Effects of profound hypothermia and circulatory arrest on cerebral oxygen metabolism and cerebrospinal fluid electrolyte composition in dogs

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Cerebral oxygen metabolism was studied in the dog at brain temperatures ranging from 37° to 8°C. As brain temperature decreased, the cerebral oxygen metabolism (CMRO₂) decreased following the Arrhenius equation. The natural logarithm of the CMRO₂ was a linear function of the reciprocal of the absolute (K) brain temperature. Oxygen metabolism, although much decreased, continued at very low brain temperatures. The CSF composition was unchanged after 1 hour at brain temperatures down to 10°C. Circulatory arrest for tolerable periods and longer caused changes only in the CSF potassium concentration. The interval between the onset of circulatory arrest and the beginning of the CSF K concentration increased with decreasing temperature and the rate of CSF K increase was increasingly slower at lower temperatures. At all temperatures the rate of CSF K changed gradually increased with time.

The interval before the CSF K started to increase was dependent upon the amount of O₂ available in the brain and the length of this interval was inversely proportional to the CMRO₂. The amount of CSF K concentration was not clearly related to the tolerable periods of circulatory arrest, but at normal temperatures an obviously increased CSF K following a period of acute cerebral anoxia without CSF hemorrhage may indicate brain damage.

Key Words: hypothermia • circulatory arrest • cerebral metabolism • cerebrospinal electrolytes

This is a study of cerebrospinal fluid (CSF) electrolyte changes during circulatory arrest at brain temperatures ranging from 37° to 10° C and their relationship to cerebral oxygen metabolism.

The maintenance of the intracellular sodium and potassium content is dependent on the metabolic processes which excludes or removes sodium from cells (the “sodium pump”). As the cerebral metabolism is, under normal conditions, almost entirely aerobic, the cerebral sodium pump is dependent directly on the availability of oxygen to the brain. Anoxia generated by circulatory arrest will eventually affect the sodium pump causing increases in intracellu-
lar sodium and extracellular potassium, changes which may be related to the tolerance of circulatory arrest. The brain extracellular fluid communicates freely with the CSF and the composition of these two fluids is equivalent so that any change in brain extracellular fluid composition will be reflected by similar changes in CSF composition and a corollary of this is that a CSF composition can be a reflection of cerebral metabolic changes. To evaluate changes in CSF composition, studies of oxygen metabolism at all temperatures needed to be carried out.

Materials and Methods

Mongrel dogs, each weighing about 20 kg, were the experimental animals used. For temperatures above 27°C the dogs were surface-cooled, but for temperatures below 25°C an extracorporeal blood circulation system was used. For these experiments, intrathoracic cannulation of the inferior and superior vena cavae and coronary sinus was used for venous drainage and arterial inflow was into the femoral artery. Inflow blood pressure, sagittal sinus venous pressure, and CSF pressure either in a lateral ventricle or the cisterna magna were monitored. Electrocardiograms, and in some cases, the electroencephalogram were recorded. Intratracheal respiration was maintained with a positive pressure respirator. Temperatures were recorded from thermister thermometer needles within the brain, in the temporal muscle, the lower limb muscles, the esophagus, the rectum, the heart and the liver. The cooling rates were dependent on blood flow rate and arterial oxygen tension, and coronary sinus pressure was monitored. When extracorporeal arrest was carried out, samples were taken at appropriate times before, during, and after arrest and during rewarming. These samples were analyzed for pH, PO₂, PCO₂, total osmotic pressure, sodium, potassium, chloride, and CSF protein. To demonstrate oxygen utilization at very low temperatures, the cerebral blood flow rate and arterial oxygen saturation were varied and the arteriovenous oxygen (A-VO₂) differences measured while the temperature held constant. Very little oxygen is used at lower temperatures, and hemoglobin saturation methods for oxygen determination are of no value, so the methods of Van Slyke and Nie1 which included dissolved oxygen were used. Cerebral blood flow (CBF) was measured using the nitrous oxide methods of Kety and Schmitt modified for the extracorporeal circuit and for the hypothermic conditions. All procedures were carried out under aseptic techniques with proper concern for anesthesia and the welfare of the animal.

Results

The data for this study are derived from 43 experiments. An A-VO₂ difference was demonstrated at all temperatures. It decreased steadily as the temperature decreased, indicating a decrease in cerebral oxygen metabolism (CMRO₂). At any one temperature the A-VO₂ difference was related to the cerebral blood flow which in turn was controlled by the arterial blood pressure and cerebral vascular resistance. The A-VO₂ increased when the blood flow decreased as expected. Figures 1 and 2 show this as it occurred at 12°C.

The CMRO₂ decreased as temperatures fell, following the Arrhenius equation. This means that the natural logarithm of the oxygen consumption decreased linearly with the reciprocal of the body temperature measured on the absolute scale (°K) as shown in Fig. 3.

The regression line for CMRO₂ and the reciprocal of the absolute temperature is:

\[
CMRO₂ (\pm 0.2904) = -1.1248 \times 10^4 \frac{1}{T(°K)} + C, \tag{1}
\]

Edgar A. Bering, Jr.
Effects of profound hypothermia and circulatory arrest

where CMRO$_2$ is the brain oxygen consumption in CCO$_2$/100 gm brain wt/min, $T$ is the brain temperature in absolute degrees (°K), and $C$ is a constant of thermodynamic significance. This agrees with work on monkeys over a higher temperature range.$^{3,14}$

Electroencephalographic brain activity decreased as brain temperatures decreased.$^{4,5,18}$ with very little recognizable activity below 19° C. The EEG when measured became isoelectric very quickly after circulatory arrest.$^4$ The importance of the EEG in these experiments was in predicting survival.

The tolerance to varying periods of circulatory arrest was not a major objective of this study, but survival after 52 to 59 minutes of circulation arrest at 10° C to 12° and 35 minutes at 17° C confirmed the work of others showing increasing tolerance for circulatory arrest with decreased temperature.$^6,9,16,19,22-24$ The increase in survival time with decreasing temperature, like CMRO$_2$, seems to be a function of the reciprocal of the absolute (°K) brain temperature but with a slightly shallower slope. An assumed line of tolerance for circulatory arrest projected from the more detailed studies at 37° to 20° C as well as from previous work$^9$ is shown in Fig. 4. All surviving animals fall below this line.

The CSF and blood were sampled before cooling, during cooling, at the experimental temperature, serially during circulatory arrest, after restarting the circulation and during rewarming. Only one temperature and one period of circulatory arrest were studied in any one animal. Because of the large number of samples required and the small amount of CSF available, the CSF results are a composite of many experiments at the same temperature and period of circulatory arrest.

The blood serum and CSF levels of sodium, potassium, chloride, total osmolality and protein did not change significantly with decreasing total body and brain temperatures from 37° to 10° C. This is in agreement with other work on intact animals at moderate hypothermic levels,$^8$ but others have shown some serum electrolyte changes in hypothermia.$^{20}$ The CSF and serum data during cooling in a typical experiment are given in Table 1.

Serial samples of CSF after circulatory arrest were taken at many temperatures.
TABLE 1

CSF composition during brain cooling at a rate of 0.33°C/min

<table>
<thead>
<tr>
<th>Brain Temp. (°C)</th>
<th>Osmolality (mOsm)</th>
<th>Sodium (mEq/l)</th>
<th>Potassium (mEq/l)</th>
<th>Chloride mEq (mEq/l)</th>
<th>Protein (mg%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum CSF</td>
<td>Serum CSF</td>
<td>Serum CSF</td>
<td>Serum CSF</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>298</td>
<td>301</td>
<td>141</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>302</td>
<td>319</td>
<td>156</td>
<td>160</td>
<td></td>
</tr>
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</tr>
<tr>
<td>18</td>
<td>298</td>
<td>305</td>
<td>146</td>
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<td></td>
</tr>
<tr>
<td>10</td>
<td>305</td>
<td>301</td>
<td>145</td>
<td>156</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 2

CSF electrolytes during circulatory arrest at a brain temperature of 18°C

<table>
<thead>
<tr>
<th>Time After Circulatory Arrest (min)</th>
<th>Na (mEq/l)</th>
<th>K (mEq/l)</th>
<th>Cl (mEq/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum CSF</td>
<td>Serum CSF</td>
<td>Serum CSF</td>
</tr>
<tr>
<td>0</td>
<td>158</td>
<td>157</td>
<td>3.49</td>
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<td>4</td>
<td>157</td>
<td>2.61</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>154</td>
<td>2.81</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>157</td>
<td>2.87</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>158</td>
<td>3.55</td>
<td>113</td>
</tr>
<tr>
<td>50</td>
<td>157</td>
<td>4.81</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 4. Assumed safe circulatory arrest plotted against the reciprocal of the brain temperature in degrees Kelvin.

Between 39° and 8° C. The only changes seen were in the CSF potassium concentration while both serum and CSF sodium, chloride, total osmolality, and CSF protein remained essentially unchanged, and any small variations occasionally seen were not greater than the possible analytical errors. Table 2 shows the data from samples taken during a circulatory arrest experiment at a brain temperature of 18°C.

When an animal at normal temperature dies the CSF potassium concentration begins to rise almost at once; the time being so short that it could not be precisely measured in these experiments. This, of course, is similar to circulatory arrest at normal temperature where the CSF K concentration also starts to increase almost at once. The beginning of the increase in CSF K concentration was delayed with decreasing brain temperature, and at 13°C no concentration change was noted for 12 minutes. The rate of CSF K concentration increase was greater at the warmer temperatures than the cold temperatures; however, the concentration increase was not linear with time at any temperature, but increased in rate with time. This is shown graphically in Fig. 5 where CSF K after circulatory arrest is plotted against time at 37°C, 19°C, and 13°C.

After blood circulation was re-established the CSF K concentration returned to its normal level. The data for this were widely scattered as might be expected from the variations in time before starting rewarming, rewarming rates, and recirculation rates. Usually by the time an animal was rewarmed and ready to come off the pump the CSF K concentration had returned to nearly normal levels.
Effects of profound hypothermia and circulatory arrest

![Image of graph showing changes in CSF potassium after circulatory arrest]

**Discussion**

The detailed study and demonstration of brain oxygen utilization at low temperatures were required to establish with certainty the utilization of oxygen by the brain at low temperatures and the amount used. The CMRO$_2$ as measured here is an average of the whole brain in a basal state and does not take into account regional differences which certainly exist in normal activities at 37°C and probably at lower temperatures as well.

Hypothermia alone did not cause significant changes of CSF composition. This was somewhat unexpected because of the known effects of hypothermia on the blood brain barrier$^1$ and the kidney.$^9$ The similarity between the renal tubule and the choroid plexus has been pointed out in connection with the formation of CSF by the choroid plexuses.$^7$ If the sodium excretion by the choroid plexuses followed that of the kidney at low temperature one might expect the CSF potassium to rise when brain temperatures are under about 25°C. However, CSF production which may be dependent on Na transport$^7$ does decrease with hypothermia$^8$ and decreased CMRO$_2$ so that the plexuses simply may not be making CSF, but also, significantly, they are not leaking a dialysate of serum with a high potassium content into the CSF.

The rise in CSF potassium after circulatory arrest reflects a failure of the cellular sodium pump to exclude sodium, and as sodium enters the cells potassium leaves, causing an increase in the extracellular K. The brain extracellular fluid and the CSF are in free and rapid communication$^7$ so the CSF K also rises. This rise in CSF K, and the Na pump failure are the result of the brain running out of oxygen as can be shown by the constant relationship between the time interval between circulatory arrest and the onset of the CSF K concentration increase. This time interval is inversely related to the CMRO$_2$ by the simple relationship:

$$t_k = \frac{C}{CMRO_2},$$

where $t$= time before CSF K concentration increase starts after circulatory arrest, CMRO$_2$ = cerebral oxygen metabolism, and $C$ = a constant of proportionality which has units of ml O$_2$. The $t_k$ for 37°C, 19°C, and 13°C was 0.8, 7, and 12 min respectively (Fig. 5), and CMRO$_2$ 3.4, 0.43, and 0.25 CCO$_2$/100 gm brain wt/min respectively. C was calculated at 37°C C as 2.9 ml O$_2$; at 19°C C, 3.0 ml O$_2$; and at 13°C C, 3.0 ml O$_2$.

The constant relationship at all brain temperatures between the time before CSF K concentration starts to rise and CMRO$_2$ at various temperatures clearly indicates dependence. The proportionality constant has the units of ml O$_2$, which is an apparent volume of oxygen available to the brain when the circulation is arrested.

Since the CMRO$_2$ is known, it should be possible to calculate the time cerebral oxygen metabolism can continue after circulatory arrest and check this result. It can be done, but the results are questionable as assumptions about the available oxygen in the brain must be made. It must also be recognized that the assumed brain blood content is an average as various parts of the brain differ considerably in their blood content.

These calculations which assumed a maximum oxygen availability$^{11,21}$ gave oxygen use times which were short of CSF K rise times at all temperatures; however, some delay between the theoretical time when the tissue oxygen is exhausted and when the CSF K starts to rise is to be expected as the K movement out of cells...
starts slowly as the sodium pump gradually becomes ineffective, and different cell types would not be affected equally rapidly or in the same way. The movement of K to CSF from the brain extracellular space is by diffusion which is a slow process and to get enough K into the CSF to cause a measurable concentration change takes some time.

The ratios of the calculated time required to use the assumed available brain O₂ and the observed time when CSF K starts to rise are .75 ml to 37° C, .69 ml at 19° C and .70 ml at 13° C, which are in very close agreement. This suggests that the difference between the two calculations is indeed due to slow movement of K from cells to CSF, and it seems safe therefore to conclude that the CSF K rises after circulatory arrest because all available tissue O₂ has been consumed and the intracellular composition of certain brain cells cannot be maintained anaerobically.

The difference in brain cell type to tolerance of anoxia has been demonstrated in man, who at normal temperatures can suffer brain damage from anoxia that is not lethal but seriously affects intellect and other brain functions. This is probably true for anoxia in the hypothermic state as well. Therefore, one must distinguish between survival and survival without any brain damage.

The foregoing suggests that the CSF K rise seen during the circulatory arrest is the result of the deterioration of at least some cells not vital to survival but which might be vital to the intellect and other central nervous system function. Furthermore, it might be that the ability of an animal to tolerate circulatory arrest could be measured by the rate of CSF potassium increase or the amount of potassium lost because the periods of tolerated circulatory arrest are considerably longer than the time required to use the available O₂.

To examine the period of “safe circulatory arrest” at various temperatures, the time of estimated safe circulatory arrest (3.5 min at 37° C, 31 min at 19° C, and 65 min at 13° C) was located on the various curves of CSF K increase following circulatory arrest (Fig. 4) to see if there was any agreement in CSF K concentration and tolerated circulatory arrest which might indicate a dangerous or fatal loss of intracellular K or probably more correctly an intolerable intracellular Na level.

Since the safe limits of circulatory arrest are not known for certain, precise CSF K levels associated with irreversible electrolyte leak could not be determined, but the CSF K increase seemed to continue at an increasing rate at all temperatures without a break or change in the curve which might have indicated a point of irreversible damage. The CSF K level at the end of assumed safe circulatory arrest was higher at each lower temperature studied. At 37° C it was 3.5 mEq/l after 3.5 min circulatory arrest; at 19° C it was 4.25 mEq/l after 32 min circulatory arrest; at 13° C it was 6.35 mEq/l after 65 min circulatory arrest. This suggests that the total electrolyte loss is not the controlling factor and the brain can tolerate much more drastic electrolyte dislocations as the brain temperature decreases.

The rate of loss of K might be an important factor as suggested by the changes in the rate of CSF K increase. At all temperatures the rate of CSF K increase is constantly increasing, and at the point of assumed tolerance circulatory arrest is 0.12 mEq/l/min at 37° C; 0.09 mEq/l/min at 19° C, and 0.12 mEq/l/min at 13° C. This suggests that the rate of cellular K loss is more important than the total amount, but more data are required to be conclusive. The progressively faster rate of K loss probably indicates a larger and larger number of cells being involved.

The restoration of the intra- and extracellular electrolyte compositions is a very important problem but these experiments do not provide adequate relevant data to completely evaluate it. While it was noted that, on restarting the circulation and rewarming the CSF, K gradually returned to normal levels, the data gathered do not present any consistent picture because there were too many uncontrolled variables.

Because in animals that did survive after periods of circulatory arrest the CSF K did return to normal, a persistently high CSF K after a period of acute cerebral anoxia without hemorrhage suggests some brain damage.
Effects of profound hypothermia and circulatory arrest

Studies of CSF sodium and potassium in anoxia produced in monkeys at normal temperature have been reported by Meyer, et al.15 These experiments differ considerably from those reported here in that anoxia was not carried to irreversibility and the method producing anoxia, by nitrogen inhalation, is much less drastic than circulatory arrest. Their results, however, are in agreement with those reported here in showing an increase in potassium with anoxia. The CSF sodium concentration change Meyer, et al., report is what might be expected with the electrolyte shift, but sodium changes in these experiments were obscured by large differences from animal to animal, although some single experiments did show such a trend (Table 2).

References


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