution through the courtesy of L. D. Bechtol, M.D., Ph.D., Travenol Laboratories, Morton Grove, Illinois.
the extracorporeal circuit, but the loss of blood was also reduced perhaps as a result of the osmotic diuresis and the avoidance of plasma expanders.

Profuse bleeding under profound hypothermia, according to Murphey and Dugdale, is often due to the clot-lysing activity of fibrinolysin (plasmin) which may appear in the blood during cardiopulmonary bypass. In their experience the administration of a drug which interferes with the formation and action of fibrinolysin, epsilon aminocapric acid, prevents most of the abnormal bleeding encountered during hypothermic perfusion. The value of this drug cannot be assessed in the present series as it was given only to one patient; however, the loss of blood during this operation was minimal.

**Duration of Perfusion.** The time spent in cooling and rewarming on the cardiopulmonary bypass averaged 58 minutes per patient in the present series compared with 96 minutes in the series reported in 1963. This saving of 38 minutes resulted probably from the higher rates of flow obtainable with diluted blood; the median rate increased from 1500 cc. per minute in the early series to 1900 cc. per minute in the present series. The efficiency of cooling and rewarming was also

**TABLE 3**

<table>
<thead>
<tr>
<th>Weight</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 kg.</td>
<td>17-45 kg.</td>
<td></td>
</tr>
<tr>
<td>Time to cool</td>
<td>25 mins.</td>
<td>15-35 mins.</td>
</tr>
<tr>
<td>Time to warm</td>
<td>23 mins.</td>
<td>15-35 mins.</td>
</tr>
<tr>
<td>Low esophageal temperature</td>
<td>7°C</td>
<td>4-14°C</td>
</tr>
<tr>
<td>Low rectal temperature</td>
<td>13°C</td>
<td>4-15°C</td>
</tr>
<tr>
<td>Defibrillation required</td>
<td>8 of 24</td>
<td></td>
</tr>
<tr>
<td>Average no. shocks required</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>22 of 25</td>
<td></td>
</tr>
</tbody>
</table>

**Results of Clinical Experience**

In the present series an average of 1500 cc. of acid citrate-dextrose (ACD) blood was administered to each of the 8 patients, a substantial reduction from the minimum of 1000 cc. of ACD and 3000 cc. of fresh heparinized blood formerly required with the disc oxygenator. This saving occurred largely because blood was no longer needed to prime the extracorporeal circuit, but the loss of blood was also reduced perhaps as a result of the osmotic diuresis and the avoidance of plasma expanders.

**TABLE 4**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Number</th>
<th>Range</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>5</td>
<td>51.6-69 kg.</td>
<td>59.5 kg.</td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
<td>18-57 yrs.</td>
<td>39 yrs.</td>
</tr>
<tr>
<td>Location of aneurysm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cerebral</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle cerebral</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior communicating</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior communicating</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time after hemorrhage</td>
<td>1-24 days</td>
<td>15 days</td>
<td></td>
</tr>
<tr>
<td>Time to cool</td>
<td>17-28 mins.</td>
<td>22 mins.</td>
<td></td>
</tr>
<tr>
<td>Time to warm</td>
<td>22-38 mins.</td>
<td>31 mins.</td>
<td></td>
</tr>
<tr>
<td>Low brain temperature</td>
<td>7-14°C</td>
<td>11.7°C</td>
<td></td>
</tr>
<tr>
<td>Duration of circulatory arrest</td>
<td>9-29 mins.</td>
<td>16 mins.</td>
<td></td>
</tr>
<tr>
<td>Defibrillation necessary</td>
<td>6 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of shocks</td>
<td>1 in 5 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood used</td>
<td>1000-2500 cc.</td>
<td>1500 cc.</td>
<td></td>
</tr>
</tbody>
</table>
Hypothermia by Disposable Bubble Oxygenation

improved by the addition of a second heat exchanger in later cases.

Morbidity and Mortality. Two of the 8 patients died. One death occurred in a 57-year-old woman who was admitted to the hospital unconscious after a third subarachnoid hemorrhage. Her condition improved sufficiently after 13 days to attempt repair of a saccular aneurysm arising from the right internal carotid artery at the junction with the posterior communicating artery. Because the neck of the aneurysm fragmented during repair the carotid artery was occluded with a clip. Though angiograms had shown good cross-filling from the opposite side, she never regained consciousness and succumbed after 48 hours. Postmortem examination was not obtained but cerebral infarction was believed to be a likely cause of death.

The second death occurred in a 52-year-old woman who also appeared to have sustained three subarachnoid hemorrhages. An aneurysm of the left anterior cerebral artery at the genu of the corpus callosum was identified and displacement of the arteries on angiography suggested the presence of a hematoma in the right frontal lobe. As the patient was stuporous a tracheostomy was performed and operation delayed in hope that improvement might occur. After 48 hours, however, she was even less responsive and so evacuation of the hematoma and repair of the aneurysm was attempted. Though hemorrhagic soft brain was aspirated from the right frontal lobe and a clip placed across the neck of the aneurysm without difficulty she never regained consciousness and died 2 days following operation. Permission for autopsy was denied.

Of the 6 survivors, 1 sustained a hemiparesis which gradually cleared over several weeks and a second patient who incurred a hemiparesis and mild aphasia recovered almost completely prior to discharge 18 days after operation. Following repair of an internal carotid aneurysm a 3rd patient developed a transient 3rd nerve palsy and in addition, a contralateral peripheral facial paralysis, weakness of both quadriceps, loss of stretch reflexes and an elevated spinal fluid protein. Progressive recovery followed this illness which had the characteristics of a polyneuritis of the Guillain-Barre type.

Discussion

Several types of heat exchangers, pumps and oxygenators have been used successfully to effect profound hypothermia for intracranial surgery. An extracranial circuit which does not require priming with blood is of special value since operation may proceed without the expense and delay of finding a large number of blood donors. As described in this paper a disposable bubble oxygenator has proven entirely satisfactory and can be primed solely with a solution of saline and dextrose.

Troublesome bleeding sometimes occurs during operations under profound hypothermia when plasma expanders such as low molecular weight dextran are employed or excess fluids are administered. Abnormal bleeding may also be encountered if the perfusion activates fibrinolysin in the blood. As epsilon aminocaproic acid reverses the effects of fibrinolysin this drug can be valuable in maintaining normal hemostasis during and after the perfusion.\textsuperscript{10,12,14}

Hypothermia with circulatory arrest is a practical method of preventing bleeding during intracranial surgery. The danger of accidental rupture of an aneurysm may also be reduced by other, simpler methods such as application of a temporary clip to the proximal artery. However, much of the morbidity and mortality associated with the repair of a saccular aneurysm is due to cerebral infarction because manipulation of a cerebral artery already in spasm may thrombose the artery.\textsuperscript{15} Occlusion of a major vessel supplying the brain is not always well tolerated even if accomplished at a low body temperature, but arrest of the circulation under profound hypothermia removes the possibility of sudden hemorrhage and permits repair of an aneurysm with minimum dissection of its parent vessel. Whether or
not this advantage is important enough to lower surgical mortality remains to be seen.

Summary

An extracorporeal circuit incorporating a disposable bubble oxygenator was used to induce profound hypothermia first in dogs and later in patients undergoing intracranial aneurysmorrhaphy. The oxygenator proved entirely satisfactory and could be primed solely with a solution of saline and dextrose. Hemodilution improved the perfusion especially at low temperatures, modified the loss of blood during surgery and greatly reduced the amount of blood needed for the procedure.

References

12. Murphy, F., and Dugdale, M. Personal communication.